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Total Syntheses of the Gregatins A–D and Aspertetronin A: Structure Revisions of These Compounds and of Aspertetronin B, Together with Plausible Structure Revisions of Gregatin E, Cyclogregatin, Graminin A, the Penicilliols A and B, and the Huaspenones A and B

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Comprehensive comparisons of ^{1}H and ^{13}C NMR chemical shift values in the furanone cores **a**, **b**, and **c** provide plausible support for a reassessment of the furanone nuclei of the title compounds from **b** to **c**. Total syntheses via enantiomerically pure lactic esters were based on the Seebach–Fráter "self-reproduction of stereocenters" methodology. Attachment of the hexadienyl side-chain in a *trans*,*trans*-selective manner was achieved by addition of the Seebach–Fráter enolate to *trans*-hex-4-en-1-al rather than to *trans*-hex-3-en-1-al. The type-**c** furanone cores of the synthetic materials were reached by single or double acylation of a model γ-hydroxy-β-oxo ester (compound **50**) and its hexadiene-containing counterpart **29**. Our syntheses confirmed the novel connectivities in six compounds. In addition, they required revision of the configuration of a quaternary carbon atom in five cases. Moreover, they allowed elucidation of the configurations of four previously unassigned stereocenters. Hindsight analyses of why the furanone cores of the title compounds had been misinterpreted as **a** and/or **b** instead of **c** are given. Why the stereocenters in the heterocycles had been incorrectly configured, on the bases (a) of relay studies in the 1960s, and (b) of a 1984 total synthesis of gregatin B, is also discussed.

A Structurally Deceptively Simple Class of Natural Products

Between 1969 and 1980 nine furanones were isolated, which founded the family of the gregatins, aspertetronins, graminin A, and one closely related compound, which remained unnamed. These compounds (Figure 1) were gregatin A [(–)-**2**,[1–3]], gregatin B [(+)-**1**[1,2]], gregatin C [(+)-**4′**[1]], gregatin D [(+)-**4**[1,2]], gregatin E [(+)-**6**[1]], aspertetronin A [(+)-**2**[4]], aspertetronin B [(–)-**4**[4]], graminin A [(–)-**3**[5]], and metabolite 704-II [(+)-**5**[6]]. At the time the core structures of these compounds were held to be 3-acyl-4-methoxyfuran-2(5*H*)-ones ("**a**" in Figure 1). Accordingly, their originally published ("first-generation") structures were (+)-**1a** through (+)-**6a**.

In 1980 the configurations of the quaternary stereocenters in aspertetronin A [(+)-**2**], aspertetronin B [(–)-**4**], and gregatin A [(–)-**2**] supposedly became clear – namely as drawn in Figure 1. This was because at that point in time a 10-step synthesis[7,8] was believed to have converted the lactone acid (–)-(*S*)-**27** (formula: Scheme 4, below) into the tetronic acid "(+)-(*S*)-**18**" (formula: Scheme 4). Dextrorotatory **18** had previously been obtained by degradation of gregatin A [(–)-**2**].[2] In contrast, levorotatory **18** had been obtained by degradations both of aspertetronin A [(+)-**2**] and B [(–)-**4**].[4] It was inferred that gregatin A [(–)-**2**] had the same C_{quat} configuration as "(+)-(*S*)-**18**", whereas C_{quat} in the aspertetronins A [(+)-**2**] and B [(–)-**4**] had the opposite configuration.

Compounds *rac*-**1a**[9–11] and *rac*-**2a**[9] were synthesized in the 1980s by Pattenden,[9] Yoshii,[10] and R. R. Schmidt[11] and their co-workers. The distinctness of their spectral properties from those of the natural products gave rise to the suggestion that the latter compounds rather possess the constitutions **1b**[9] (Figure 2) and **2b**,[9] respectively. By extrapolation, the same kind of structure revision was suggested[9] for all other gregatins, aspertetronin B, graminin A, and metabolite 704-II. The resulting "second-generation" 4-acyl-5-methoxyfuran-3(2*H*)-one ("**b**") formulas of the natural products from Figure 1 constitute the major part of Figure 2. In addition, Figure 2 also displays the originally published ("first-generation") structures of three natural products that have reinforced the gregatin family since: cyclogregatin [(+)-**7**[12]], penicilliol A [(+)-**8**[13]], and

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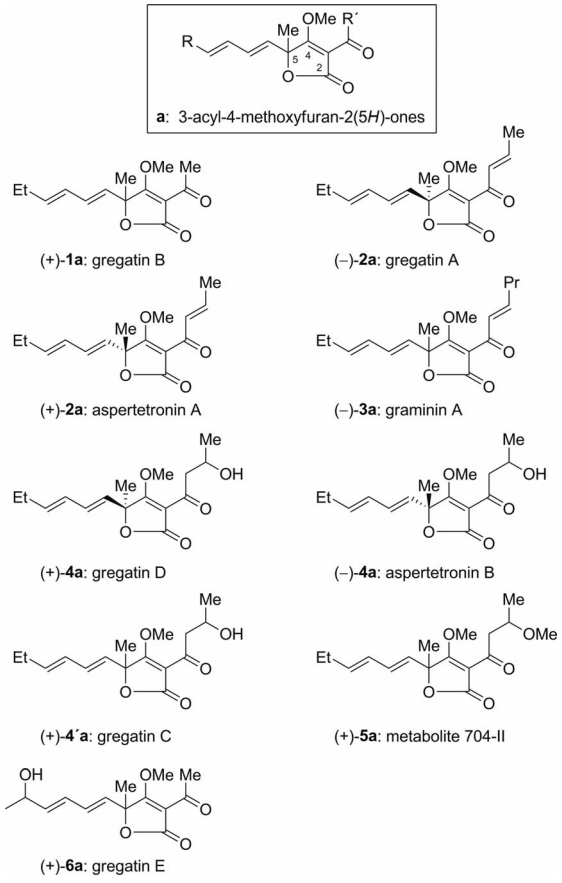


Figure 1. Originally published ("first-generation") structures of gregatins A [(–)-**2**[1–3]], B [(+)-**1**[1,2]], C [(+)-**4**[1]], D [(+)-**4**[1,2]], and E [(+)-**6**[1]], aspertetronins A [(+)-**2**[4]] and B [(–)-**4**[4]], graminin A [(–)-**3**[5]], and metabolite 704-II [(+)-**5**[6]].

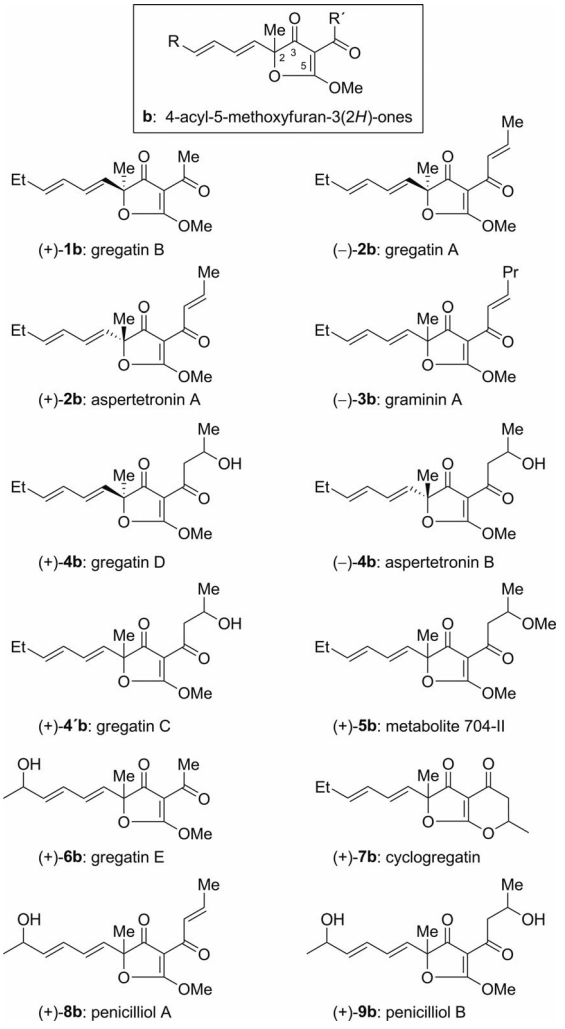


Figure 2. Revised[9] ("second-generation") structures of the natural products from Figure 1 [absolute configurations, if any, derived from purported total[15] and formal syntheses[16] of (+)-gregatin B (**1**); otherwise same as in first-generation structures]. Additionally: originally published ("first-generation") structures of cyclogregatin [(+)-**7**[12]], penicilliol A [(+)-**8**[13]], and penicilliol B [(+)-**9**[13]].

penicilliol B [(+)-**9**[13]].[14] From the beginning the furanone cores of these newly found compounds had been formulated in compliance with the **b** structures of their predecessors [i.e., as (+)-**7b**, (+)-**8b**, and (+)-**9b**]. Shortly after the **a**→**b** revisions, a total synthesis of (+)-gregatin B (**1**) seemingly was successful.[15] As a consequence this molecule was henceforth represented as (*S*)-**1b** (cf. Figure 2). A formal total synthesis of (+)-gregatin B followed in 2005.[16] It appeared to corroborate the 3D structure.

A while ago, *we* embarked on a synthesis of (+)-gregatin B. It provided the natural product,[17] but revealed to our considerable surprise that synthetic (+)-gregatin B was not (*S*)-**1b** but (*R*)-**1c** (Figure 3). Core **c**, from which (*R*)-**1c** is derived, is a dihydrofuranone-based methyl ester. Importantly, the identical core **c** appears to be present in all other members of the gregatin family (Figure 3). This is what we concluded from ^{1}H NMR comparisons between four reference compounds and several other members of the gregatin group.[17] Tables 1[18] and 2[18] (below) come to the same conclusion based on more comprehensive ^{1}H NMR analyses of type-**b** versus type-**c** compounds in $CDCl_3$ and C_6D_6 solutions, respectively.[19] These comparisons involve more compounds than formerly,[17] partly because we included further gregatin-type compounds originating from the present study. Table 3[18] (below) corroborates our reassignment of the gregatin group members as **c**- rather than **b**-based heterocycles by comparing ^{13}C NMR evidence.

The essence of Table 1 is that in $CDCl_3$ the 2-OCH_3 singlets of type-**b** compounds are ca. 0.4 ppm downfield from the 3-CO_2CH_3 singlets of type-**c** compounds. Conversely, the O=C–CH_3 resonances of type-**b** compounds are ca. 0.3 ppm upfield from the C=C–CH_3 resonances of type-**c** compounds. In C_6D_6 these relationships are reversed (Table 2): the 2-OCH_3 groups in type-**b** compounds resonate ca. 0.3 ppm upfield from 3-CO_2CH_3 in type-**c** compounds, whereas the O=C–CH_3 groups of type-**b** compounds resonate ca. 0.5 ppm downfield from the C=C–CH_3 groups of type-**c** compounds.

Ancillary support for our conclusions is provided by a number of ^{13}C NMR criteria for distinguishing type-**b** and type-**c** structures (Table 3): (i) the C-3 atoms are

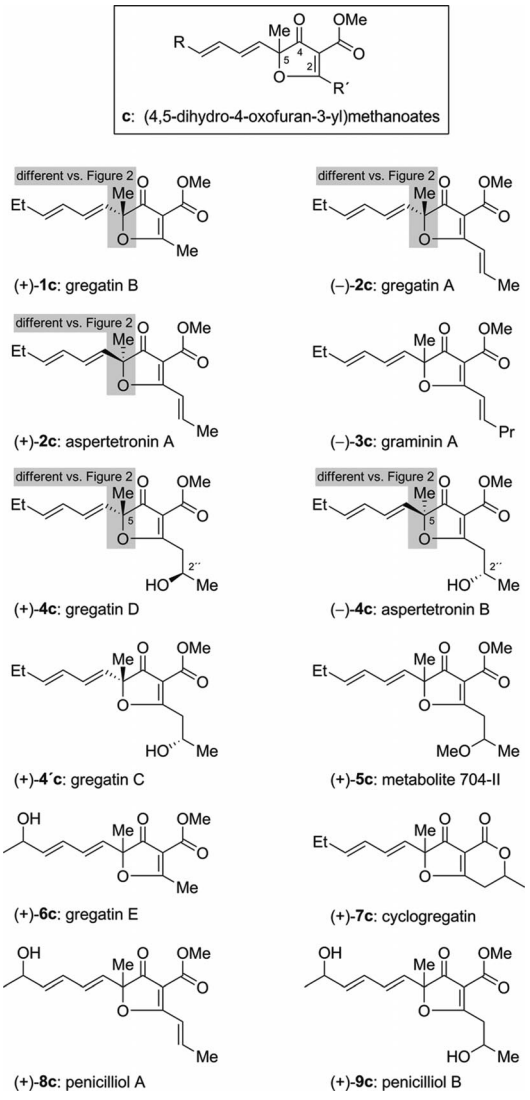


Figure 3. Re-revised ("third-generation") and revised ("second-generation") structures of the compounds from Figure 1 and Figure 2, respectively, as established or concluded in this study (vide infra).

shielded by ≥10 ppm in structures **b** relative to those of structures **c**, (ii) the 2-OCH_3 groups in structures **b** are deshielded by 4–5 ppm relative to the 3-CO_2CH_3 groups in structures **c**, (iii) the chemical shifts of the three lowest-field ^{13}C nuclei (C-2, 3-C=O, and C-4; δ =160.19 ppm ≤ δ ≤ 201.2 ppm) add up to 563–567 ppm in **b** cores in contrast with 545–560 ppm in **c** cores,[26] and (iv) in type-**b** compounds, unlike in type-**c** compounds, there are C_{quat} resonances between δ = 160 and 165 ppm.

Apart from the preceding reasoning, which argues for **c**-type rather than **b**-type cores in all members of the gregatin family we established irrefutable direct confirmation that gregatin B possesses structure **1c** rather than the "second-generation structure" **1b** (or the "first-generation structure" **1a**). This second proof of the gregatin B structure need not take recourse whatsoever to reference compounds. It stemmed from subjecting synthetic (–)-**1c**[17] – the unnatural enantiomer of gregatin B – to a *2 day-long* Pd-catalyzed hydrogenation *at 3 bar H_2 pressure* (Scheme 1).

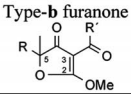
These relatively forcing conditions made our hydrogenation proceed further than the known hydrogenations of aspertetronin A[4] [→ (–)-**17c** as in Scheme 3, below], aspertetronin B[4] [→ (–)-**17c**, Scheme 3; the overall transformation includes a dehydration and another Pd-catalyzed hydrogenation], and gregatin A[2] [→ (+)-**17c**, Scheme 3] at *1 atm H_2 pressure* for 8–15 h. Our hydrogenation conditions made the tetrasubstituted C=C bond in (–)-**1c** *disappear* in the resulting diastereomers H_6-(–)-**1c** (60 rel-%) and *iso*-H_6-(–)-**1c** (40 rel-%). In contrast, the analogous C=C bonds in aspertetronin A, aspertetronin B (and the diene intermediate derived from it), and gregatin A *survived* under the literature conditions. Both H_6-(–)-**1c** and *iso*-H_6-(–)-**1c** were more easily structurally elucidated than (–)-**17c** (≡ "H_4-aspertetronin A") or (+)-**17c** (≡ "H_4-gregatin A"), because their scaffolds each contributed two extra ^1H NMR signals. Admittedly, the extra doublet at $\delta_{H_6\text{-(–)-1c}} = \delta_{iso\text{-}H_6\text{-(–)-1c}}$ = 2.95 ppm was unrevealing, because a similar signal would have been observed if the hydrogenation products had been H_6-(–)-**1a**/*iso*-H_6-(–)-**1a** or H_6-(–)-**1b**/*iso*-H_6-(–)-**1b**. However, the extra doublet of quartets at $\delta_{H_6\text{-(–)-1c}}$ = 4.59 ppm and $\delta_{iso\text{-}H_6\text{-(–)-1c}}$ = 4.55 ppm showed that the new C–H bond was vicinal to a CH_3 group. This structural feature is unique to H_6-(–)-**1c**/*iso*-H_6-(–)-**1c** and would have been absent both in H_6-(–)-**1a**/*iso*-H_6-(–)-**1a** and in H_6-(–)-**1b**/*iso*-H_6-(–)-**1b**.

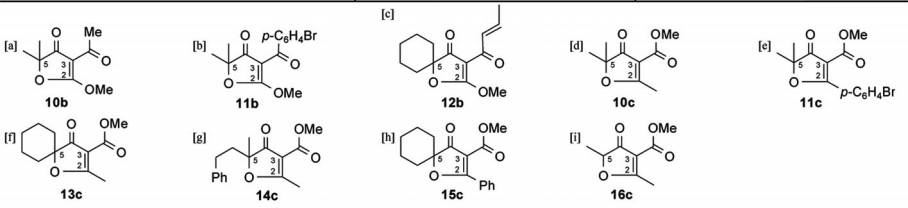
Analysis of Former Structural Assignment Errors

The degradation reactions of (+)-aspertetronin A [(+)-**2**],[4] aspertetronin B [(–)-**4**],[4] and gregatin A [(–)-**2**],[2] leading to the attribution of their "first-generation furanone structures" (+)-**2a**, (–)-**4a**, and (–)-**2a**, are shown in Scheme 2 as they were published. Pattenden's reassignment of the structures of the substrates of Scheme 2 ("replace structure **2a** by structure **2b**" and "replace structure **4a** by structure **4b**")[9] implied that the same kind of reassignment was also due for formula **17a**, which had been attributed[2,4] to an intermediate of the described degradation reactions: from Pattenden's perspective structure **17a** would have been replaced by structure **17b** (not depicted in Scheme 2). The underlying mix-up would have paralleled the "first-generation" versus "second-generation" mix-up of the structures of the natural products. However, from today's vantage point the misassignments of **2a**, **4a**, and **17a** concern the replacement of "first-generation" by "third-generation" structures. Accordingly, the transformations of Scheme 2 must be reformulated as in Scheme 3, which contains structures **2c**, **4c**, and **17c**, instead.

It is readily apparent that by NMR spectroscopy structures **17a**, **17b**, and **17c** are just as hard to tell apart from one another as each set of furanone isomers **1a**–**6a**, **1b**–**6b**, and **1c**–**6c** from Figure 1, Figure 2, and Figure 3, respectively. Accordingly, the flawed inference[2,4] "since degrada-

Table 1. ^{1}H NMR comparison of type-**b** and type-**c** furanones (solvents = $CDCl_3$, CCl_4, or [D_6]acetone). Positional numbers chosen for easiest comprehension; this, however, makes the numbering of **b** different from its IUPAC numbering (which was used in Figure 2).[18] Structure-differentiating nuclei and shifts are displayed on a gray background.

Type-**b** furanone 	Field strength [MHz]	Solvent	$\delta_{methyl\ singlets}$ [ppm] 5-Me	3-C(=O)Me	2-OMe
10b[a][17]	500	$CDCl_3$	1.41	2.30	4.11
11b[b][17]	300	$CDCl_3$	1.56	absent	4.21
12b[c][10]	200	$CDCl_3$	absent	absent	4.21
(*R*)-**1b**[17]	300	$CDCl_3$	1.62	2.42	4.23
Type-**c** furanone 			5-Me	2-Me	3-CO_2Me
10c[d][17]	300	$CDCl_3$	1.42	2.61	3.84
56	400	$CDCl_3$	1.40	2.58	absent
11c[e][17]	300	$CDCl_3$	1.52	absent	3.84
13c[f][20]	400 or 500	$CDCl_3$	absent	2.60	3.83
14c[g][20]	400 or 500	$CDCl_3$	1.44	2.60	3.85
15c[h][20]	400 or 500	$CDCl_3$	absent	absent	3.83
16c[i,j][21,22]	60 or 100	$CDCl_3$	(1.50)	2.63	3.84
Synthetic "(+)-**1b**[22,15]" ≡[17] *rac*-**1c**	100	$CDCl_3$	1.52	2.64	3.82
Synthetic (*R*)-**1c**[17]	400	$CDCl_3$	1.52	2.64	3.83
Synthetic (*R*)-**1c**[k]	400	$CDCl_3$	1.52	2.64	3.83
Natural (+)-**1c** (gregatin B) ref.[1a]	90	CCl_4	1.48	2.6	3.74
Natural (+)-**1c** (gregatin B) ref.[2]	90	$CDCl_3$	1.53	2.6	3.83
Natural (−)-**2c** (gregatin A[2])	250	$CDCl_3$	1.53	absent	3.83
Synthetic (*S*)-**2c**	400	$CDCl_3$	1.54	absent	3.83
Natural (+)-**2c** (aspertetronin A) ref.[4]	60	CCl_4	1.48	absent	3.74
Natural (+)-**2c** (aspertetronin A) ref.[4]	220	CCl_4	1.48	absent	3.72
Natural (−)-**3c** (graminin A[5])	90	CCl_4	1.48	absent	3.74
Synthetic (5*R*,2'*R*)-**4c**	250	$CDCl_3$	1.55	absent	3.84
Natural (+)-**4c** (gregatin D) ref.[5]	90	CCl_4	1.50	absent	3.74
Natural (+)-**4c** (gregatin D) ref.[2]	250	$CDCl_3$	1.53	absent	3.83
Natural (−)-**4c** (aspertetronin B[4])	60	CCl_4	1.50	absent	3.75
Synthetic (5*S*,2'*R*)-enantiomer of (5*R*,2'*S*)-**4'c**	300	$CDCl_3$	1.55	absent	3.84
Natural (+)-**4'c** (gregatin C[1a])	90	CCl_4	1.50	absent	3.74
Natural (+)-**5c** (metabolite 704-II[2])	90	$CDCl_3$	1.53	absent	3.83
Natural (+)-**6c** (gregatin E[1a])	90	CCl_4	1.50	2.60	3.74
Natural (+)-**7c** (cyclogregatin[j][12])	200	[D_6]acetone	1.56	absent	absent
Natural (+)-**8c** (penicilliol A[13])	400	$CDCl_3$[23]	1.57	absent	3.84
Natural (+)-**9c** (penicilliol B[13])	400	$CDCl_3$[23]	1.56	absent	3.84

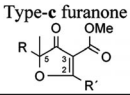


[j] The structure of this compound does not correspond fully to the furanone formula **c**. [k] This sample of (*R*)-**1c** resulted from the "*O*-acylation route" shown in Scheme 12.

tions of the aspertetronins A and B and of gregatin A delivered **17a** (or **17b**, as implied by ref.[9]) these natural products are furanones **a** (or **b**, as suggested in ref.[9])" can be understood. Differently expressed, what led the original researchers astray was that they performed the hydrogenations shown in Scheme 3 under such mild conditions that the furanone C=C bonds survived. Had these bonds also been saturated – like the corresponding C=C bond of *ent*-gregatin B [(–)-**1c**] under the harsher hydrogenations in Scheme 1 [→ H_6-(–)-**1c**/*iso*-H_6-(–)-**1c**] – the **c**-type cores of **2**, **4**, and **17** would have been recognized as unequivocally as in H_6-(–)-**1c**/*iso*-H_6-(–)-**1c**, i.e., in (–)-**1c** (cf. discussion of Scheme 1).

In the absence of the desirable hydrogenation experiments (cf. above) the crux for pinpointing the furanone core structure **c** of the compounds in question was the interference of the rearrangement **17c** → **19** en route both from

Table 2. ^{1}H NMR comparison of type-**b** and type-**c** furanones (solvent: C_6D_6). Positional numbers chosen for easiest comprehension; this, however, makes the numbering of **b** different from its IUPAC numbering (which was used in Figure 2).[18] Structure-differentiating nuclei and shifts are displayed on a gray background.

Type-**b** furanone 	Field strength [MHz]	$\delta_{methyl\ singlets}$ [ppm] 5-Me	3-C(=O)Me	2-OMe
10b[a][24]	400	1.05	2.63	3.12
11b[b][24]	500	1.10	absent	3.21
(*S*)-**1b**[17]	500[25]	1.31	2.61	3.21
Type-**c** furanone 		5-Me	2-Me	3-CO_2Me
10c[c][24]	500	1.05	2.14	3.52
11c[d][24]	500	1.12	absent	3.48
Synthetic (*R*)-**1c**[17]	500[25]	1.29	2.17	3.50
Synthetic (*R*)-**1c**[e]	500	1.28	2.17	3.50
Synthetic (*S*)-**1c**[17]	500[25]	1.29	2.17	3.50
Synthetic (*S*)-**1c**[f]	300	1.29	2.17	3.50
Synthetic *cis*,*trans*-(*R*)-**1c**	500	1.28	2.15	3.49
Synthetic (*R*)-**2c**	500	1.38	absent	3.53
Synthetic (5*R*,2'*R*)-**4c**	500	1.33	absent	3.47
Synthetic *cis*,*trans*-(5*R*,2'*R*)-**4c**	500	1.31	absent	3.44
Synthetic (5*S*,2'*R*)-enantiomer of (5*R*,2'*S*)-**4'c**	500	1.34	absent	3.45
Synthetic *cis*,*trans*-(5*R*,2'*S*)-**4'c**	500	1.33	absent	3.44

[a] Formula: Table 1, footnote [a]. [b] Formula: Table 1, footnote [b]. [c] Formula: Table 1, footnote [d]. [d] Formula: Table 1, footnote [e]. [e] This sample of (*R*)-**1c** resulted from the "*O*-acylation route" shown in Scheme 12 (below). [f] This sample of (*S*)-**1c** resulted from the "*C*-acylation route" shown at the bottom of Scheme 12 (below); it was a 94:6 mixture with *cis*,*trans*-(*S*)-**1c**.

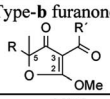
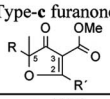
degradation product (+)-**17c** to oxo lactone (+)-*tautom*-**18** and from degradation product (–)-**17c** to oxo lactone (–)-*tautom*-**18** (Scheme 3). This rearrangement transforms the furanone core structure **c** into furandiones (*tautom*-**18**) or into a tetronic acid [(–)-**19**], which contain cores that resemble demethyl-**a** or demethyl-**b**. We are aware of two precedents of rearrangements of this kind: (i) the conversion of furanone **21** into tetronic acid **22** in the presence of NaOH[29] appears to start with **21** rearranging to give **26** (Scheme 3, bottom), and (ii) the dehydration of cyclogregatin [(+)-**7c**] with dilute NaOH delivered compound **83**.[12,30] By starting from the misconception that the substrate was (+)-**7b**[12] the involvement of a rearrangement was overlooked.

In 1980 Nakada et al. claimed to have determined the absolute configurations of aspertetronin A [(+)-**2c**] and aspertetronin B [(+)-**4c**] by an independent synthesis (Scheme 4)[7] of the dextrorotatory enantiomer of their common degradation product (–)-*tautom*-**18** (cf. Scheme 3). Also in 1980, gregatin A [(–)-**2**] was degraded to give (+)-*tautom*-**18** (cf. Scheme 3),[2] so Nakada's work was also relevant for determining the absolute configuration of gregatin A. According to their publication,[7] the lactone-based carboxylic acid (–)-(*S*)-**27**[31–34] was converted into "(+)-**18**" – that is, into (+)-*tautom*-**18**[28] – in 10 steps.[7] Accordingly, the product was understood as (+)-(*S*)-*tautom*-**18**.[7] This led to the conclusion[7] that the quaternary stereocenters in aspertetronin A and aspertetronin B are (*R*)-configured and implied that gregatin A is (*S*)-configured [cf. Figure 1, formulas (+)-**2a**, (+)-**4a**, and (–)-**2a**, respectively]. Our total syntheses of aspertetronin A, *ent*-aspertetronin B, and gregatin A (Scheme 15) call for correction of their core structures from **a** to **c** and for inversion of their quaternary stereocenters to (*S*), (*S*), and (*R*) configurations, respectively. With regard to the work of Nakada et al.[7] (Scheme 4), our findings mean that either no (+)-*tautom*-**18** or no (*S*)-*tautom*-**18** had resulted. In the first case the wrong sign for the specific rotation for (*S*)-*tautom*-**18** would have been published (Scheme 4, "interpretation 1"). In the second case the synthesis would have started from the antipodal lactone-based carboxylic acid (+)-(*R*)-**27** (Scheme 4, "interpretation 2"); taking one enantiomer of **27** for the opposite enantiomer of **27** seems conceivable, because both enantiomers originated from the resolution of racemic **27**.[7]

Reassuringly we gathered an ancillary piece of evidence for our assertion that "(*S*)-*tautom*-**18** = (–)-*tautom*-**18**". Some γ-hydroxy-β-oxo ester (*S*)-**29** was taken from a later stage of our work (Scheme 12, below), and the hexadienyl chain of this compound was hydrogenated (Scheme 4). The resulting γ-hydroxy-β-oxo ester (*S*)-**30** was cyclized through an HCl-catalyzed transesterification. It provided the tetronic acid (*S*)-*tautom*-**18** (albeit only in 8.5% yield[35]). This compound was levorotatory – unlike what had been reported,[7] but in agreement with our reasoning above.

Scheme 5 summarizes the findings that caused Pattenden and Clemo[9] – and subsequently also the groups of Schmidt[11] and Yoshii[10] – to reject the "first-generation" furanone cores **a** of all gregatin family members known at

Table 3. ^{13}C NMR comparison of type-**b** and type-**c** furanones. Positional numbers chosen for easiest comprehension; this, however, makes the numbering of the **b** system different from its IUPAC numbering (which was used in Figure 2).[18] Chemical shift values between parentheses are due to nuclei in furanones that deviate from **c** structurally, so the corresponding positions might experience different (de)shieldings than if they were embedded in genuine type-**c** furanones. Structure-differentiating nuclei and shifts are displayed on a gray background. Darker backgrounds indicate four chemical shifts that deviate from those of the other representatives with the same furanone core; these shifts are plausibly due to (an)other substituent effect(s), so we disregard them in our comparisons.

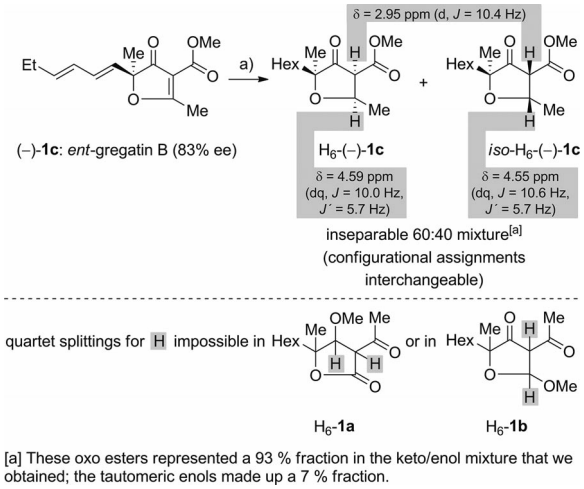
Type-**b** furanone 	Field strength [MHz]	Solvent	δ [ppm] 5-Me	C-5	C-4	C-3	3-C(=O)	C-2	OMe
10b[a][17]	100	C_6D_6[25]	22.69	91.89	196.22	95.84	190.20	180.93	55.90
11b[b][17]	126	C_6D_6[25]	22.76	91.97	194.56	94.79	186.01	182.18	56.28
12b[c][10]	No ^{13}C-NMR spectrum of this compound was included in ref.[10]								
(*S*)-**1b**[17]	126	C_6D_6[25]	22.11	93.09	194.18	96.20	189.97	181.26	56.06
Type-**c** furanone 									
10c[d][17]	126	C_6D_6[25]	22.59	89.35	198.46	106.97	163.69	194.35	50.84
56	101	$CDCl_3$	22.94	90.08	200.41	106.79	163.08	194.97	–
11c[e][17]	126	C_6D_6[25]	22.80	88.66	199.77	107.49	163.51	184.46	51.43
13c[f][20]	100 or 126	$CDCl_3$[g]	–	92.2	201.2	107.1	163.7	195.3	51.5
14c[h][20]	100 or 126	$CDCl_3$[g]	22.1	92.4	199.8	107.9	163.3	196.0	51.6
15c[i][20]	100 or 126	$CDCl_3$[g]	–	91.3	201.2	106.8	163.6	187.3	51.9
16c[j,k][21,22]	100	$CDCl_3$[l]	(17.9 or 29.4)	(83.5)	(198.5)	108.1	163.2	197.1	51.6
Synthetic "(+)-**1b**[15,22]" ≡[17] *rac*-**1c**	No ^{13}C-NMR spectrum of this compound was included in ref.[22,15]								
Synthetic (*R*)-**1c**[17]	126	C_6D_6[25]	22.34	90.93	196.21	107.26	163.56	194.63	50.87
Synthetic (*S*)-**2c**	126	C_6D_6	22.50	90.15	196.66	104.62	163.74	184.69	50.99
Synthetic (5*R*,2'*R*)-**4c**	126	C_6D_6	22.38	91.29	196.41	108.08	164.45	195.57	51.13
Synthetic *cis*,*trans*(5*R*,2'*R*)-**4c**	126	C_6D_6	22.54	91.31	196.20	107.98	164.41	195.60	51.11
Synthetic (5*S*,2'*R*) enantiomer of (5*R*,2'*S*)-**4'c**	126	C_6D_6	22.36	91.21	196.37	108.23	164.53	195.43	51.15
Synthetic *cis*,*trans*-(5*R*,2'*S*)-**4'c**	126	C_6D_6	22.46	91.21	196.20	108.20	164.47	195.40	51.12
Natural (+)-**7c** (cyclogregatin[k][12])	100	[D_6]acetone	20.79	94.39	196.56	104.30	160.19	194.99	–
Natural (+)-**8c** (penicilliol A[13])	100	$CDCl_3$[23]	22.5	90.2	198.1	103.6	163.4	185.3	51.7
Natural (+)-**9c** (penicilliol B[13])	100	$CDCl_3$[23]	22.4	91.5	197.6	107.7	164.1	196.0	51.9

[a] Formula: Table 1, footnote [a]. [b] Formula: Table 1, footnote [b]. [c] Formula: Table 1, footnote [c]. [d] Formula: Table 1, footnote [d]. [e] Formula: Table 1, footnote [e]. [f] Formula: Table 1, footnote [f]. [g] None of these signals was assigned in ref.[20] [h] Formula: Table 1, footnote [g]. [i] Formula: Table 1, footnote [h]. [j] Formula: Table 1, footnote [i]. [k] The structure of this compound does not correspond fully to the furanone formula **c**. [l] None of these signals was assigned in ref.[22]

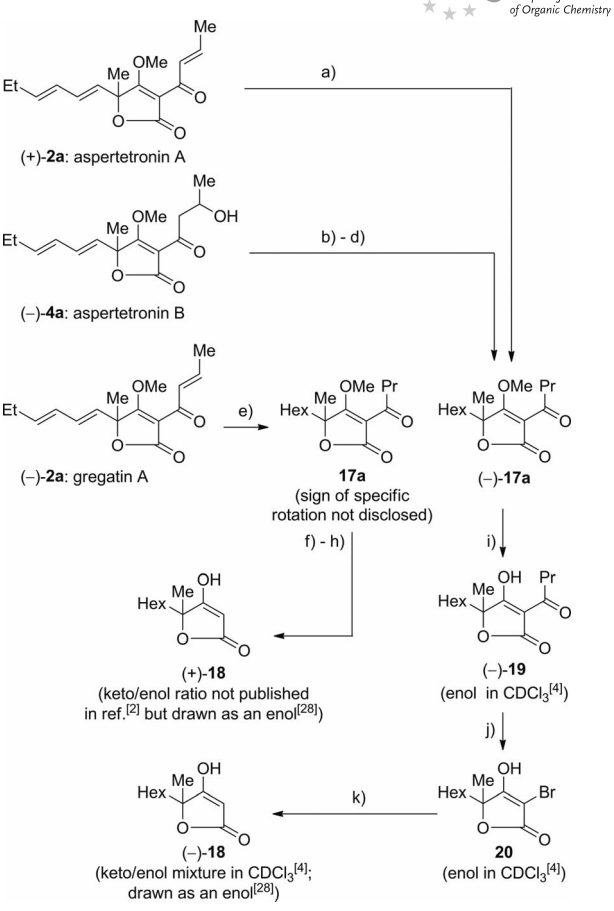
that time (**1a**–**6a**). Introduction of Li into the tetronic ester **31** by treatment with LDA,[36] treatment with acetaldehyde[9] or crotonaldehyde,[9b] and oxidation with PDC[9a] or MnO_2[9b] afforded *rac*-**1a** ("iso-gregatin B") and *rac*-**2a** ("iso-gregatin A" = "iso-aspertetronin A"), respectively. The latter compound similarly resulted from the Br/Li exchange product of bromotetronic ester **32** and *n*BuLi.[10] ^1H NMR shift differences like those highlighted in Scheme 5 established that the natural products had a core different from **a**.

Although the rejection of formulas **1a**–**6a**[9] was unavoidable, the advocation of the "second-generation" formulas **1b**–**6b**[9] must be judged risky. This is, because positive evidence was scarce – to say the least. Comparisons of C=O stretch frequencies (from the corresponding IR spectra) and λ_{max} values (from the corresponding UV/Vis spectra) of furanones **35**[9b,37] versus **34**[9b,37] and **37**[38] versus **36**[38] (Figure 4) were believed to reveal differences paralleling the differences between **1b** ("gregatin B") and **1a** ("iso-gregatin B") and between **2b** ("aspertetronin A") and **2a** ("iso-aspertetronin A"), respectively. Surprisingly, this line of reasoning neglected the fact that the conjugated π-systems in **34**–**37** were smaller than in **1a**, **1b**, **2a** or **2b** (i.e., these comparisons were like between apples and oranges). Yoshii et al. used a similar "logic" in support of formulas **1b**–**6b**.[10] This was even though they possessed the acylfuranone **12b**[10] (formula: Table 1, footnote [c]; access: from **33**), which contains the same type of π-system as **1b**–**6b**. Oddly, the deshielding of δ_{OCH_3} in **12b** by 0.4 ppm with respect to the natural products did not arouse doubts about the **b** core.[10]

The constitution (**1b**) and the absolute configuration [(*S*)] of (+)-gregatin B had seemingly been established by purported total syntheses of both racemic **1b**[22,15] and (+)-(*S*)-**1b**[15] by Takaiwa and Yamashita. This endeavor is summarized in Scheme 6 jointly with what seemed to be a formal total synthesis of (+)-(*S*)-**1b**.[16] The starting materials were the lactone-containing carboxylic acid (*S*)-**27**[31] and D-lactic acid, respectively. The β-oxo ester (*S*)-**38** was a late-stage intermediate in both approaches. It was Dieckmann-con-



Scheme 1. Exhaustive hydrogenation of synthetic[17] *ent*-gregatin B [(–)-(*R*)-**1c**]. In contrast to the hydrogenations shown in Scheme 2 the endocyclic C=C bond was also saturated. ^{1}H NMR analysis (500 MHz, C_6D_6) allowed constitutions H_6-**1a** and H_6-**1b** to be excluded and constitution H_6-**1c** to be assigned. *Reagents and conditions*: (a) H_2 (3 bar), Pd (5% on C, 5 mol-%), MeOH, room temp., 2 d (81%).



Scheme 2. Degradation reactions of (+)-aspertetronin A [(+)-**2**],[4] aspertetronin B [(–)-**4**],[4] and gregatin A [(–)-**2**],[2] leading to the attribution of their "first-generation furanone stuctures" (+)-**2a**, (–)-**4a**, and (–)-**2a**. *Reagents and conditions*: (a) H_2 (1 bar), Pd (10% on C), benzene, room temp., 15 h (97%). (b) H_2 (1 bar), Pd (10% on C), benzene, room temp., 8 h (78%). (c) $SOCl_2$ in DMF (62%). (d) H_2 (1 bar), Pd (presumably 10% on C), benzene, room temp., presumably between 8 h and 15 h (39%). (e) H_2 (1 bar), Pd (10% on C), AcOEt, room temp., 12 h (yield not given). (f) NaOH (yield not given).[27] (g) "Degradation with Br_2" (yield not given). (h) "Dehalogenation with H_2, Pd/C" (yield not given). (i) NaOH (45%). (j) Br_2, HOAc/H_2O (1:1). (k) H_2, Pd (10% on C) (58% over the two steps).

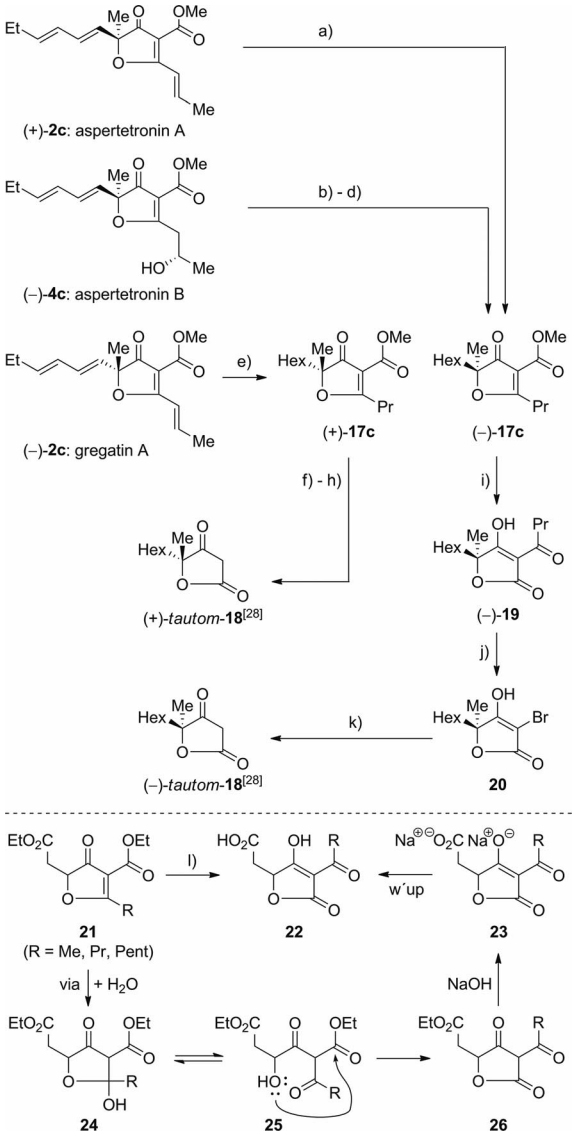
densed to give the acyltetronic acid (*S*)-**39**. The enantiomeric purities of (*S*)-**38** and (*S*)-**39** were not ascertained by chromatography. The considerable spread of the specific rotations of these compounds is disconcerting. Ref.[16] speculates whether (*S*)-**38** → (*S*)-**39** was accompanied by a "partial racemization".

Takaiwa's and Yamashita's ultimate synthetic step with regard to gregatin B was a low-yielding methylation of (*S*)-**39** with ethereal diazomethane "in the presence of a small amount of boron trifluoride etherate" (Scheme 6).[15] Preparative TLC and chromatography on Sephadex allowed the isolation of the undesired compound **1a** ("iso-gregatin B", 11%) and of an isomer (1.2%) that appeared to be identical with (+)-gregatin B.[15] Its structure was depicted as "(+)-(*S*)-**1b**".[15] That structures (*E*)-*iso*-**1** or (*Z*)-*iso*-**1** look like viable alternatives was not a consideration.[15] That the alleged compound "(+)-(*S*)-**1b**" would turn out to be "*rac*-**1c**" was not suspected at the time,[15] but we were forced to conclude just that[17] after establishing through synthesis for the first time that (+)-gregatin B = (+)-(*R*)-**1c**.[17]

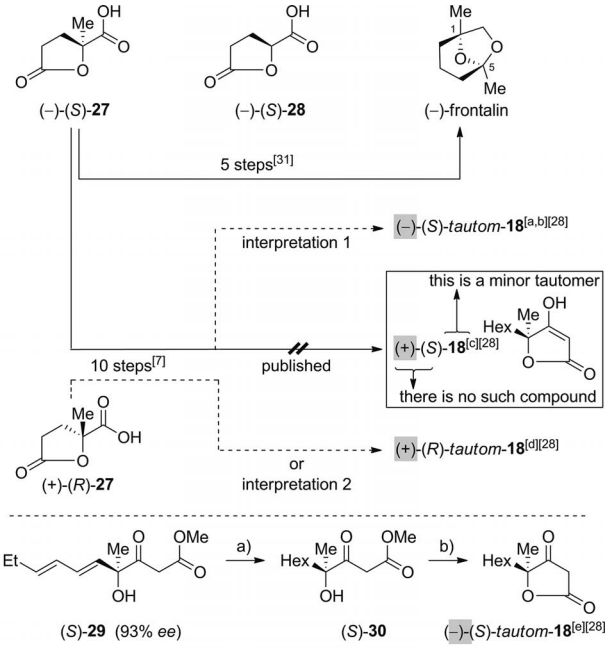
Scheme 7 explains how Takaiwa and Yamashita[15] must have obtained the unexpected compound *rac*-**1c**: through a Lewis-acid-catalyzed rearrangement of their alleged end-product (+)-(*S*)-**1b**. This transformation is mirrored by our isomerization (–)-(*S*)-**1b** + TsOH hydrate → *rac*-**1c** (46% yield).[17] It also proceeds with complete racemization but under Brønsted-acid catalysis.[17] It is noteworthy that alternatively the same substrate (–)-(*S*)-**1b** in the presence of MnO_2 rearranges with complete retention of configuration to give (–)-(*S*)-**1c**.[17]

In view of how long the unraveling of the structures of the gregatins lasted, one wonders whether today's repertoire of NMR techniques could have produced the correct furanone scaffold **a**, **b**, or **c** without a need for reference compounds. Table 4 summarizes our efforts towards distinguishing the corresponding isomers *rac*-**1a** (which we synthesized as described by Pattenden[39]), (*S*)-**1b** (from our previous study[17]), and (*R*)-**1c** (first obtained a while ago[17] and now once more as shown in Scheme 12, below).

– C-5 and C-3 are not individually assignable from their ^{13}C NMR shifts (82 ppm ≤ δ ≤ 107 ppm) alone. However, in each scaffold C-5 has a long-range C,H coupling with 2′-H (because $^3J_{C\text{-}5,2'\text{-}H}$ is measurable), whereas C-3 has not (because $^5J_{C\text{-}5,2'\text{-}H}$ is too small). This allowed the identification of C-3. Unfortunately, in each of the scaffolds **a**, **b**, or **c** C-3 is three bonds away from CH_3* and four bonds away both from 5-CH_3 and from OCH_3. This precludes distinguishability of **a**–**c** through different numbers of HMBC crosspeaks.

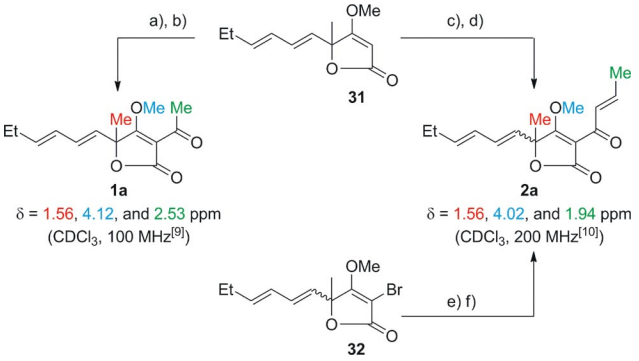


Scheme 3. Reinterpretation of the degradations of Scheme 2 starting from the corrected (stereo)structures (+)-**2c**, (–)-**4c**, and (–)-**2c** of aspertetronin A, aspertetronin B, and gregatin A, respectively. We suggest that each enantiomer of furanone **17c** undergoes a previously unidentified base-mediated rearrangement to afford the corresponding enantiomer of tetronic acid **19**. The same kind of rearrangement (i.e., **21** → **26**) must be invoked as part one of the NaOH-promoted conversion of type-**c** furanone **21** into tetronic acid **22**.[28] *Reagents and conditions*: (a)–(k) Same as in Scheme 2. (l) Dilute NaOH (49% for R = Me, 35% for R = Pr, 24% for R = Pent).



[a] A sample of this compound, obtained by the degradation (Scheme 3) of aspertetronin A [(+)-**2c**], revealed $[\alpha]_D^{\text{no temp.}} = -9.7$ ($c = 0.30$ in $CHCl_3$).[4] [b] The degradation of aspertetronin B [(+)-**4c**] as in Scheme 3 gave compound (–)-**17c**,[4] which was also obtained from aspertetronin A.[4] A continuation of *this* degradation to compound (–)-*tautom*-**18** was not reported in ref.[4] [c] $[\alpha]_D^{22} = +8.5$ ($c = 0.24$ in $CHCl_3$).[7] [d] A sample of this compound, obtained by the degradation (Scheme 3) of gregatin A [(–)-**4c**], revealed $[\alpha]_D^{\text{no temp.}} = +10$ ($c = 0.3$ in $CHCl_3$).[2] [e] $[\alpha]_D^{20} = -13.6$ ($c = 0.18$ in $CHCl_3$).

Scheme 4. Top: Verification of the stereostructure of (–)-(*S*)-**27** by its conversion[7] into (–)-frontalin, the 3D structure of which was established independently.[33,34] Middle: Synthesis[7] of "(+)-(*S*)-**18**" [which was intended to mean "(+)-(*S*)-*tautom*-**18**"[28] but must have meant either (–)-(*S*)-*tautom*-**18** or (+)-(*R*)-*tautom*-**18**] from (–)-(*S*)-**27**. Previously "(–)-**18**" [which meant (–)-*tautom*-**18**[28]] had been obtained both from aspertetronin A [(+)-**2**] and from aspertetronin B [(–)-**4**],[4] whereas "(+)-**18**" [which meant (+)-*tautom*-**18**[28]] had been obtained from gregatin A [(–)-**2**][2] (Scheme 3). Bottom: Our proof that (+)-*tautom*-**18**[28] is not (*S*)- but (*R*)-configured [access to starting material (*S*)-**29**: Scheme 12, below]. *Reagents and conditions*: (a) H_2 (1 bar), Pd/C (10 mol-%), MeOH, room temp., 1 h (21%). (b) THF/HCl (10% in H_2O)/MeOH (4:2:1), 2 h, room temp. (8.5%).



Scheme 5. Refutation of constitution **1a** for (+)-gregatin B[9] and of constitution **2a** for (+)-aspertetronin A.[9b,10] *Reagents and conditions*: (a) LDA, HMPA, THF, –78 °C; crotonaldehyde (64%). (b) MnO_2, CH_2Cl_2, room temp. (55%). (c) LDA, HMPA, THF, –78 °C; acetaldehyde (84%). (d) MnO_2, CH_2Cl_2, room temp. (55%). No NMR spectrum of the resulting compound **2a** was published. (e) *n*BuLi, THF, –78 °C; crotonaldehyde. (f) MnO_2, CH_2Cl_2, room temp. (34% over the two steps).

– C-2, C-4, and C-1′′ were also indistinguishable through their chemical shifts (164 ppm ≤ δ ≤ 196 ppm). Nonetheless, C-4 could be told apart from C-2/C-1′′, because it displayed three-bond coupling both with 5-CH_3 and with 1′-H in scaffolds **a**–**c**, giving rise to the corresponding crosspeaks. In contrast, C-2 and C-1′′ are separated by five heteroatom-free bonds from protons 5-CH_3 and 1′-H. This is too remote for crosspeaks to arise. Knowing C-4, we counted the number of C-4,CH_3 crosspeaks in the HMBC spectra of **1a**–**c**. There were two crosspeaks in *rac*-**1a**, one

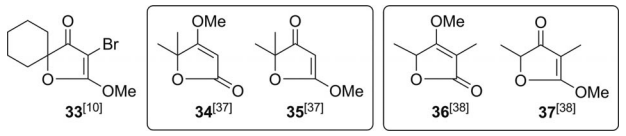
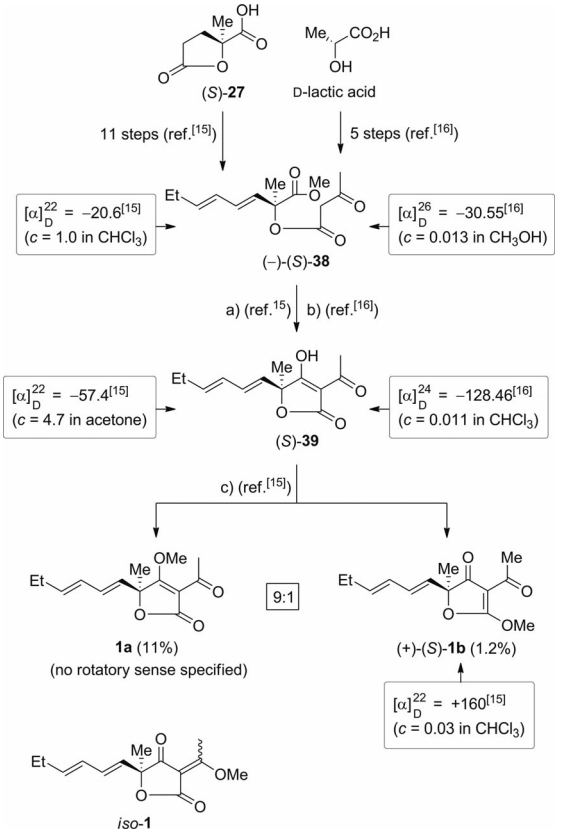
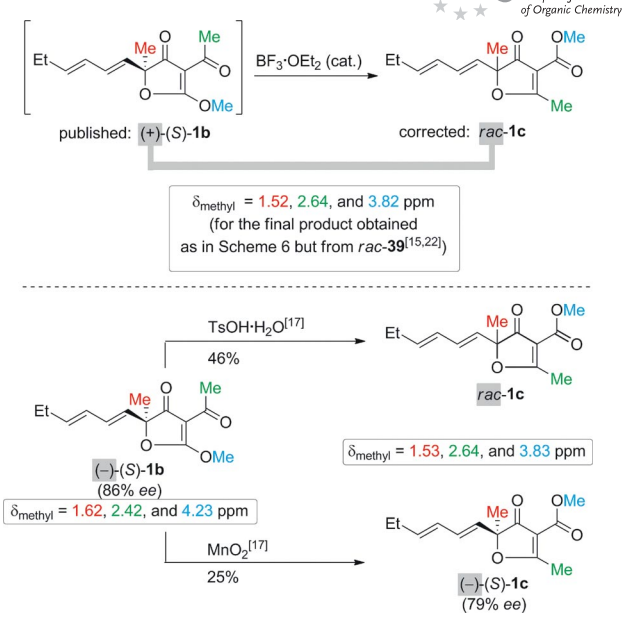


Figure 4. Compounds relevant for the assignment of **b**-type furanone cores as second-generation structures to the natural products **1**–**6**.[9,10]



Scheme 6. Purported synthesis[15] of the (*S*) enantiomer of the second-generation structure **1b** of (+)-gregatin B but in actual fact racemic synthesis[22,15] of the third-generation structure **1c** from (*S*)-**27**[31] (left). Analogous formal total synthesis from D-lactic acid[16] (right). *Reagents and conditions*: (a) NEt_3 (2.4 equiv.), acetone, reflux, 2 d (97%). (b) NaOMe (1.5 equiv.), MeOH, room temp. → reflux, 30 min (97%). (c) CH_2N_2, $BF_3{\cdot}Et_2O$ (cat.), solvent not indicated, 0 °C.



Scheme 7. Reinterpretation of the terminating step of the sequence of Scheme 6[15] (top) based on our serendipitous discovery[17] of the isomerizability of **1b** to give **1c** (bottom).

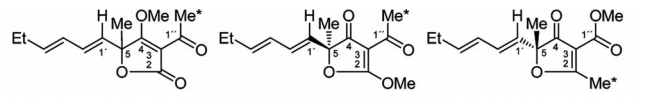
crosspeak in (*S*)-**1b**, and one crosspeak in (*R*)-**1c**. With the assumption that such crosspeaks are more likely due to $^3J_{C\text{-}4,5\text{-}CH_3}$ or to $^3J_{C\text{-}4,OCH_3}$ than to $^4J_{C\text{-}4,CH_3*}$, scaffold **a** showed different HMBC behavior from scaffolds **b** and **c**. Because this distinction is predictable – within the limits of the mentioned assumption – this criterion could have allowed the fallacy that the gregatin structure is derived from **a** to be avoided.

– The ^{13}C NMR shift pairs 181 ppm/190 ppm for (*S*)-**1b** and 164 ppm/195 ppm for (*R*)-**1c** cannot be assigned to C-2 and C-1′′ individually if one does not rely on chemical shift expectancies. This bars an NMR distinction of scaffolds **b** and **c**. The HMBC crosspeaks for $\delta_{(S)\text{-}\mathbf{1b}}$ = 181 ppm and $\delta_{(S)\text{-}\mathbf{1b}}$ = 190 ppm summed up to two, whereas the total number of HMBC crosspeaks for $\delta_{(R)\text{-}\mathbf{1c}}$ = 164 ppm and $\delta_{(R)\text{-}\mathbf{1c}}$ = 195 ppm was three. This means that (*R*)-**1c** displayed one $^4J_{C,CH_3}$ coupling and (*S*)-**1b** none. We cannot see, however, how such a difference would be foreseeable.

Syntheses of the Natural Enantiomers of Gregatin A, Gregatin B, Gregatin D, and Aspertetronin A and of the Unnatural Enantiomers of Gregatins B and C

Our previously published synthesis of (+)-gregatin B was serendipitous.[17] Accordingly, we were motivated to complement an intentional approach. Ideally, it would be suitable to provide not only (+)-gregatin B [(+)-(*R*)-**1c**] but also the third-generation structures **2c**–**10c** of the other members of the gregatin/aspertetronin family. A whole array of existing 3(2*H*)-furanone approaches[40–47] held little promise for such a strategy. In contrast, the γ-acyloxy-β-oxo ester **43** had been reported to give type-**c** furanone **40** upon exposure to basic methanol (Scheme 8).[48] Such a transformation looked tempting for finishing (+)-gregatin B [(+)-(*R*)-**1c**] and the other natural products in a straightforward manner. We felt that the corresponding substrate (i.e., the γ-acyloxy-β-oxo ester **42**) would not be accessible analogously to the γ-acyloxy-β-oxo ester **43**, namely by a Pd-catalyzed hydroxy(methoxycarbonyl)ation of a propargyl acetate akin to **45**.[48] The presence of two C=C bonds in the putative product **42** seemed to preclude such a route. Fortunately, we found one acetylation of an α,α-unsubstituted γ,γ-disubstituted γ-hydroxy-β-oxo ester **44** (→ **41**) in

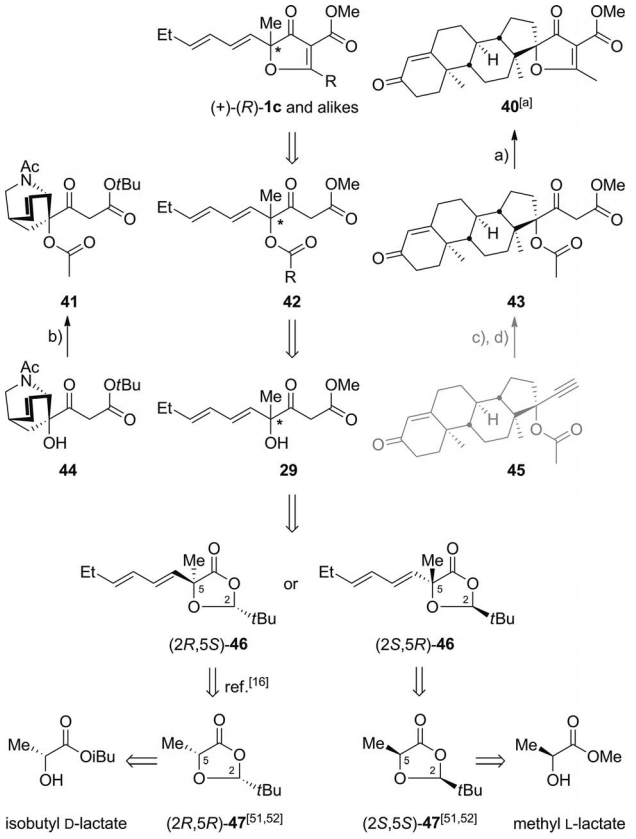
Table 4. Selected ^{1}H NMR (500 MHz, C_6D_6) and ^{13}C NMR (126 MHz, C_6D_6) resonances of furanones *rac*-**1a**, (*S*)-**1b**,[17] and (*R*)-**1c**.[a] C,H long-range coupling constants determined through crosspeaks in the corresponding HMBC spectra (C_6D_6, 500 MHz/126 MHz).



synthetic [b] *rac*-**1a** synthetic [c] (*S*)-**1b** synthetic [d] (*R*)-**1c**: gregatin B

^{1}H	δ [ppm]		
	rac-**1a**	(*S*)-**1b**	(*R*)-**1c**
1'-H	5.34	5.44	5.48
2'-H	6.37	6.29	6.34
OMe	3.55	3.21	3.50
5-Me	1.22	1.31	1.29
Me*[e]	2.51	2.61	2.17
^{13}C	δ [ppm]		
	rac-**1a**	(*S*)-**1b**	(*R*)-**1c**
C-2	168.96	181.26	194.63
C-3	103.46	96.20	107.26
C-4	183.34	194.18	196.21
C-5	82.02	93.09	90.93
5-Me	23.09	22.11	22.34
OMe	63.11	56.06	50.87
Me*[e]	30.43	29.73	17.09
C-1"	194.23	189.97	163.56
	C,H couplings revealed by respective $^{13}C_{quat}$		
C-2	no $^nJ_{C\text{-}3,H}$ observed	$^3J_{C\text{-}2,OMe}$	$^2J_{C\text{-}2,Me*}$
C-3	$^3J_{C\text{-}3,Me*}$	$^3J_{C\text{-}3,Me*}$	$^3J_{C\text{-}3,Me*}$
C-4	$^3J_{C\text{-}4,OMe}$ $^3J_{C\text{-}4,5\text{-}Me}$ $^3J_{C\text{-}4,1'\text{-}H}$	$^3J_{C\text{-}4,5\text{-}Me}$ $^3J_{C\text{-}4,1'\text{-}H}$	$^3J_{C\text{-}4,5\text{-}Me}$ $^3J_{C\text{-}4,1'\text{-}H}$
C-5	$^2J_{C\text{-}5,5\text{-}Me}$ $^2J_{C\text{-}5,1'\text{-}H}$ $^3J_{C\text{-}5,2'\text{-}H}$	$^2J_{C\text{-}5,5\text{-}Me}$ $^2J_{C\text{-}5,1'\text{-}H}$ $^3J_{C\text{-}5,2'\text{-}H}$	$^2J_{C\text{-}5,5\text{-}Me}$ $^2J_{C\text{-}5,1'\text{-}H}$ $^3J_{C\text{-}5,2'\text{-}H}$
C-1"	$^2J_{C\text{-}1",Me*}$	$^2J_{C\text{-}1",Me*}$	$^3J_{C\text{-}1",OMe}$ $^4J_{C\text{-}1",Me*}$

[a] Positional numbers chosen for easiest comparisons; this, however, makes the numbering of (*R*)-**1b** different from the IUPAC numbering used in Figure 2. [b] See ref.[39] [c] See ref.[17] [d] See Scheme 12. [e] This methyl group would be characterized by different positional numbers in *rac*-**1a** or (*S*)-**1b** versus (*R*)-**1c** and is more easily identified by a code (i.e., *).



[a] Compounds **13c**, **14c**, and **15c** were prepared similarly.[48]

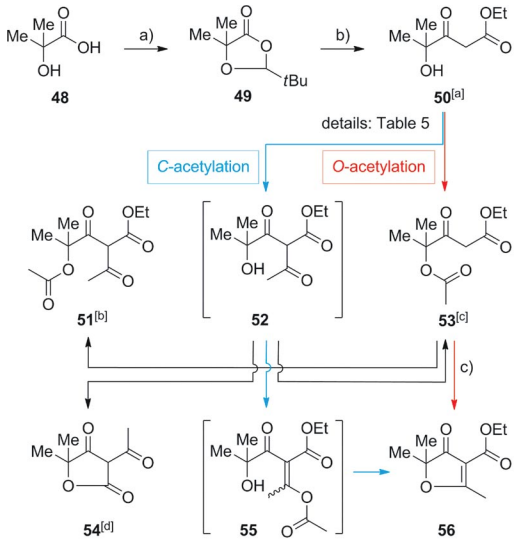
Scheme 8. Retrosynthetic analysis of the third-generation structures ("**c**") of the gregatins and aspertetronins: assembly of the furanone moiety based on literature observations. *Reagents and conditions* (a) Ac_2O, NEt_3, DMAP.[49] (b) $PdCl_2(CH_3CN)_2$ (5 mol-%), *para*-benzoquinone (1.6 equiv.), CO (1 bar), MeOH, 0 °C, 15 h (100%).[48] (c) HCl (10%), MeOH, room temp., 30 min (88%).[48] (d) K_2CO_3, MeOH, room temp., 1 h (92%).[48]

the literature.[49] Since the γ-hydroxy-β-oxo ester **29** is substituted similarly to **44** we expected that **29** should be as readily esterifiable (→ **42**).

The γ-hydroxy-β-oxo ester **29** has the constitution of a crossed Claisen condensation product between the appropriate enantiomer of the pivaldehyde acetal **46** and methyl acetate (Scheme 8). Compound (2*R*,3*S*)-**46** served as an intermediate on the route from D-lactic acid to the β-oxo ester (–)-(*S*)-**38** (Scheme 6).[16] Compound (2*R*,3*S*)-**46** originated from a *trans*-selective hydroxyalkylation[16,50] of the Fráter–Seebach acetal (2*R*,5*R*)-**47**,[51,52] which in turn originates from D-lactic acid and pivaldehyde.[51,52] The mirror-image acetal (2*S*,5*S*)-**47**[51,52] can be obtained from L-lactic acid,[53,54] which guaranteed that the (2*S*,3*R*) enantiomer of **46** would also be accessible. This variation would be of interest if the quaternary stereocenter of (2*S*,3*R*)-**46** turned out to be configured such as required in the γ-hydroxy-β-oxo ester **29** for proceeding to the corresponding natural product.

Being unaware of precedence for the Claisen condensation **46** + ester enolate → **42** anticipated in Scheme 8 we assured ourselves of its feasibility by the first part of the model study shown in Scheme 9. Isobutyric aid and pivaldehyde were condensed to give the model acetal **49**. After exposure to the lithium enolate of ethyl acetate first at –78 °C and subsequently at gradually increased temperatures, the desired condensation product **50** was isolated in 74% yield.

Compound **50** was *O*-acetylated with Ac_2O and DMAP [→ **53** (76%); Scheme 9]. Ester **53** delivered the desired **c**-type furanone **56** in 96% yield in the presence of $NaHCO_3$ and EtOH. In the presence of K_2CO_3 and EtOH, which resembles the best conditions for the *O*-acylation **43** → **40**, an 82% yield of **56** resulted. This two-step conversion could be shortened to a single step after considerable experimen-



[a] Mixture (95:5) of hydroxy-oxo ester (shown) and its enol tautomer according to 400 MHz ^{1}H NMR spectrum in $CDCl_3$. [b] This compound was one tautomer according to its ^{1}H NMR (400.1 MHz) and ^{13}C NMR spectra (100.6 MHz) in $CDCl_3$, but we could not determine which one.[78] [c] Mixture (97:3) of oxo diester (shown) and its enol tautomer according to 400 MHz ^{1}H NMR spectrum in $CDCl_3$. [d] This compound was one tautomer according to the ^{1}H NMR (400.1 MHz) and ^{13}C NMR spectra (100.6 MHz) in $CDCl_3$, but we could not determine which one.[79]

Scheme 9. Exploratory experiments unraveling *O*-acetylation (red) and *C*-acetylation (blue) cyclocondensation pathways to the model 3(2*H*)-furanone **56** (for details cf. Table 5). *Reagents and conditions*: (a) Pivaldehyde (1.2 equiv.), $BF_3{\cdot}OEt_2$ (1.5 equiv.), Et_2O, room temp., 4 h (83%). (b) LDA (2.0 equiv.), EtOAc (2.0 equiv.), THF, –78 °C; **49** (1.0 equiv.), –78 °C, 25 min; –78 °C → room temp. (74%). (c) Either $NaHCO_3$ (2.0 equiv.), EtOH, room temp., 2 d (96%) or DBU (2.0 equiv.), CH_2Cl_2, room temp., 1 d (84%).

tation (Table 5) and after identification of several undesired acetylation (**51**) and cyclization (**54**) products. The γ-hydroxy-β-oxo ester **50**, AcCl (2 equiv.), and NEt_3 formed furanone **56** in 58% yield within 30 min (Entry 9). In an attempt to interpret these findings we speculate that Ac_2O/DMAP acetylates the OH group of compound **50** through the favored (in calculations) trimolecular transition state.[55] Conversely, we suggest that the enolate obtained from **50** by an equilibrium deprotonation of the active methylene site by NEt_3 is *C*-acetylated by AcCl. The resulting intermediate **52** (or a tautomer) would then be *O*-acetylated by the second equivalent of AcCl, providing the advanced intermediate **55**. This contains a β-acetoxylated Michael acceptor motif, which should lend itself for a ring-closing substitution by an addition/elimination mechanism.

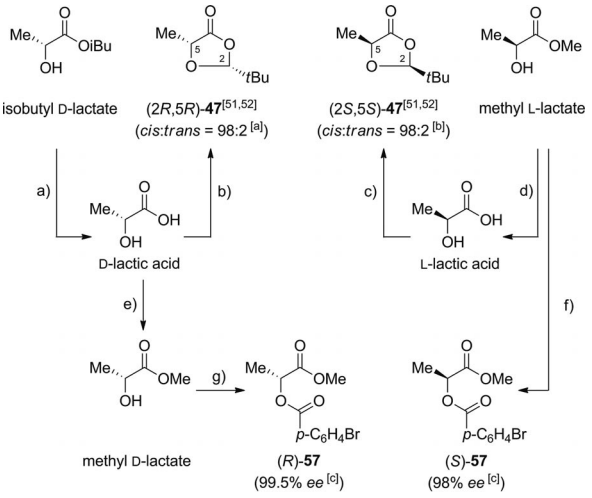
Scheme 10 depicts our syntheses of the Fráter–Seebach acetals (2*R*,5*R*)-**47** and (2*S*,5*S*)-**47**. D-Lactic acid was not purchased but was prepared by saponification of isobutyl D-lactate with $LiOH{\cdot}H_2O$. Acidification and a day-long continuous extraction provided D-lactic acid in 77% yield. Similarly, L-lactic acid was produced from methyl L-lactate in 80% yield. The enantiopurities of the specimens were determined by HPLC analyses of the *para*-bromobenzoates **57** of the methyl lactates, which we prepared from D-lactic acid and which had led to L-lactic acid, respectively. Our sample of D-lactic acid had 99.5% *ee*, the L-lactic acid 98% *ee*. The acetalizations of D- and L-lactic acid with pivaldehyde were performed as described.[54b] Acetal (2*R*,5*R*)-**47** was obtained in 75% yield as a 98:2 *cis*/*trans* mixture. The mirror-image acetal (2*S*,5*S*)-**47** was produced in 72% yield as an identically composed mixture.

The hydroxyalkylation of the lithium enolate of acetal (2*R*,5*R*)-**47** by (*E*)-hex-2-enal was first described by Matsuo et al.[16] They reported that the 1-hydroxyhex-2-ene substituent ended up exclusively *trans* relative to the *t*Bu group [87% yield of the 1′-epimers of compound (2*R*,5*S*)-**58**, Scheme 11];[16] concomitantly the simple diastereoselectivity was nil.[16] We reproduced their result to some extent (Scheme 11, reaction a) on starting from (2*R*,5*R*)-**47**, but in 7% of our product the 1-hydroxyhex-2-ene substituent and the *t*Bu group were *cis*. This was aggravating, because the quaternary stereocenter is differently configured in the desired [i.e., (2*R*,5*S*)-**5**] isomer and in the undesired [i.e. (2*R*,5*R*)-**5**] isomer. Carrying on both (pairs of) compounds would be tantamount to jeopardizing the stereochemical integrity of the emerging gregatins unless isomer separation became feasible at a later stage.

In the enantiomeric series [i.e., when we hydroxyalkylated the lithium enolate of acetal (2*S*,5*S*)-**47** with (*E*)-hex-2-enal], the result was similar (Scheme 11, box). Hydroxyalkylation of the lithium enolate of (2*R*,5*R*)-**47** with (*E*)-hex-3-enal[56,57] (i.e., with a nonconjugated aldehyde) instead

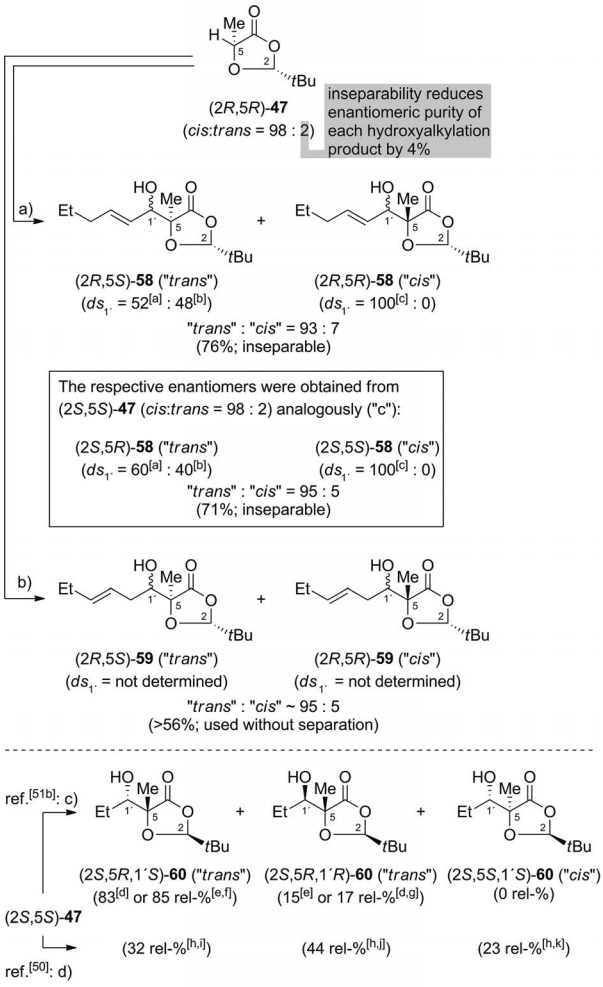
Table 5. Exploration of the third step in Scheme 9: double acetylation (→ **51**), *O*-acetylation (→ **53**), and *C*-acetylation (→ **54** + **56**) of hydroxy-oxo ester **50**.

Entry	Conditions							Products			
	Reagent	[equiv.]	Activator	[equiv.]	Solvent	*T*	*t*	**51**	**53**	**54**	**56**
1	Ac_2O	10	$FeCl_3$	cat.	CH_2Cl_2	room temp.	1 h	–	93%	–	–
2	Ac_2O	as solvent	$BF_3{\cdot}OEt_2$	1.5	–	room temp.	1.5 h	–	79%	–	–
3	Ac_2O	10	DMAP	0.1	THF	room temp.	7 h	–	76%	–	–
4	Ac_2O	2.0	DMAP	0.1	THF	room temp.	12 h	–	69%	–	–
5	Ac_2O	as solvent	$TsOH{\cdot}H_2O$	cat.	–	room temp.	20 h	–	41%	26%	–
6	Ac_2O	as cosolvent	pyridine	as cosolvent	Ac_2O/pyridine (2:1)	50 °C	1 h	65%	24%	–	–
7	AcCl	1.1	pyridine	as solvent	pyridine	75 °C	3 h	16%	44%	–	–
8	AcCl	2.5	DBU/DMAP	1.1:0.2	CH_2Cl_2	room temp.	30 min	–	–	30%	–
9	AcCl	2.0	NEt_3	2.2	CH_2Cl_2	room temp.	30 min	–	–	–	58%
10	AcCl	1.5	NEt_3/DMAP	3.0:0.1	CH_2Cl_2	room temp.	24 h	–	53%	–	21%



[a] This ratio was deduced from the integrals of the 2-H singlets in the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) at δ = 5.14 ppm for (2*R*,5*R*)-**47** versus δ = 5.29 ppm for (2*S*,5*R*)-**47**. [b] This ratio was determined from the integrals of the 2-H singlets in the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) at δ = 5.14 ppm for (2*S*,5*S*)-**47** versus δ = 5.29 ppm for (2*R*,5*S*)-**47**. [c] This value was determined by HPLC (cf. Experimental Section).

Scheme 10. Synthesis of the Fráter–Seebach acetals (2*R*,5*R*)- and (2*S*,5*S*)-**47** and analysis of the enantiomeric purities of the underlying lactic acids. *Reagents and conditions*: (a) $LiOH·H_2O$ (3.0 equiv.), H_2O/THF (2:1), 0 °C; 0 °C → room temp., 2 d (77%). (b) Trimethyl orthoformate (3.0 equiv.), cyclohexane, reflux, 1 h; evaporation of solvent; *p*$TsOH·H_2O$ (2.5 mol-%), hexanes, 0 °C, pivaldehyde (1.0 equiv.), 0 °C → room temp., 2 h (75%); *cis*/*trans* = 98:2. (c) Same as (b) (72%; ref.[54b] 71%), *cis*/*trans* = 98:2 (ref.[54b] *cis*/*trans* = 98:2). (d) Same as (a) (80%). (e) (Trimethylsilyl)diazomethane (1.0 equiv.), Et_2O, 0 °C, 30 min; used as a crude product. (f) *p*-Bromobenzoyl chloride (1.1 equiv.), NEt_3 (1.5 equiv.), DMAP (10 mol-%), CH_2Cl_2, room temp., 65 min (71%). (g) *p*-Bromobenzoyl chloride (1.0 equiv.), NEt_3 (1.0 equiv.), DMAP (10 mol-%), CH_2Cl_2, room temp., 65 min (15% over the two steps).



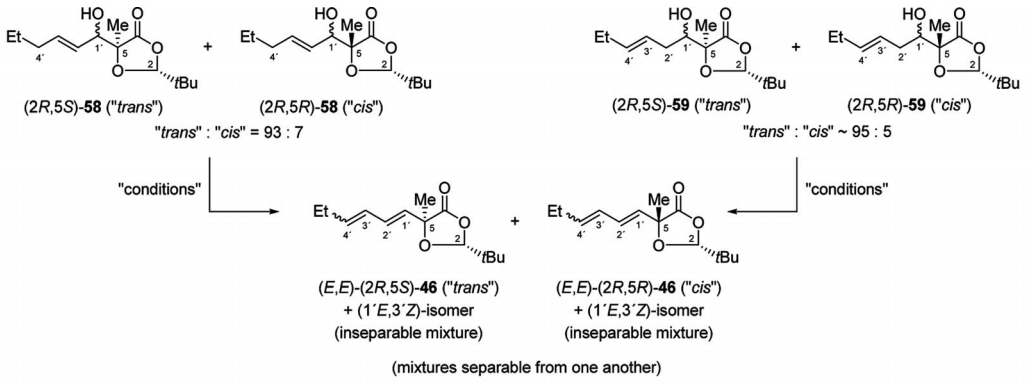
[a] $\delta_{2\text{-H}}$ = 5.38 ppm (400 MHz, $CDCl_3$). [b] $\delta_{2\text{-H}}$ = 5.41 ppm (400 MHz, $CDCl_3$). [c] $\delta_{2\text{-H}}$ = 5.18 ppm (400 MHz, $CDCl_3$). [d] This *ds* value is from the Experimental Part of ref.[51b] [e] This *ds* value is from the Theoretical Part of ref.[51b] [f] $\delta_{2\text{-H}}$ = 5.23 ppm (according to the Theoretical Part) or 5.32 ppm (according to the Experimental Part; 90 or 100 MHz, $CDCl_3$).[51b] [g] $\delta_{2\text{-H}}$ = 5.16 ppm (90 or 100 MHz, $CDCl_3$)].[51b] [h] The sum of the relative amounts of the three aldol adducts is 99 % in ref.[50] rather than 100 %. [i] $\delta_{2\text{-H}}$ = 5.36 ppm (400 MHz, $CDCl_3$).[50] [j] $\delta_{2\text{-H}}$ = 5.34 ppm (400 MHz, $CDCl_3$).[50] [k] $\delta_{2\text{-H}}$ = 5.20 ppm (400 MHz, $CDCl_3$).[50]

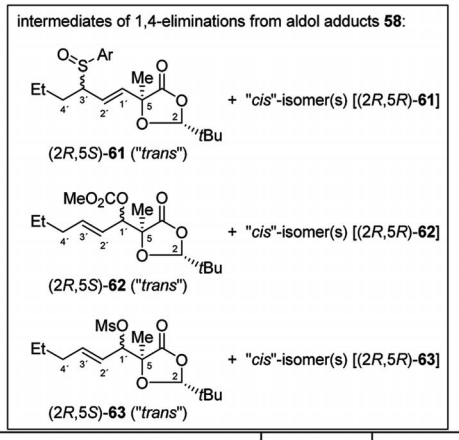
Scheme 11. Hydroxyalkylations of the Fráter–Seebach acetals (2*R*,5*R*)- and (2*S*,5*S*)-**47**. Reaction a: Our hydroxyalkylation of (2*R*,5*R*)-**47** with (*E*)-hex-2-enal (original report: ref.[16]); box: hydroxyalkylation of (2*S*,5*S*)-**47** with (*E*)-hex-2-enal. Reaction b: Hydroxyalkylation of (2*R*,5*R*)-**47** with (*E*)-hex-3-enal.[56] Reactions c and d: Hydroxypropylations of (2*S*,5*S*)-**47**.[51b,50] *Reagents and conditions*: (a) LDA (1.4 equiv.), THF, –78 °C, 1 h; (*E*)-hex-2-enal (1.4 equiv.), 1 h; → room temp. over the course of 1 h (76%). (b) LDA (1.4 equiv.), THF, –78 °C, 1 h; freshly prepared (*E*)-hex-3-enal (as a THF solution, ≤2.0 equiv.[57]), 1 h; → room temp. over the course of 1 h; mesylated as a crude product [→ **63**; 56% yield over the two steps (cf. Table 6)]. (c) Ref.[51b]: LDA (1.05 equiv.), THF/hexane (9:1), –78 °C, 45 min; propanal (1.5 equiv.), → –30 °C over the course of 2 h (80%).[d,e] (d) Ref.[50]: LDA (1.5 equiv.), THF, –78 °C, 15 min; propanal (1.5 equiv.), → –15 °C over the course of 3 h (68%).[h]

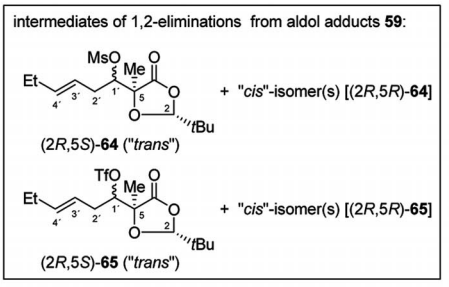
did not improve the *trans* selectivity [Scheme 11, reaction b; → mixture (95:5) of (2*R*,5*S*)-**59** and (2*R*,5*R*)-**59**]. We had hoped for the contrary because of Seebach's account of a *perfectly trans*-selective addition of the lithium enolate of acetal (2*S*,5*S*)-**47** to propionaldehyde (Scheme 11, reaction c).[51b] However, there are conflicting data about the outcome of that reaction (Scheme 11, reaction d).[50] On the other hand, the Matsuo group published another allegedly *trans*-selective aldol addition of lithio-(2*R*,5*R*)-**47**, namely to (*E*)-dodec-2-enal.[58]

Our 93:7 mixture of the acetals (2*R*,5*S*)-**58** and (2*R*,5*R*)-**58** had to be dehydrated to produce the hexadiene-substituted scaffold **46** (Table 6). This constitutes a 1,4-elimination. We attempted this via the derived[60] carbonate **62** and $Pd(PPh_3)_4$ catalysis[61] or via the corresponding mesylate **63** by treatment with DBU in toluene at reflux. The results disappointed in terms both of yield (39% and 22%, respectively, over the two steps) and stereoselectivity [→ 74 rel-% and 78 rel-% of the (*E*,*E*)-configured hexadiene substituent]. Alternatively, we sulfenylated the OH group of acetal **58**, performed a [2,3]-rearrangement in the resulting ester, and subjected the resulting allyl sulfoxide **61** to pyrolysis (i.e., to a β-elimination), which established the $C^{3'}$=$C^{4'}$ bond in the hexadiene substituent. The identical transformation had been reported by Matsuo et al.[16] who, by treating an allegedly pure 1:1 mixture of the 1′-epimers of (2*R*,5*S*)-**58** [which we had been unable to obtain without ca. 7 rel-% of (2*R*,5*R*)-**58** as a contaminant; vide supra] with 2,4-$(O_2N)_2C_6H_3SCl$ and NEt_3 in CH_2Cl_2 at reflux claimed

Table 6. Dehydrations of aldol adducts (2*R*,5*S*)-**58** (in a 93:7 "*trans*"/"*cis*" mixture, prepared as described in Scheme 11, reaction a), (2*S*,5*R*)-**58** (in a 95:5 "*trans*"/"*cis*" mixture, prepared as described in Scheme 11, box), and (2*R*,5*S*)-**59** (in an unassigned mixture of stereoisomers, prepared as described in Scheme 11, reaction b) leading to various isomers of the Fráter–Seebach-type acetal (2*R*,5*S*)-**46**.







Substrate	Conditions for conversion into "intermediate"	Intermediate	Conditions for conversion into dienes	Dienes	Yield [from substrate]	"*trans*"/"*cis*" [a]	(*E*,*E*)/(1′*E*,3′*Z*)[b,c]	*ee*
(2*R*,5*S*)-**58**	2,4-$(O_2N)_2C_6H_3$–S–Cl (2.4 equiv.), NEt_3 (2.6 equiv.), CH_2Cl_2, reflux, 12 h (≡ conditions of ref.[16])	(2*R*,5*S*)-**61**	reacts in situ	(2*R*,5*S*)-**46**	12%	94:6	90:10	
	2,4-$(O_2N)_2C_6H_3$–S–Cl (2.4 equiv.), NEt_3 (2.6 equiv.), $ClCH_2$–CH_2Cl, reflux, 5 h		reacts in situ		84%	94:6	87:13 (93:7)	93%
	$ClCO_2Me$ (4.0 equiv.), pyridine (4.0 equiv.), DMAP (0.2 equiv.), CH_2Cl_2, 0 °C → room temp., 24 h		$Pd(PPh_3)_4$ (5 mol-%), THF, room temp., 16 h[d]		39%	95:5	74:26	
	MsCl (4.0 equiv.), pyridine (4.0 equiv.), DMAP (0.2 equiv.), CH_2Cl_2, 0 °C → room temp., 12 h		DBU (10 equiv.), toluene, reflux, 24 h		22%	94:6	78:22	
(2*S*,5*R*)-**58**	2,4-$(O_2N)_2C_6H_3$–S–Cl (2.4 equiv.), NEt_3 (2.6 equiv.), $ClCH_2$–CH_2Cl, reflux, 5 h	(2*S*,5*R*)-**61**	reacts in situ	(2*S*,5*R*)-**46**	78%	95:5	87:13 (93:7)	90%
(2*R*,5*S*)-**59**	MsCl[e] (4.0 equiv.), pyridine (4.0 equiv.), DMAP (0.5 equiv.), CH_2Cl_2, 0 °C → room temp., 15 h; 56% over the 2 steps from (2*R*,5*R*)-**47** and (*E*)-hex-3-enal (cf. Scheme 11)	(2*R*,5*S*)-**64**	DBU[f] (30 equiv.), neat, 60 °C, 2 h	(2*R*,5*S*)-**46**	73% [from (2*R*,5*S*)-**64**]	95:5	98:2	91%
	Tf_2O (10 equiv.), pyridine (10 equiv.), CH_2Cl_2, 0 °C → room temp., 12 h	(2*R*,5*S*)-**65**	reacts in situ		24% [from (2*R*,5*R*)-**47**]	95:5	98:2	

[a] Separable. [b] Inseparable. [c] Values in parentheses: after I_2-catalyzed (*E*) → (*Z*) isomerization (benzene, room temp., 12–24 h). [d] Use of $Pd(OAc)_2$ (5 mol-%) and Bu_3P (10 mol-%) in THF (room temp., 5 h[59]) gave (2*R*,5*S*)-**46** in 25% yield (over the two steps) as an (*E*,*E*)/(1′*E*,3′*Z*) 84:16 mixture. [e] Under identical conditions (2*R*,5*S*)-**59** was inert towards TsCl. [f] Under the same conditions neat DBN provided (2*R*,5*S*)-**46** in 51% yield from (2*R*,5*S*)-**64**.

to have obtained (*E*,*E*)-(2*R*,5*S*)-**46** exclusively (76% yield). In our hands the same conditions delivered **46** in 12% yield as an inseparable mixture [(*E*,*E*)/(1′*E*,3′*Z*) 90:10]. In 1,2-dichloroethane at reflux[62] the yield was 84% and the

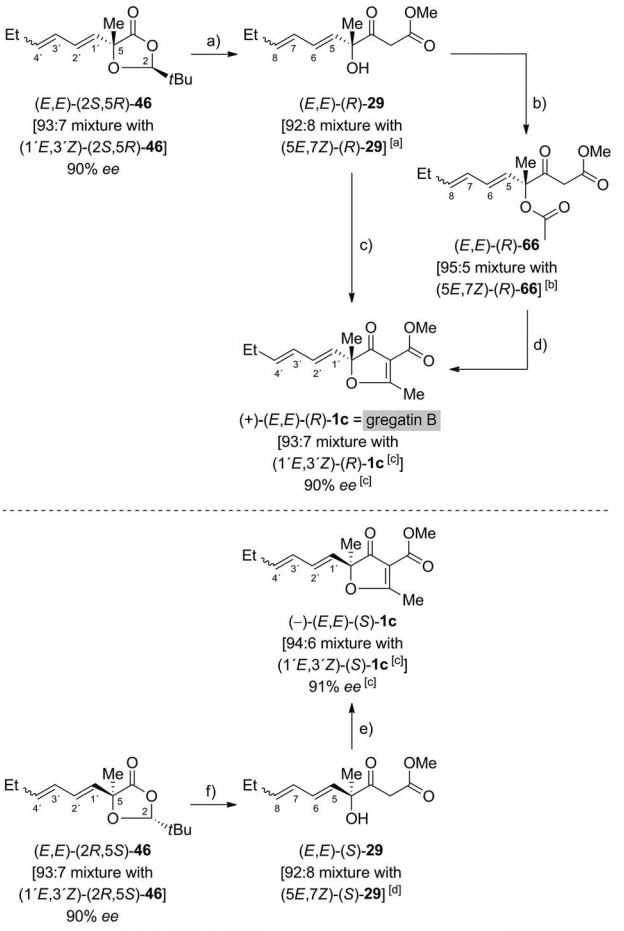
(*E*,*E*)/(1′*E*,3′*Z*) selectivity 87:13. An iodine-catalyzed isomerization in benzene solution increased this (*E*,*E*)/(1′*E*,3′*Z*) ratio to 92:8. Quite generally, the (*E*) selectivities of diene-delivering sulfoxide pyrolyses attain this order of magnitude without exceeding it.[58,62–66]

Our 95:5 mixture of the acetals (2*R*,5*S*)-**59** and (2*R*,5*R*)-**59** turned out to be a superior source of the hexadiene-substituted scaffold **46** (Table 6), because it could be dehydrated through a β-elimination of the corresponding mesylates (2*R*,5*S*)-/(2*R*,5*R*)-**64** in neat DBU at 60 °C in 73% yield, and the C$^{1'}$=C$^{2'}$ bond in the hexadiene substituent was produced with an unprecedented (*E*,*E*)/(1′*E*,3′*Z*) selectivity of 98:2. Compound (2*R*,5*S*)-**46** was obtained with the same (*E*,*E*) selectivity but only in 51% yield on swapping DBU for DBN. The yield of (2*R*,5*S*)-**46** decreased to 24% (over the three steps) when the (2*R*,5*S*)-/(2*R*,5*R*)-**59** mixture reacted via the triflates (2*R*,5*S*)- and (2*R*,5*R*)-**65**. Activation of **59** with TsCl in pyridine failed.

In summary, configurational control in the hexadiene substituent of the acetal (2*R*,5*S*)-**46** was high when starting from the homoallylic alcohol **59** as a precursor and distinctly better than when starting from the allylic alcohols **58** (Table 6). This kind of modification could have improved a number of closely related aldol addition/dehydration sequences in the literature.[58,63,64,65]

An unexpected drawback of either route to **46** was a lack of enantiopurities of the three samples, which we checked: 93% *ee*, 91% *ee*, and 90% *ee*, respectively. This was less than expected. The aldol additions of Scheme 11 had been effected with 98:2 *cis*/*trans* mixtures of the Fráter–Seebach acetals **47**. Since the *trans* isomer leads to the mirror image of the aldol adduct resulting from the *trans* isomer, the *ee* values of both **58** and **59** should have been 96%. If one accepts their lower values (93–90% *ee*) as meaningful the discrepancy must be due to underestimation of the proportions of the *trans* isomer in the Fráter–Seebach acetals **47** (which we determined from ^{1}H NMR integrals) and/or to a diminution of enantiopurity during the formation of the Fráter–Seebach acetals (cf. Scheme 10). Unfortunately, we had not examined the isomeric composition of **47** more thoroughly (i.e., by GLC).

Our second syntheses of (+)-gregatin B [(*E*,*E*)-(*R*)-**1c**] and (–)-gregatin B [(*E*,*E*)-(*S*)-**1c**] began by crossed Claisen condensations between the lithium enolate of methyl acetate and the acetals (*E*,*E*)-(2*S*,5*R*)-**46** and (*E*,*E*)-(2*R*,5*S*)-**46** (Scheme 12; first syntheses: ref.[17]). The conditions of our corresponding model transformation **49** → **50** (74%; Scheme 9) were transferable and gave similar yields of the γ-hydroxy-β-oxo esters (*E*,*E*)-(*R*)-**29** (77%) and (*E*,*E*)-(*S*)-**29** (76%), respectively. These were transformed into their corresponding gregatin targets in exactly the same way, in which the model γ-hydroxy-β-oxo ester **50** had been transformed into the type-**c** furanone **56** (cf. Scheme 9). That is, the γ-hydroxy-β-oxo esters **29** were either first *C*-acetylated with excess AcCl/NEt$_3$ and subsequently activated/cyclized in situ in what we call the "*C*-acylation route". It provided (+)-gregatin B in 61% yield and (–)-gregatin B in 53% yield. Alternatively, the enantiomer (*E*,*E*)-(*R*)-**29** was *O*-acetylated with Ac$_2$O/DMAP to provide the γ-acetoxy-β-oxo ester (*E*,*E*)-(*R*)-**29** (63% yield) in the introductory step of a two-step route to (+)-gregatin B that we call the "*O*-acylation route". Ring-closure of (*E*,*E*)-(*R*)-**29** in the presence of NaHCO$_3$ in MeOH furnished the target structure in 78% yield.



[a] Mixture (96:4) with the tautomeric enol(s). [b] Mixture (97:3) with the tautomeric enol(s). [c] Product ratios were determined by chiral HPLC (cf. Figure 5 and Experimental Section). [d] Mixture (95:5) with the tautomeric enol(s).

Scheme 12. The *O*-acylation (two steps from **29**) and *C*-acylation (one step from **29**) routes to gregatin B and its unnatural enantiomer. *Reagents and conditions*: (a) LDA (4.0 equiv.), MeOAc (4.0 equiv.), THF, –78 °C, 30 min; (2*S*,5*R*)-**46**, 30 min; –78 °C → room temp., 60 min (77%). (b) Ac$_2$O (10 equiv.), DMAP (10 mol-%), THF, room temp., 3 h (63%). (c) NEt$_3$ (2.5 equiv.), CH$_2$Cl$_2$, room temp., 5 min; AcCl (2.5 equiv.), CH$_2$Cl$_2$, room temp., 45 min (61%). (d) NaHCO$_3$ (2.0 equiv.), MeOH, room temp., 24 h (78%). (e) Same as (c), but with 2.2 equiv. both of NEt$_3$ and AcCl (53%). (f) Same as (a), but with (2*R*,5*S*)-**46** (76%).

None of the gregatin B samples obtained as shown in Scheme 12 was isomerically pure right away. Initially, "(+)-gregatin B" was of course mainly (*E*,*E*)-(*R*)-**1c**. However, it contained 5% of the enantiomer (*E*,*E*)-(*S*)-**1c**, because its *ee* was only 90%, and in addition 7 rel-% of its diastereomer (1′*E*,3′*Z*)-(*R*)-**1c**. This was a left-over from the deficiency of stereocontrol in the dehydration of the aldol addition product (2*R*,5*S*)-**58** (cf. Table 6), which had actually been – rather than (2*R*,5*S*)-**59** – the precursor of the sample of acetal (2*R*,5*S*)-**46**, from which we had derived "(+)-(*R*)-gre-

gatin B".[66] For analogous reasons our "(–)-gregatin B" emerged from the synthesis of Scheme 12 not as isomerically pure (*E*,*E*)-(*S*)-**1c** but admixed with 4.5% of the enantiomer (*E*,*E*)-(*R*)-**1c** and 6 rel-% of the diastereomer (1′*E*,3′*Z*)-(*S*)-**1c**. Separation of these mixtures by chiral HPLC was feasible both analytically (HPLC traces: Figure 5) and on a preparative scale. The latter technique allowed (+)-gregatin B and (–)-gregatin to be isolated 100% enantiomerically pure and devoid of any (*E*,*Z*) isomer. *These* samples were used for the recording of ^{1}H and ^{13}C NMR spectra and for the measurement of specific rotations. The latter were used for the comparison of synthetic versus natural materials in Table S3 in the Supporting Information.

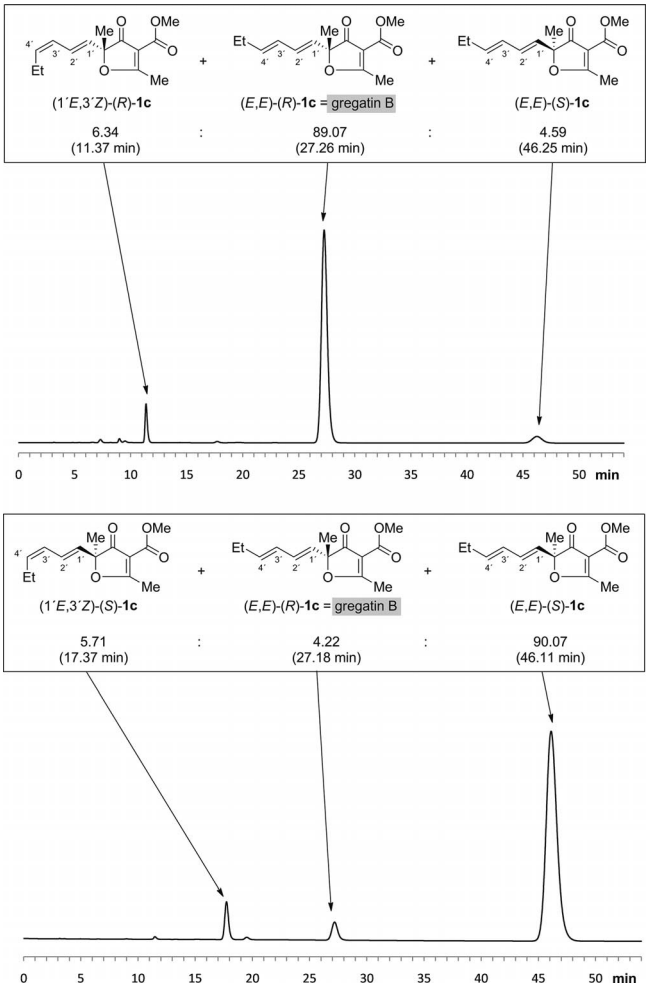


Figure 5. HPLC traces of compounds "(*E*,*E*)-(*R*)-**1c**" (top; gregatin B) and "(*E*,*E*)-(*S*)-**1c**" (bottom; *ent*-gregatin B). Chiralpak AD-H column; *n*-heptane/MeOH (100:1), 1.0 mL min^{-1}; $\lambda_{detector}$ = 230 nm. Top: $t_{r\,(E,E)\text{-}(R)\text{-}\mathbf{1c}}$ = 27.26 min, $t_{r\,(E,E)\text{-}(S)\text{-}\mathbf{1c}}$ = 46.25 min, $t_{r\,(1'E,3'Z)\text{-}(R)\text{-}\mathbf{1c}}$ = 11.37 min [(*E*,*E*)-(*R*)-**1c**/(*E*,*E*)-(*S*)-**1c** = 95:5 (→ 90% *ee*); (*E*,*E*)-(*R*)-**1c**/(1′*E*,3′*Z*)-(*R*)-**1c** = 93:7]. Bottom: $t_{r\,(E,E)\text{-}(R)\text{-}\mathbf{1c}}$ = 27.18 min, $t_{r\,(E,E)\text{-}(S)\text{-}\mathbf{1c}}$ = 46.11 min, $t_{r\,(1'E,3'Z)\text{-}(S)\text{-}\mathbf{1c}}$ = 17.73 min [(*E*,*E*)-(*S*)-**1c**/(*E*,*E*)-(*R*)-**1c** = 95.5:4.5 (→ 91% *ee*); (*E*,*E*)-(*S*)-**1c**/(1′*E*,3′*Z*)-(*S*)-**1c** = 94:6].

These HPLC separations also provided the stereoisomers (1′*E*,3′*Z*)-(*R*)-**1c** and (1′*E*,3′*Z*)-(*S*)-**1c** of gregatin B as pure specimens. Their NMR spectra (cf. Figure 6) corroborated in retrospect that we had been correct all along with respect to how we interpreted the contaminants that we had observed NMR spectroscopically in all intermediates between the Fráter–Seebach acetals and synthetic gregatin B.

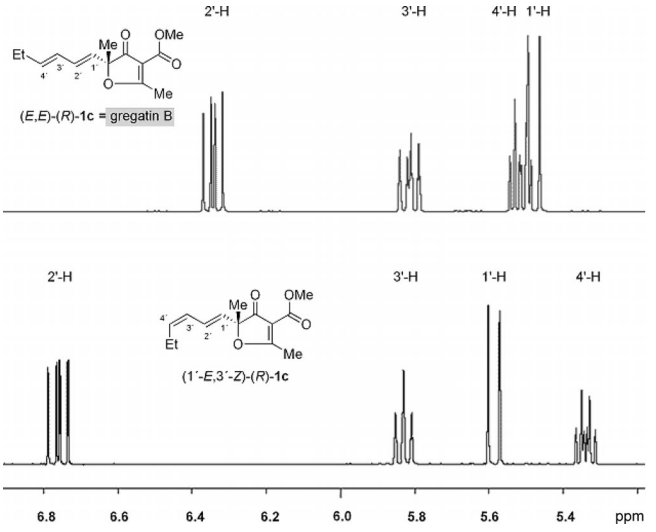
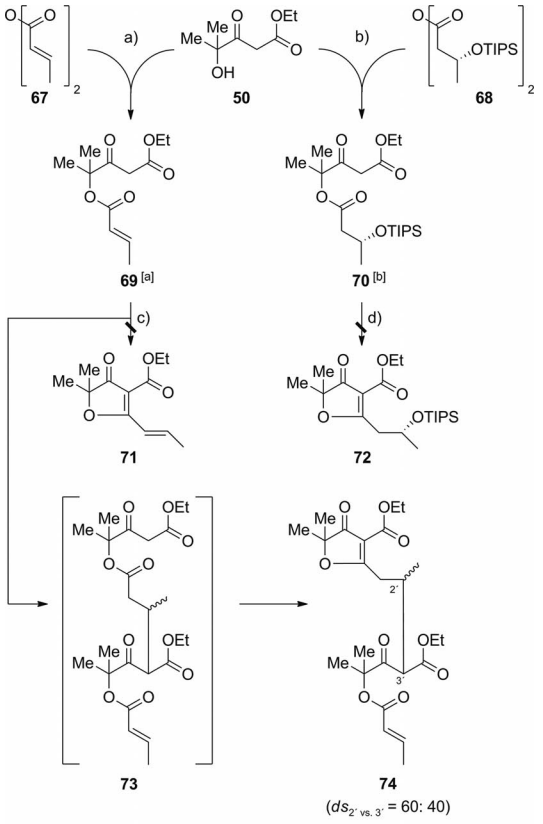


Figure 6. Sections from the ^{1}H NMR spectra (500 MHz, C_6D_6) of isomerically and also enantiomerically pure samples of (*E*,*E*)-(*R*)-**1c** (top; gregatin B) and (1′*E*,3′*Z*)-(*R*)-**1c** (bottom; *trans*,*cis*-gregatin B).

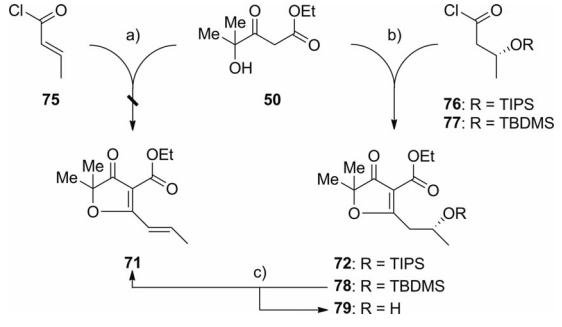
We immediately attempted to extend the strategy for converting the hexadiene-containing γ-hydroxy-β-oxo ester **29** into gregatin B (Scheme 12) to the synthesis of gregatin A/aspertetronin A (both of which required acylations with an activated form of *trans*-crotonic acid) and of gregatin C/gregatin D (both of which required acylations with an activated and protected form of a β-hydroxybutanoic acid). Not meeting success at once, we began rather by introducing the corresponding motifs into the model compound **50** (Scheme 13 and Scheme 14).

O-Acylation of the γ-hydroxy-β-oxo ester **50** with carboxylic anhydrides **67** and **68**[67–69] succeeded in 52% (→ **69**) and 64% yields (→ **70**), respectively (Scheme 13). Surprisingly, the γ-acyloxy-β-oxo esters **69** and **70** did not undergo the $NaHCO_3$-promoted cyclocondensation (→ **71** and **72**, respectively), which had functioned smoothly elsewhere (**43** → **40**, Scheme 8; **53** → **56**, Scheme 9; **66** → **1c**, Scheme 12). Instead, the γ-acyloxy-β-oxo esters **69** appeared to dimerize initially. The enolate of its β-oxo ester moiety underwent an intermolecular Michael addition to the α,β-unsaturated ester present in the crotonate moiety. A bis(γ-acyloxy-β-oxo ester), namely intermediate **73**, is formed in this way. Therein the *saturated* γ-acyloxy group becomes involved in an $NaHCO_3$-promoted cyclocondensation to afford type-**c** furanone **73**. This was the only product that we isolated, in 58% yield and in the form of a 60:40 mixture of the two conceivable diastereomers. Differently expressed, the γ-acyloxy-β-oxo esters **69** escaped the intended transformation through the dominance of a different reaction. In contrast, the γ-acyloxy-β-oxo ester **70** was essentially inert under the reaction conditions. It was



[a] Mixture (96:4) with the tautomeric enol(s). [b] Mixture (97:3) with the tautomeric enol(s). [c] Product ratios were determined by chiral HPLC (cf. Figure 5 and Experimental Section). [d] Mixture (95:5) with the tautomeric enol(s).

Scheme 13. Exploratory experiments I with the model 3(2*H*)-furanones **71** and **72**. *Reagents and conditions*: (a) Compound **67** (2.0 equiv.), DMAP (15 mol-%), THF, room temp., 3 d (52%). (b) Compound **68** (2.4 equiv.), DMAP (20 mol-%), THF, room temp, 24 h (64%). (c) $NaHCO_3$ (2.0 equiv.), EtOH, 3 d (58% **74**; the diastereomers were separated by HPLC). (d) $NaHCO_3$ (2.0 equiv.), EtOH, 3 d; **72** (2%) was separated from unchanged **70** (95%).



Scheme 14. Exploratory experiments II with the model 3(2*H*)-furanones **71**, **72**, and the analogue **78**. *Reagents and conditions*: (a) NEt_3 (2.2 equiv.), CH_2Cl_2, room temp., 5 min; **75** (2.0 equiv.), 30–45 min (2%). (b) Same as (a), but with **76** (→ **72**) or **77** (→ **78**); 67% **72** (66% **78**). (c) Aq. HCl (10%), THF/EtOH (4:1), 70 °C, 20 min; 68% **79** and 4% **71**.

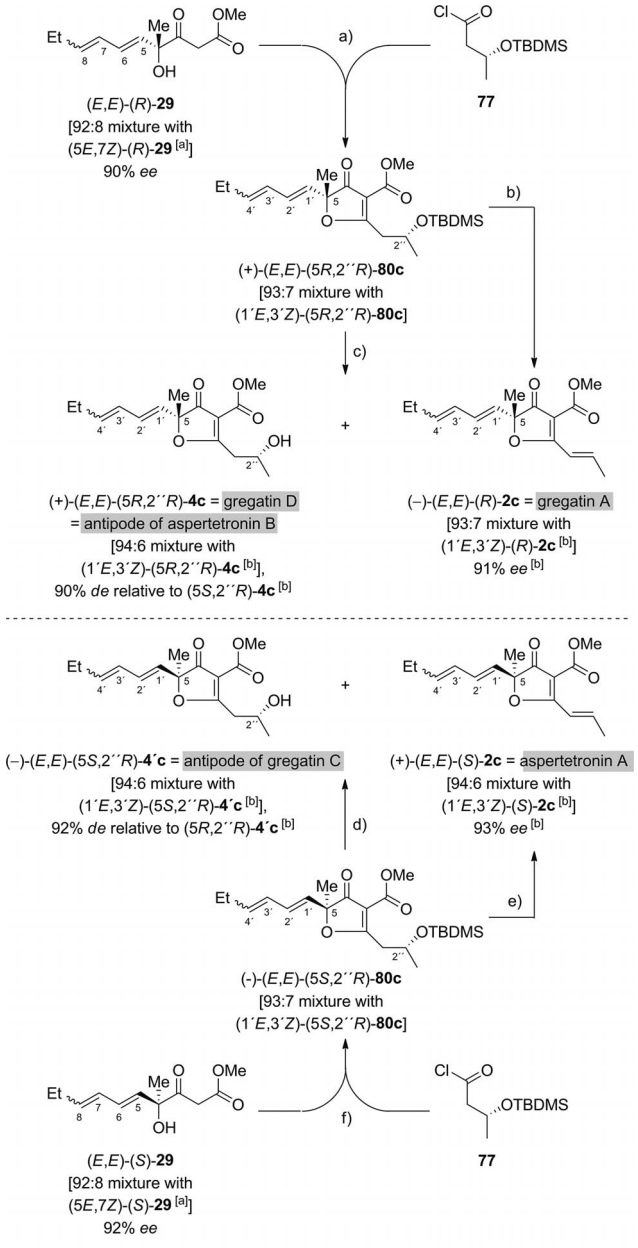
retrieved in 95% yield after separation from just 2% of the furanone **72**. Attaining the transition state must be severely hindered by the bulky iPr_3SiO group.

The "*C*-acylation route" also was not a viable means for converting the model γ-hydroxy-β-oxo ester **50** and *trans*-crotonyl chloride (**75**) into the type-**c** furanone **71** (Scheme 14). In the presence of NEt_3 this process resulted in only a 2% yield with a whole variety of other products – according to TLC – also appearing. None was identified. With DBU as a base, the same starting materials **50** and **75** underwent a different reaction, providing the tetronic acid **98** in 58% yield.[70] Similarly, γ-hydroxy-β-oxo ester **50** and either of the β-siloxycarboxylic chlorides **76**[71–74] or **77**[71] gave the tetronic acids **99**[70] (64%) and **100**[70] (60%), respectively, when the reactants were combined in the presence of DBU. However, the same starting materials gave the desired furanones **72** (67% yield) and **78** (66%), respectively, when DBU was replaced by NEt_3. The sensitivity of these varieties of reactions is impressive but beyond our capacity of interpretation.

Last but not least, the *tert*-butyldimethylsiloxylated furanone **78** was deprotected with HCl in hot aqueous ethanol (Scheme 14). This furnished the hydroxylated furanone **79** in 68% yield. In addition, a 4% yield of the corresponding β-elimination product was formed; this was the elusive furanone **71** of our crotonylation attempts. This cross-over from a furanone with a β-hydroxypropyl substituent (**79**) to another one with a prop-1-enyl side-chain (**71**) had occurred unintentionally in the context of Scheme 14. It was the clue, though, for how we provided gregatin A and aspertetronin A with their prop-1-enyl groups (Scheme 15).

Scheme 15 depicts the application of the *C*-acylation strategy of the model study from Scheme 14 to the γ-hydroxy-β-oxo esters (*E*,*E*)-(*R*)-**29** (top) and its enantiomer (*E*,*E*)-(*S*)-**29** (bottom). The former compound, the β-siloxycarboxyl chloride (*S*)-**77**, and NEt_3 gave the type-**c** furanone (*E*,*E*)-(5*R*,2′′R)-**80c** in 67% yield (Scheme 15, top). Desilylation with HCl in hot aqueous ethanol gave gregatin D [(*E*,*E*)-(5*R*,2′′R)-**4c**] in 88% yield and, separately, a 3.4% yield of the corresponding β-elimination product, which was gregatin A [(*E*,*E*)-(*R*)-**2c**]. The latter product was obtained more efficiently, namely in 29% yield over the three steps from (*E*,*E*)-(*R*)-**29**, when gregatin D was sulfonylated without prior purification and a β-elimination was performed in the same operation. In the presence of NEt_3 the γ-hydroxy-β-oxo esters (*E*,*E*)-(*S*)-**29** and the β-siloxycarboxylic chloride (*S*)-**77** reacted analogously to the diastereomeric reactant pair (*E*,*E*)-(*R*)-**29**/(*S*)-**77**; accordingly, the type-**c** furanone (*E*,*E*)-(5*S*,2′′*R*)-**80c** was obtained (70% yield; Scheme 15, bottom). Desilylation of (*E*,*E*)-(5*S*,2′′*R*)-**80c** afforded the unnatural enantiomer of gregatin C [(*E*,*E*)-(5*S*,2′′*R*)-**4′c**]. Desilylation of (*E*,*E*)-(5*S*,2′′*R*)-**80c** combined with tosylation and elimination paved the way to synthetic aspertetronin A [(*E*,*E*)-(*S*)-**2c**].

For the reasons discussed previously (Scheme 12) with regard to the initial steric integrity of our synthetic specimens of gregatin B, our samples of aspertetronin A and the gregatins A, C, and D from Scheme 15 were initially contaminated with small amounts both of one enantiomer and of one diastereomer. Each of these three-component mixtures was separated by chiral HPLC both analytically



[a] The (*E*,*E*)/(*E*,*Z*) ratio of this compound was slightly lower than in the material used in Scheme 12. [b] The diastereomer and enantiomer ratios of this product were determined by chiral HPLC (cf. Figure 7 and Figure 8 and Experimental Section).

Scheme 15. *C*-Acylation routes to the gregatins A and D, aspertetronin A, and the unnatural enantiomers of gregatin C and aspertetronin B. *Reagents and conditions*: (a) NEt_3 (2.2 equiv.), CH_2Cl_2, room temp., 5 min; **77** (2.0 equiv.), room temp., 45 min (67%). (b) Aq. HCl (10%)/THF/MeOH (2:4:1), 60 °C, 30 min; isolation of the crude product [(5*R*,2′′*R*)-**4c**]; *p*TsCl (2.5 equiv.), DMAP (1.0 equiv.), NEt_3 (2.5 equiv.), CH_2Cl_2, room temp., 4 h [27% from (*R*)-**29**]. (c) Aq. HCl (10%)/THF/MeOH (2:4:1), room temp., 6 h [88% (5*R*,2′′*R*)-**4c** as an (*E*,*E*)/(1′*E*,3′*Z*) mixture (94:6), separated from (*R*)-**2c** (3.4%)]. (d) Same as (c) [90% (5*S*,2′′*S*)-**4c** as an (*E*,*E*)/(1′*E*,3′*Z*) mixture (94:6), separated from (*S*)-**2c** (2.2%)]. (e) Same as (b) [41% from (*S*)-**29**]. (f) Same as (a) (70%).

(HPLC traces: Figure 7, Figure 8) and on the preparative scale. This furnished each main component 100% enantiomerically pure and devoid of the corresponding (*E*,*Z*) isomer, which could, however, be isolated separately. The ^1H NMR and ^{13}C NMR spectroscopic data registered for these purified samples retrospectively confirmed our earlier assignments in diastereomeric mixtures. The comparisons between various synthetic and natural materials in Table S3 in the Supporting Information contain the specific rotations of our HPLC-pure stereoisomers {exception: unnatural = (–)-gregatin B, which emerged from our synthesis according to Scheme 12 with 90% *ee* was not upgraded by HPLC before measurement of its $[\alpha]_D$ value}.

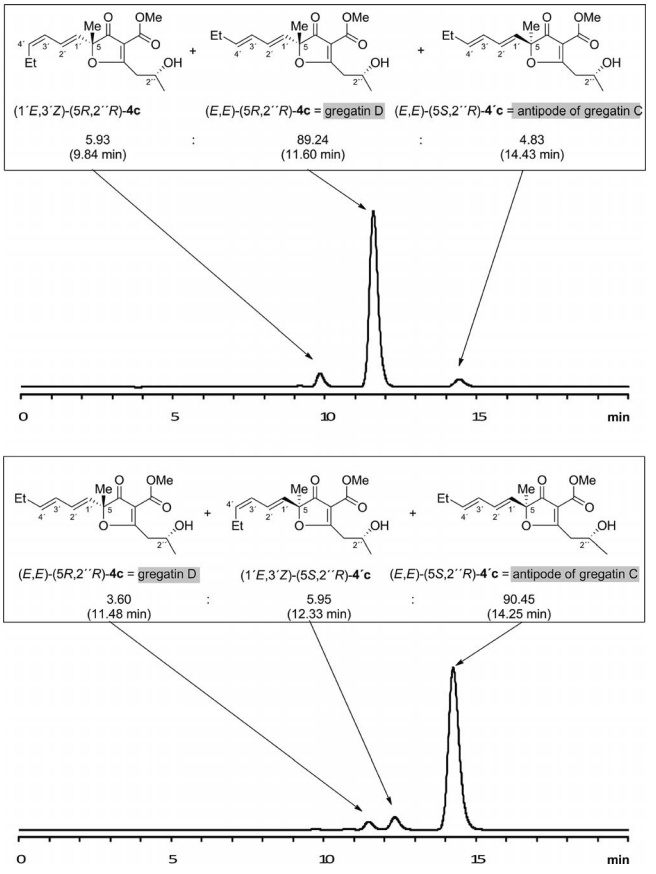


Figure 7. HPLC traces of compounds "(*E*,*E*)-(5*R*,2′′*R*)-**4c**" (top; gregatin D) and "(*E*,*E*)-(5*S*,2′′*R*)-**4′c**" (bottom; antipode of gregatin C). Chiralpak AD-H column; *n*-heptane/*i*PrOH 9:1, 1.0 mL min^{-1}; $\lambda_{detector}$ = 230 nm. Top: $t_{r\,(E,E)\text{-}(5R,2''R)\text{-}\mathbf{4c}}$ = 11.60 min, $t_{r\,(E,E)\text{-}(5S,2''R)\text{-}\mathbf{4c}}$ = 14.43 min, $t_{r\,(1'E,3'Z)\text{-}(5R,2''R)\text{-}\mathbf{4c}}$ = 9.84 min [(*E*,*E*)-(5*R*,2′′*R*)-**4c**/(*E*,*E*)-(5*S*,2′′*R*)-**4c** = 95:5 (→ 90% *de*); (*E*,*E*)-(5*R*,2′′*R*)-**4c**/(1′*E*,3′*Z*)-(5*R*,2′′*R*)-**4c** = 94:6]. Bottom: $t_{r\,(E,E)\text{-}(5R,2''R)\text{-}\mathbf{4'c}}$ = 11.48 min, $t_{r\,(E,E)\text{-}(5S,2''R)\text{-}\mathbf{4'c}}$ = 14.25 min, $t_{r\,(1'E,3'Z)\text{-}(5S,2''R)\text{-}\mathbf{4'c}}$ = 12.33 min [(*E*,*E*)-(5*S*,2′′*R*)-**4′c**/(*E*,*E*)-(5*R*,2′′*R*)-**4′c** = 96:4 (→ 92% *de*); (*E*,*E*)-(5*S*,2′′*R*)-**4′c**/(1′*E*,3′*Z*)-(5*S*,2′′*R*)-**4′c** = 94:6].

We are not in possession of natural = (–)-gregatin A, natural = (+)-gregatin C, natural = (+)-gregatin D, or natural = (–)-aspertetronin A. That we have indeed synthesized these compounds [(–)-gregatin A, (+)-gregatin D, (–)-aspertetronin A] or antipodes [(–)-gregatin C] is therefore supported best by comprehensive (i.e., resonance-by-resonance) comparisons of the NMR characteristics of the corresponding pairs of compounds (Table S2 and Table S3 in the Supporting Information). Additional support is provided by pairwise comparisons of the signs and absolute

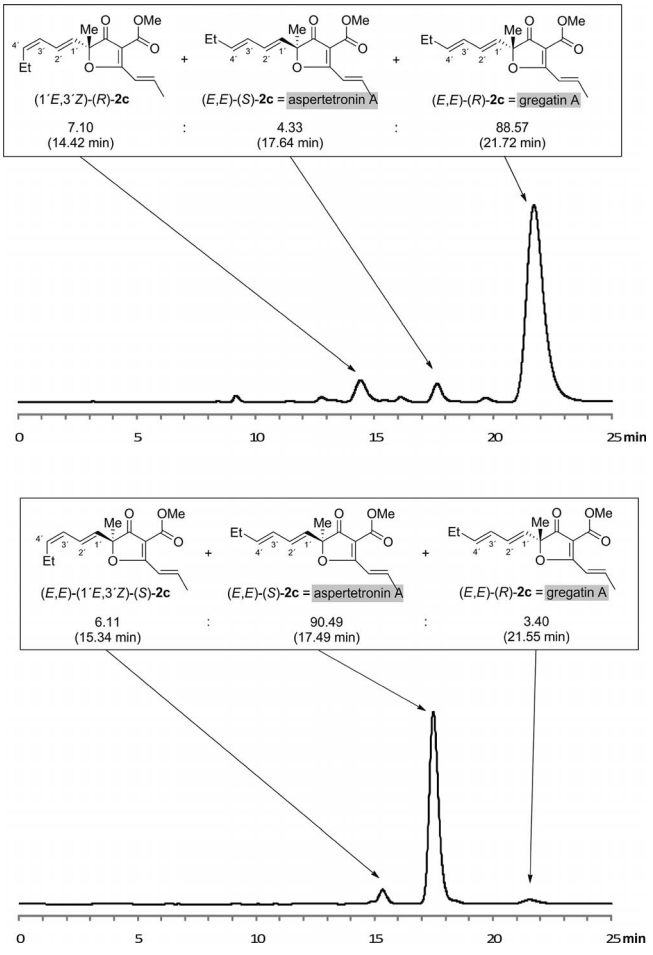


Figure 8. HPLC traces of compounds "(*E*,*E*)-(*R*)-**2c**" (top; gregatin A) and "(*E*,*E*)-(*S*)-**2c**" (bottom; aspertetronin A). Chiralpak AD-H column; *n*-heptane/MeOH 100:1, 1.0 mL min^{-1}; $\lambda_{detector}$ = 230 nm. Top: $t_{r\,(E,E)\text{-}(R)\text{-}\mathbf{2c}}$ = 21.72 min, $t_{r\,(E,E)\text{-}(S)\text{-}\mathbf{2c}}$ = 17.64 min, $t_{r\,(1'E,3'Z)\text{-}(R)\text{-}\mathbf{2c}}$ = 14.42 min [(*E*,*E*)-(*R*)-**2c**/(*E*,*E*)-(*S*)-**2c** = 95.5:4.5 (→ 91% *ee*); (*E*,*E*)-(*R*)-**2c**/(1′*E*,3′*Z*)-(*R*)-**2c** = 93:7]. Bottom: $t_{r\,(E,E)\text{-}(R)\text{-}\mathbf{2c}}$ = 21.55 min, $t_{r\,(E,E)\text{-}(S)\text{-}\mathbf{2c}}$ = 17.49 min, $t_{r\,(1'E,3'Z)\text{-}(S)\text{-}\mathbf{2c}}$ = 15.34 min [(*E*,*E*)-(*S*)-**2c**/(*E*,*E*)-(*R*)-**2c** = 96.5:3.5 (→ 93% *ee*); (*E*,*E*)-(*S*)-**2c**/(1′*E*,3′*Z*)-(*S*)-**2c** = 93:7].

values of the specific rotations (within plausible error margins) of the compounds in question (Table S1 in the Supporting Information; natural and synthetic gregatin B are included). The inferences of these juxtapositions for the constitutions and configurations of the discussed natural products and aspertetronin B have been included in Scheme 12 and Scheme 15 and have already been shown collectively in Figure 3.

Beyond listing all available NMR spectroscopic data for pairs of synthetic and natural members of the gregatin/aspertetronin family, Table S2 and Table S3 in the Supporting Information contain extra (i.e., unpaired) compounds. One column of Table S2 in the Supporting Information supplements the ^{1}H and ^{13}C NMR spectroscopic data for natural = (+)-penicilliol B[13] but reassigned to our revised structure **9c** rather than to the published structure **9b**.[13] Similarly, the last column in Table S3 in the Supporting Information supplements the ^{1}H and ^{13}C NMR spectroscopic data for natural = (+)-penicilliol A,[13] but reassigned to our revised structure **9c** rather than to the published structure **9b**.[13] These extra compounds are included in Table S2 and Table S3 in the Supporting Information for corroboration of the correctness of our reassignments of their structures in more detail than just by the conclusive, but limited ^{1}H and ^{13}C NMR criteria, which allowed us to distinguish the furanone cores **b** and **c** by the homologies in Table 1, Table 2, and Table 3. Such supporting analogies exist because of the structural similarity between penicilliol B and our synthetic antipode (*E*,*E*)-(5*S*,2′′*R*)-**4′c** of gregatin C (Table S2 in the Supporting Information). Additional analogies exist because of the structural similarity between penicilliol A and our synthetic (*E*,*E*)-(*S*)-**2c**, which equals aspertetronin A, and our synthetic (*E*,*E*)-(*R*)-**2c**, which equals gregatin A (Table S3 in the Supporting Information). Hitherto these NMR comparisons were less telling than those presently possible, because the published ^{1}H NMR characterizations of natural gregatin C[1a] and of natural gregatin A[2,75] contained fewer details than our evaluations. Moreover, no ^{13}C NMR shifts at all had been published for the gregatins C and A. In contrast, we have completely characterized synthetic *ent*-gregatin C and synthetic gregatin D by ^{13}C NMR spectroscopy.

Conclusions

We have accomplished total syntheses of four natural products [(–)-gregatin A, (+)-gregatin B, (+)-gregatin D, (+)-aspertetronin A] and of the enantiomers [(–)-gregatin C, (+)-aspertetronin B] of two natural products; in addition, we have synthesized the unnatural (–)-enantiomer of gregatin B. As a consequence, the corresponding six natural products' constitutions were reassigned [→ formulas (+)-**1c**, (+)- and (–)-**2c**, (+)- and (–)-**4c**, and (+)-**4′c**]. Configurational reassignments were necessary for five natural products [→ formulas (+)-**1c**, (+)- and (–)-**2c**, and (+)- and (–)-**4c**]. The stereostructures of the side-chains of three natural products were established for the first time [→ formulas (+)- and (–)-**4c** and (+)-**4′c**] and in one case the stereostructure of the heterocycle [→ formula (+)-**4′c**]. Altogether, these findings, combined with ^{1}H and ^{13}C NMR analogies that we consider compelling, require revision of all second-generation structures **1b**–**9b** and **4′b** of the gregatin/aspertetronin furanone family to the third-generation structures **1c**–**9c** and **4′c**. The discussed NMR analogies allowed us to derive criteria that from now on should allow an infallible distinction between a second-generation (**b**) and a third-generation furanone structure (**c**). If these criteria had been available earlier, the structure elucidation of the natural products in question would not have been error-prone.

It must be admitted, however, that in the absence of (our) reference data (i.e., when the discussed natural products were studied for the first time), probably not even today's NMR repertoire would have allowed the furanone **c** rather than **b** cores to be established right away. This might remind those who deduce structures from NMR spectra that an

error may intervene at a much lower level of structural complexity than in many other cases in which a once-proposed natural product structure has been disproved – and a flawless structure reassigned – by the synthetic community.[76] Of course, any interference of rearrangement steps in natural product degradations (in the current context: **17** → **19**, Scheme 3) and in natural product syntheses (in the current context: **1b** → **1c**, Scheme 7) represents an aggravating add-on in the business of making correct structure assignments.

From a synthetic viewpoint, the aldol addition/dehydration approach to the (*E*,*E*)-diene-containing Fráter–Seebach acetals **46** is noteworthy. This is because it exhibited a distinctly higher stereoselectivity when the unconjugated rather than the conjugated (*E*)-hexenal was incorporated. Also worth mentioning is that γ-hydroxy-β-oxo esters can be transformed into type-**c** furanones not only via γ-acyloxy-β-oxo esters ("*O*-acylation route") but more generally by a "*C*-acylation route".

Note Added in Proof

While our manuscript was typeset, we became aware of the recently published structures (+)-**101b** and (+)-**102b** of the natural products huaspenone A and huaspenone B (Figure 9), which were isolated from *Aspergillus* sp. XW-12 by Shan et al.[81] Scrutiny of their ^{1}H and ^{13}C NMR spectroscopic properties (500 and 125 MHz, respectively) in $CDCl_3$ (huaspenone A) and [D_6]acetone (huaspenone B) and comparisons with the corresponding data of the revised structure of penicilliol B [(+)-**9c**; formula: Figure 3] and with the third-generation structure of gregatin B [(+)-**1c**; formula: Figure 3], respectively, reveals that the correct formulas of huaspenone A and B should be (+)-**101c** and (+)-**102c**, respectively (Figure 10). The comparisons, from which we draw this conclusion are included in Tables S3 and S4 of the Supporting Information.

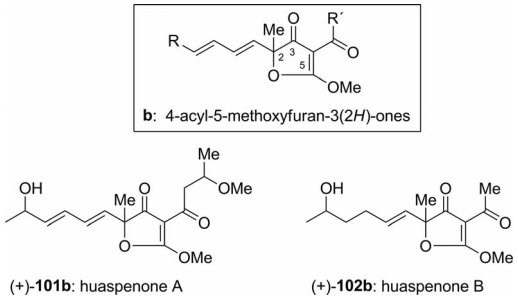


Figure 9. Originally published ("1st generation") structures of huaspenone A [(+)-**101b**[81]] and huaspenone B [(+)-**102b**[81]].

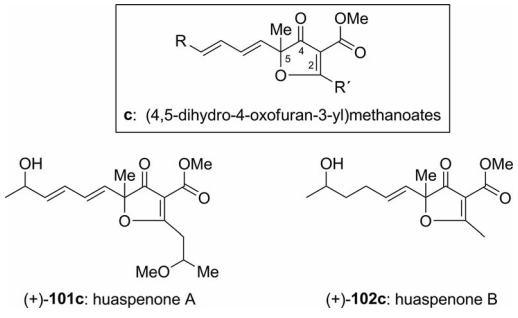
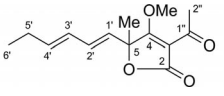


Figure 10. Revised ("2nd generation") structures of the compounds from Figure 9, as deduced in the present study.

Experimental Section

General Information: Reactions were performed under N_2 in glassware dried with a heatgun under vacuum. Products were purified by flash chromatography on silica gel[77] (filling height, column diameter, and eluent are given in parentheses; which fractions contained the isolated product is indicated as "fractions *xx*–*yy*") on silica gel 60 (Macherey–Nagel & Co., 0.040–0.063 mm, 230–400 mesh, ASTM). Yields refer to analytically and/or spectroscopically pure samples. ^{1}H NMR [TMS (δ = 0.00 ppm) or $CHCl_3$ (δ = 7.26 ppm) as internal standards in $CDCl_3$, or C_6HD_5 (δ = 7.15 ppm) as an internal standard in C_6D_6]: Bruker AC 250, Varian Mercury VX 300, Bruker AM 400, and Bruker DRX 500 instruments. ^{1}H NMR hyperfine structures were interpreted by first-order analysis with the exception of AB spectra or AB parts of ABX spectra, ABX_2 spectra, etc. ^{13}C NMR [$CDCl_3$ (δ = 77.10 ppm) as an internal standard in $CDCl_3$, or C_6D_6 (δ = 128.00 ppm) as an internal standard in C_6D_6]: Bruker AM 400 and Bruker DRX 500 instruments. Assignments of ^{1}H and ^{13}C NMR resonances refer to IUPAC nomenclature except within substituents, for which primed numbers may be used (cf. formulas in the Experimental Section). IR spectra: Perkin–Elmer Paragon 1000. NMR: Dr. M. Keller, M. Schonhard, F. Reinbold, Institut für Organische Chemie and Biochemie, Universität Freiburg. MS: Dr. J. Wörth, C. Warth, Institut für Organische Chemie and Biochemie, Universität Freiburg; combustion analyses: F. Tönnies, Institut für Organische Chemie and Biochemie, Universität Freiburg; HPLC: G. Fehrenbach, Institut für Organische Chemie and Biochemie, Universität Freiburg.

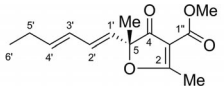
3-Acetyl-5-[(1*E*,3*E*)-hexa-1,3-dienyl]-4-methoxy-5-methyl-2(5*H*)-furanone (*rac*-1a)[39]



MnO_2 (680 mg, 7.80 mmol, 20.0 equiv.) was added at room temp. to a solution of alcohol **89** (98.6 mg, 391 μmol) in CH_2Cl_2 (2.0 mL). The resulting mixture was stirred for 3.5 h, diluted with EtOAc (5.0 mL), and filtered through Celite. The solvent was removed under reduced pressure. The residue was purified by flash chromatography[77] [2.0 cm, 15 cm, 20 mL, C_6H_{12}/EtOAc 5:1, #10–15]. The title compound (46.3 mg, 47%; ref.[9b] 62%) was obtained as a yellowish oil. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.01 (t, $J_{6',5'}$ = 7.5 Hz, 3 H, 6′-H_3), 1.57 (s, 3 H, 5-CH_3), 2.12 (m_c, possibly interpretable as qd, $J_{5',6'} = J_{5',4'} \approx$ 7.5 Hz, 2 H, 5′-H_2), 2.57 (s, 3 H, 2′′-H_3), 4.14 (s, 3 H, 4-OCH_3), 5.53 (d, $J_{1',2'}$ = 15.4 Hz, 1 H, 1′-H), 5.85 (dt, $J_{4',3'}$ = 15.3, $J_{4',5'}$ = 6.4 Hz, 1 H, 4′-H), 6.00 (br. dd, $J_{3',4'}$ = 15.2, $J_{3',2'}$ = 10.4 Hz, 1 H, 3′-H), 6.35 (dd, $J_{2',1'}$ = 15.3, $J_{2',3'}$ = 10.3 Hz, 1 H, 2′-H) ppm. ^{1}H NMR [499.7 MHz, C_6D_6; sample contained 2.5% *rac*-(1′*E*,3′*Z*)-**1b** (as evidenced by δ = 6.80, dd, 1 H, 2′-H)]: δ = 0.82 (t, $J_{6',5'}$ = 7.4 Hz, 3 H, 6′-H_3), 1.22 (s, 3 H, 5-CH_3), 1.85 (m_c, possibly interpretable as qd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.3 Hz, 2 H, 5′-H_2), 2.51 (s, 3 H, 2′′-H_3), 3.55 (s, 3 H, 4-OCH_3), 5.34 (d, $J_{1',2'}$ = 15.5 Hz, 1 H, 1′-H), 5.48 (dt, $J_{4',3'}$ = 15.1, $J_{4',5'}$ = 6.6 Hz, 1 H, 4′-H), 5.82 (br. dd, $J_{3',4'}$ = 15.1, $J_{3',2'}$ = 10.4 Hz, 1 H, 3′-H), 6.37 (dd, $J_{2',1'}$ = 15.5, $J_{2',3'}$ = 10.4 Hz, 1 H, 2′-H) ppm. ^{13}C

NMR (125.7 MHz, C_6D_6): δ = 13.35 (C-6′)[A], 23.09 (5-CH_3)[A], 25.88 (C-5′)[A], 30.43 (C-2′′)[A], 63.11 (4-OCH_3)[A], 82.02 (C-5)[B], 103.46 (C-3)[B], 127.33 (C-1′)[A], 128.05 (C-3′)[A], 132.23 (C-2′)[A], 139.36 (C-4′)[A], 168.96 (C-2), 183.34 (C-4)[B], 194.23 (C-1′′)[B] ppm; [A] the indicated ^{13}C nuclei are primary, secondary or tertiary and were distinguished in an HMBC (!) spectrum ["long-range C,H-COSY spectrum" (499.7 MHz/125.7 MHz), C_6D_6] by their crosspeaks due to a ^1J (!) coupling to the directly bound proton(s); the latter had previously been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 0.82 (t, 6′-H_3) $\leftrightarrow \delta_C$ = 13.35 (C-6′), δ_H = 1.22 (s, 5-CH_3) $\leftrightarrow \delta_C$ = 23.09 (5-CH_3), δ_H = 1.85 (m_c, 5′-H_2) $\leftrightarrow \delta_C$ = 25.88 (C-5′), δ_H = 2.51 (s, 2′′-H_3) $\leftrightarrow \delta_C$ = 30.43 (C-2′′), δ_H = 3.55 (s, 4-OCH_3) $\leftrightarrow \delta_C$ = 63.11 (4-OCH_3), δ_H = 5.34 (d, 1′-H) $\leftrightarrow \delta_C$ = 127.33 (C-1′), δ_H = 5.48 (dt, 4′-H) $\leftrightarrow \delta_C$ = 139.36 (C-4′), δ_H = 5.82 (dd, 3′-H) $\leftrightarrow \delta_C$ = 128.05 (C-3′), δ_H = 6.37 (dd, 2′-H) $\leftrightarrow \delta_C$ = 132.23 (C-2′); [B] the indicated ^{13}C nuclei are quaternary and were distinguished in the already mentioned HMBC spectrum ["long-range C,H-COSY spectrum" (499.7 MHz/125.7 MHz), C_6D_6] by their crosspeaks due to ^2J and/or ^3J couplings to "remote" protons (these had previously been assigned unequivocally): (1) for δ_C = 82.02 (C-5) such crosspeaks were due to $^3J_{2'\text{-H,C-5}}$, $^2J_{1'\text{-H,C-5}}$, and $^2J_{5\text{-Me,C-5}}$; (2) for δ_C = 103.46 (C-3) such a crosspeak was due to $^3J_{2''\text{-H,C-3}}$; (3) for δ_C = 183.34 (C-4) such crosspeaks were due to $^3J_{1'\text{-H,C-4}}$, $^3J_{4\text{-OMe,C-4}}$, and $^3J_{5\text{-Me,C-4}}$; (4) for δ_C = 194.23 (C-1′′) such a crosspeak was due to $^2J_{2''\text{-H,C-1''}}$; (5): δ_C = for 168.96 (C-2) no crosspeak was detected (as in accordance with the absence of both $^2J_{H,C\text{-}2}$ and $^3J_{H,C\text{-}2}$). IR ($CHCl_3$): $\tilde{\nu}$ = 3015, 2960, 2930, 2875, 1750, 1685, 1655, 1609, 1450, 1375, 1345, 1295, 1255, 1220, 1195, 1185, 1140, 1095, 1040, 995, 970, 925, 775, 725, 690, 630 cm^{-1}.

Methyl {(*R*)-5-[(*E*,*E*)-Hexa-1,3-dienyl]-2,5-dimethyl-4-oxo-4,5-dihydrofuran-3-yl}carboxylate [(+)-(*E*,*E*)-(*R*)-1c] = Gregatin B

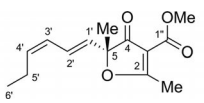


Procedure A: NEt_3 (189 μL, 138 mg, 1.36 mmol, 2.5 equiv.) was added at room temp. to a solution of a mixture (92:8, 123 mg, 545 μmol) of the hydroxy-oxo esters (*E*,*E*)-(*R*)-**29** and (1′*E*,3′*Z*)-(*R*)-**29** in CH_2Cl_2 (2.7 mL). The resulting mixture was stirred for 5 min. A solution of acetyl chloride (97.1 μL, 107 mg, 1.36 mmol, 2.5 equiv.) in CH_2Cl_2 (0.3 mL) was added dropwise over 20 min. After the mixture had been stirred for 45 min, buffered phosphate solution (pH = 7.0, 5 mL) was added. The resulting mixture was extracted with Et_2O (4× 10 mL). The combined organic phases were dried with $MgSO_4$. Removal of the volatiles under reduced pressure and purification by flash chromatography[77] [2.5 cm, 20 mL, petroleum ether (30:50)/Et_2O 3:1, #15–32] provided the title compound (83.0 mg, 61%) as a colorless solid.

Procedure B: $NaHCO_3$ (15.7 mg, 186 μmol, 2.0 equiv.) was added at room temp. to a solution of a mixture (95:5, 25.0 mg, 93.2 μmol) of the acetoxy-oxo esters (*E*,*E*)-(*R*)-**66** and (1′*E*,3′*Z*)-(*R*)-**66** in MeOH (1.0 mL). After the mixture had been stirred for 24 h, the reaction was quenched by the addition of H_2O (3.0 mL). The resulting mixture was extracted with Et_2O (4× 5 mL). The combined organic phases were dried with $MgSO_4$. Removal of the volatiles under reduced pressure and purification by flash chromatography[77] [2.0 cm, 10 mL, petroleum ether (30:50)/Et_2O 3:1, #12–25] provided the title compound (18.2 mg, 78%) as a colorless solid.

The enantiopurity of product (*E*,*E*)-**1c** from "Procedure A" corresponded to 90% *ee* and the diastereopurity of product (*R*)-**1c** from "Procedure A" to an (*E*,*E*)/(1′*E*,3′*Z*) ratio of 93:7, both by analytical HPLC: Chiralpak AD-H column; *n*-heptane/MeOH 100:1, 1.0 mL min^{-1}; $\lambda_{detector}$ = 230 nm. $t_{r\,(E,E)\text{-}(R)\text{-}1c}$ = 27.26 min, $t_{r\,(E,E)\text{-}(S)\text{-}1c}$ = 46.25 min, $t_{r\,(1'E,3'Z)\text{-}(R)\text{-}1c}$ = 11.37 min; (*E*,*E*)-(*R*)-**1c**/(*E*,*E*)-(*S*)-**1c** = 95:5; (*E*,*E*)-(*R*)-**1c**/(1′*E*,3′*Z*)-(*R*)-**1c** = 93:7. The mixture of (*E*,*E*)-(*R*)-**1c**, (1′*E*,3′*Z*)-(*R*)-**1c**, and (*E*,*E*)-(*S*)-**1c** obtained from "Procedure A" was separated into its constituents by preparative HPLC: Chiralpak AD-H column; *n*-heptane/MeOH 100:2, 16 mL min^{-1}; $\lambda_{detector}$ = 230 nm. $t_{r\,(E,E)\text{-}(R)\text{-}1c}$ = 22.0 min, $t_{r\,(E,E)\text{-}(S)\text{-}1c}$ = 37.0 min, $t_{r\,(1'E,3'Z)\text{-}(R)\text{-}1c}$ = 12.0 min. Isomer-free (*E*,*E*)-(*R*)-**1c** (obtained by preparative HPLC) gave the following data: M.p. 71 °C (ref.[1a] 80–81 °C). $[\alpha]_D^{20}$ = +208.2 (*c* = 0.52 in $CHCl_3$) and +205.7 (*c* = 0.27 in $CHCl_3$) {ref.[1a] $[\alpha]_D^{no\ temp.}$ = +207 (*c* = 0.84 in $CHCl_3$); ref.[2] $[\alpha]_D^{20}$ = +205 (*c* = 0.10 in $CHCl_3$)}. ^1H NMR (400.1 MHz, $CDCl_3$):[17] δ = 0.99 (t, $J_{6',5'}$ = 7.5 Hz, 3 H, 6′-H_3), 1.52 (s, 3 H, 5-CH_3), 2.10 (m_c, possibly interpretable as br. qd, $J_{5',6'} = J_{5',4'} \approx$ 7.5 Hz, 2 H, 5′-H_2), 2.64 (s, 3 H, 2-CH_3), 3.83 (s, 3 H, 1′′-OCH_3), 5.54 (d, $J_{1',2'}$ = 15.5 Hz, 1 H, 1′-H), 5.82 (dt, $J_{4',3'}$ = 15.2 Hz, $J_{4',5'}$ = 6.5 Hz, 1 H, 4′-H), 5.97 (br. dd, $J_{3',4'}$ = 15.0 Hz, $J_{3',2'}$ = 10.5 Hz, 1 H, 3′-H), 6.27 (dd, $J_{2',1'}$ = 15.5 Hz, $J_{2',3'}$ = 10.2 Hz, 1 H, 2′-H) ppm. ^1H NMR (499.6 MHz, C_6D_6):[17] δ = 0.82 (t, $J_{6',5'}$ = 7.4 Hz, 3 H, 6′-H_3), 1.29 (s, 3 H, 5-CH_3), 1.84 (m_c, possibly interpretable as br. qd, $J_{5',6'} = J_{5',4'} \approx$ 7.6 Hz, 2 H, 5′-H_2), 2.17 (s, 3 H, 2-CH_3), 3.50 (s, 3 H, 1′′-OCH_3), 5.48 (d, $J_{1',2'}$ = 15.8 Hz, 1 H, 1′-H), signal superimposed by 5.51 (dt, $J_{4',3'}$ = 14.9 Hz, $J_{4',5'}$ = 6.9 Hz, 1 H, 4′-H), 5.81 (dd, $J_{3',4'}$ = 15.3 Hz, $J_{3',2'}$ = 10.6 Hz, 1 H, 3′-H)[A], 6.34 (dd, $J_{2',1'}$ = 15.4 Hz, $J_{2',3'}$ = 10.4 Hz, 1 H, 2′-H)[A] ppm; [A] the indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (499.6 MHz, C_6D_6)] by their crosspeaks with protons that had been assigned unequivocally. ^{13}C NMR (125.6 MHz, C_6D_6):[17] δ = 13.40 (C-6′)[A], 17.09 (2-CH_3)[A], 22.34 (5-CH_3)[A], 25.88 (C-5′)[A], 50.87 (1′′-OCH_3)[A], 90.93 (C-5)[B], 107.26 (C-3)[B], 126.70 (C-1′)[A], 128.29 (C-3′)[A], 131.73 (C-2′)[A], 138.87 (C-4′)[A], 163.56 (C-1′′)[B], 194.63 (C-2)[B], 196.21 (C-4)[B] ppm; [A] the indicated nuclei are non-quaternary and were identified in an edHSQC spectrum ("short-range C,H-COSY spectrum"; 125.6/499.6 MHz, C_6D_6) by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally); [B] the indicated nuclei – they are quaternary – were distinguished[C] in an HMBC spectrum ["long-range C,H-COSY spectrum" (125.6 MHz/499.6 MHz), C_6D_6] by their crosspeaks due to ^2J, ^3J, and/or ^4J couplings to "remote" protons [these had previously been assigned unequivocally: (1) for δ_C = 90.93 (C-5) such crosspeaks were due to $^3J_{2'\text{-H,C-5}}$, $^2J_{1'\text{-H,C-5}}$, and $^2J_{5\text{-Me,C-5}}$; (2) for δ_C = 107.26 (C-3) such a crosspeak was due to $^3J_{2\text{-Me,C-3}}$; (3) for δ_C = 163.56 (C-1′′) such crosspeaks were due to $^3J_{1''\text{-OMe,C-1''}}$ and $^4J_{2\text{-Me,C-1''}}$; (4) for δ_C = 194.63 (C-2) such a crosspeak was due to $^2J_{2\text{-Me,C-2}}$; (5) for δ_C = 196.21 (C-4) such crosspeaks were due to $^3J_{1'\text{-H,C-4}}$ and $^3J_{5\text{-Me,C-4}}$; [C] C-1′′ and C-2 were *not* unambiguously distinguishable by these correlations, so the assignments of these nuclei take shift analogies into account (cf. Table 3). IR ($CHCl_3$):[17] $\tilde{\nu}$ = 3020, 2960, 2930, 2875, 1745 (shoulder), 1710, 1655, 1590, 1435, 1400, 1365, 1350, 1295, 1270, 1215, 1200, 1160, 1130, 1085, 1060, 1000, 945, 900, 850, 795, 770, 680 cm^{-1}. HRMS (EI, 70 eV): calcd. for $C_{14}H_{18}O_4$ $[M]^+$ 250.12051; found 250.12090 (+1.6 ppm). $C_{14}H_{18}O_4$ (250.3):[17] calcd. C 67.18, H 7.25; found C 67.03, H 7.56.

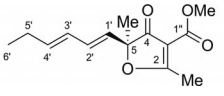
Methyl {(*R*)-5-[(1′*E*,3′*Z*)-Hexa-1,3-dienyl]-2,5-dimethyl-4-oxo-4,5-dihydrofuran-3-yl}carboxylate [(1′*E*,3′*Z*)-(*R*)-1c] = *cis*-Gregatin B



This product emerged from the HPLC purification of (+)-(*E*,*E*)-(*R*)-**1c** = gregatin B (cf. above). The yield of this compound was

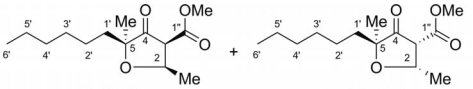
too small for determination of its $[\alpha]_D^{20}$ value with sufficient precision. ^{1}H NMR (499.6 MHz, C_6D_6): δ = 0.77 (t, $J_{6',5'}$ = 7.6 Hz, 3 H, 6′-H_3), 1.28 (s, 3 H, 5-CH_3), 1.98 (m_c, possibly interpretable as qdd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.5 Hz, $J_{5',3'}$ = 1.5 Hz, 2 H, 5′-H_2), 2.15 (s, 3 H, 2-CH_3), 3.49 (s, 3 H, 1′′-OCH_3), 5.34 (dt, $J_{4',3'}$ = 10.7 Hz, $J_{4',5'}$ = 7.6 Hz, 1 H, 4′-H), 5.59 (d, $J_{1',2'}$ = 15.4 Hz, 1 H, 1′-H), 5.83 (dd, $J_{3',4'} = J_{3',2'}$ = 10.9 Hz, 1 H, 3′-H)^A, 6.76 (ddd, $J_{2',1'}$ = 15.4 Hz, $J_{2',3'}$ = 11.2 Hz, $J_{2',1'}$ = 1.1 Hz, 1 H, 2′-H)^A ppm; ^{A} the indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (499.6 MHz, C_6D_6)] by their crosspeaks with protons that had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 5.83 (dd, 3′-H) $\leftrightarrow$ δ = 1.98 (m_c, 5′-H), δ = 5.83 (dd, 3′-H) $\leftrightarrow$ δ = 5.34 (dt, 4′-H), and δ = 5.83 (dd, 3′-H) $\leftrightarrow$ δ = 6.76 (ddd, 2′-H); δ = 6.76 (ddd, 2′-H) $\leftrightarrow$ δ = 5.59 (d, 1′-H) and δ = 6.76 (ddd, 2′-H) $\leftrightarrow$ δ = 5.83 (dd, 3′-H). ^{13}C NMR (125.6 MHz, C_6D_6): δ = 14.09 (C-6′)^A, 17.07 (2-CH_3)^A, 21.38 (C-5′)^A, 22.53 (5-CH_3)^A, 50.87 (1′′-OCH_3)^A, 90.96 (C-5)^B, 107.32 (C-3)^B, 126.38 (C-2′)^A, 126.95 (C-3′)^A, 128.91 (C-1′)^A, 136.40 (C-4′)^A, 163.49 (C-1′′)^B, 194.65 (C-2)^B, 196.09 (C-4)^B ppm; ^{A} the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ("short-range C,H-COSY spectrum"; 125.6/499.6 MHz, C_6D_6) by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 0.77 (t, 6′-H_3) $\leftrightarrow \delta_C$ = 14.09 (C-6′), δ_H = 1.28 (s, 5-CH_3) $\leftrightarrow \delta_C$ = 22.53 (5-CH_3), δ_H = 1.98 (m_c, 5′-H_2) $\leftrightarrow \delta_C$ = 21.38 (C-5′), δ_H = 2.15 (s, 2-CH_3) $\leftrightarrow \delta_C$ = 17.07 (2-CH_3), δ_H = 3.49 (s, 1′′-OCH_3) $\leftrightarrow \delta_C$ = 50.87 (1′′-OCH_3), δ_H = 5.34 (dt, 4′-H) $\leftrightarrow \delta_C$ = 136.40 (C-4′), δ_H = 5.59 (d, 1′-H) $\leftrightarrow \delta_C$ = 128.91 (C-1′), δ_H = 5.83 (dd, 3′-H) $\leftrightarrow \delta_C$ = 126.95 (C-3′), δ_H = 6.76 (ddd, 2′-H) $\leftrightarrow \delta_C$ = 126.38 (C-2′); ^{B} the indicated nuclei – they are quaternary – were distinguished in an HMBC spectrum ["long-range C,H-COSY spectrum" (125.6 MHz/499.6 MHz), C_6D_6] by their crosspeaks due to ^2J and/or ^3J couplings to "remote" protons (these had previously been assigned unequivocally): for δ_C = 90.96 (C-5) such crosspeaks were due to $^3J_{2'\text{-H,C-5}}$, $^2J_{1'\text{-H,C-5}}$, and $^2J_{5\text{-Me,C-5}}$; for δ_C = 107.32 (C-3) such a crosspeak was due to $^3J_{2\text{-Me,C-3}}$; for δ_C = 163.49 (C-1′′) such crosspeaks were due to $^3J_{1''\text{-OMe,C-1''}}$ and $^4J_{2\text{-Me,C-1''}}$; for δ_C = 194.65 (C-2) such a crosspeak was due to $^2J_{2\text{-Me,C-2}}$; for δ_C = 196.09 (C-4) such crosspeaks were due to $^3J_{1'\text{-H,C-4}}$ and $^3J_{5\text{-Me,C-4}}$.

Methyl {(*S*)-5-[(*E*,*E*)-Hexa-1,3-dienyl]-2,5-dimethyl-4-oxo-4,5-dihydrofuran-3-yl}carboxylate [(–)-(*E*,*E*)-(*S*)-1c] = *ent*-Gregatin B in a Mixture (94:6) with Methyl {(*S*)-5-[(1′*E*,3′*Z*)-Hexa-1,3-dienyl]-2,5-dimethyl-4-oxo-4,5-dihydrofuran-3-yl}carboxylate [(1′*E*,3′*Z*)-(*S*)-1c]



This compound was prepared as described for (+)-(*E*,*E*)-(*R*)-**1c** by "Procedure A" with NEt_3 (68.6 µL, 50.1 mg, 495 µmol, 2.2 equiv.), a mixture (92:8) of the hydroxy-oxo esters (*E*,*E*)-(*S*)-**29** and (1′*E*,3′*Z*)-(*S*)-**29** (51.0 mg, 225 µmol) in CH_2Cl_2 (1.0 mL), and a solution of acetyl chloride (35.3 µL, 38.9 mg, 495 µmol, 2.2 equiv.) in CH_2Cl_2 (0.3 mL). Purification by flash chromatography[77] [2.0 cm, 20 mL, petroleum ether (30:50)/Et_2O 3:1, #22–44] provided the title compound (29.6 mg, 53%) as a colorless solid. The enantiopurity of product (*E*,*E*)-**1c** corresponded to 91% *ee* and the diastereopurity of the major enantiomer (*S*)-**1c** to an (*E*,*E*)/(1′*E*,3′*Z*) ratio of 93:7, both according to analytical HPLC: Chiralpak AD-H column; *n*-heptane/MeOH 100:1, 1.0 mL min^{-1}; $\lambda_{detector}$ = 230 nm. $t_{r\ (E,E)\text{-}(R)\text{-}\mathbf{1c}}$ = 27.18 min, $t_{r\ (E,E)\text{-}(S)\text{-}\mathbf{1c}}$ = 46.11 min, $t_{r\ (1'E,3'Z)\text{-}(S)\text{-}\mathbf{1c}}$ = 17.73 min [(*E*,*E*)-(*S*)-**1c**/(*E*,*E*)-(*R*)-**1c** = 95.5:4.5 (→ 91% *ee*); (*E*,*E*)-(*S*)-**1c**/(1′*E*,3′*Z*)-(*S*)-**1c** = 94:6]. $[\alpha]_D^{20}$ = –176.0 (*c* = 0.95 in $CHCl_3$). ^{1}H NMR [300.1 MHz, C_6D_6; sample contained 6.0% (1′*E*,3′*Z*)-(*S*)-**1c**]: δ = 0.78 [t, $J_{6',5'}$ = 7.4 Hz, 3 H, (1′*E*,3′*Z*)-6′-H_3], 0.82 (t, $J_{6',5'}$ = 7.5 Hz, 3 H, 6′-H_3), 1.28 [s, 3 H, (1′*E*,3′*Z*)-5-CH_3], 1.29 (s, 3 H, 5-CH_3), 1.85 (m_c, possibly interpretable as br. qd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.5 Hz, 2 H, 5′-H_2), 1.99 [m_c, possibly interpretable as qdd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.5 Hz, $J_{5',3'}$ = 1.2 Hz, 2 H, (1′*E*,3′*Z*)-5′-H_2], 2.16 [s, 3 H, (1′*E*,3′*Z*)-2-CH_3], 2.17 (s, 3 H, 2-CH_3), 3.49 [s, 3 H, (1′*E*,3′*Z*)-1′′-OCH_3], 3.50 (s, 3 H, 1′′-OCH_3), 5.34 [dt, $J_{4',3'}$ = 10.9 Hz, $J_{4',5'}$ = 7.4 Hz, 1 H, (1′*E*,3′*Z*)-4′-H], 5.48 (d, $J_{1',2'}$ = 15.5 Hz, 1 H, 1′-H), superimposed by 5.51 (dt, $J_{4',3'}$ = 15.1 Hz, $J_{4',5'}$ = 6.6 Hz, 4 H, 4′-H), 5.82 (br. dd, $J_{3',4'}$ = 15.2 Hz, $J_{3',2'}$ = 10.5 Hz, 1 H, 3′-H), 6.34 (dd, $J_{2',1'}$ = 15.5 Hz, $J_{2',3'}$ = 10.3 Hz, 1 H, 2′-H), 6.76 [ddd, $J_{2',1'}$ = 15.2 Hz, $J_{2',3'}$ = 10.9 Hz, $J_{2',4'}$ = 0.8 Hz, 1 H, (1′*E*,3′*Z*)-2′-H] ppm.

Methyl [(2*R*,5*S*)-5-Hexyl-2,5-dimethyl-4-oxo-2,3,4,5-tetrahydrofuran-3-yl]carboxylate (H_6-1c) in a Mixture with Methyl [(2*S*,5*S*)-5-Hexyl-2,5-dimethyl-4-oxo-2,3,4,5-tetrahydrofuran-3-yl]carboxylate (*iso*-H_6-1c)



H_6-(–)-**1c** 60:40 *iso*-H_6-(–)-**1c**

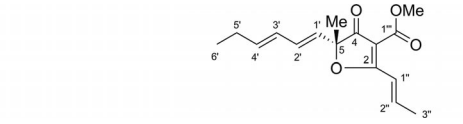
(configurational assignments interchangeable)

these keto-tautomers prevailed over the corresponding enols in 93:7 ratios

A suspension of Pd/C [5% (w/w), 8.9 mg, containing 0.44 mg, 4.2 µmol, 5.0 mol-%] in an solution of *ent*-gregatin B [(–)-(*S*)-**1c**; 20.9 mg, 83.5 µmol] in MeOH (1.5 mL) was stirred under H_2 (3 bar) at room temp. for 3 h. The mixture was filtered through a glass frit covered with a pad of silica gel. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography[77] (2.5 cm, 20 mL, C_6H_{12}/EtOAc 15:1, #15–34). This provided the title compound (17.4 mg, 81%) as a colorless oil. The absence of completely separated ^{1}H NMR resonances (499.6 MHz, C_6D_6) limited the accuracy of determination of the ratio between the major and the minor diastereomer of the keto tautomer (ca. 60:40) and of the enol tautomer (ca. 60:40) and likewise the ratio between the two keto tautomers and the two enol tautomers (ca. 93:7) to approximations; all ratios were based on peak area comparisons of the following resonances: δ = 4.55 (dq, keto tautomer of major diastereomer: 2-H), δ = 4.59 (dq, keto tautomer of minor diastereomer: 2-H), and δ = 5.01 (q, enol tautomer of minor diastereomer: 2-H) versus δ = 5.05 (q, enol tautomer of major diastereomer: 2-H), respectively. ^{1}H NMR (499.6 MHz, C_6D_6; sample somewhat impure; only the keto tautomer resonances are listed): δ = 0.83 (t, $J_{6',5'}$ = 7.1 Hz, 3 H of minor diastereomer: 6′-H_3), 0.84 (t, $J_{6',5'}$ = 7.1 Hz, 3 H of major diastereomer: 6′-H_3), 1.10–1.22 (m, 4 H, 4′-H_2, 5′-H_2), superimposed by 1.16 and 1.17 (2× s, 3 H per diastereomer, 5-CH_3) and also superimposed by 1.16 (d, $J_{2\text{-Me},2}$ = 6.0 Hz, 3 H of minor diastereomer, 2-CH_3) and 1.18 (d, $J_{2\text{-Me},2}$ = 6.0 Hz, 3 H of major diastereomer, 2-CH_3), 1.35–1.75 (m, 6 H, 1′-H_2, 2′-H_2, 3′-H_2), 2.95 (d, $J_{3,2}$ = 10.4 Hz, 2 H, 3-H), 3.30 (s, 3 H of minor diastereomer: OCH_3), 3.31 (s, 3 H of major diastereomer, OCH_3), 4.55 (dq, $J_{2,3}$ = 10.6 Hz, $J_{2,2\text{-Me}}$ = 5.7 Hz, 1 H of major diastereomer, 2-H), low-field branch of preceding resonance overlaps with high-field branch of 4.59 (dq, $J_{2,3}$ = 10.0 Hz, $J_{2,2\text{-Me}}$ = 5.7 Hz, 1 H of minor diastereomer, 2-H) ppm. ^{13}C NMR (125.6 MHz, C_6D_6): δ = 14.22 (C-6′)^A, 19.99, 20.42, 20.61, 22.15, 22.91, 22.92, 23.27, 23.82, 29.74, 29.83, 31.89, 31.95 (12 instead of 10 resonances for two diastereomers, each of which contains the following five different ^{13}C nuclei: 2-CH_3, 5-CH_3, C-3′, C-4′, C-5′), 34.67 (C-1′)^A, 38.00 (C-2′)^A, 52.02 (OCH_3)^A, 60.23 and 61.63 (C-3)^{A,B}, 72.20 and 72.64 (C-2)^{A,B}, 84.20 and 84.64 (C-5)^B, 167.58 and 167.61 (C-1′′)^B, 210.59 and 211.07 (C-4)^B ppm;

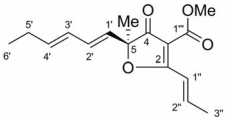
[A] the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ("short-range C,H-COSY spectrum"; 125.6/499.6 MHz, C_6D_6) by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 0.83 and 0.84 (t, 6′-H_3) ↔ δ_C = 14.22 (C-6′), δ_H = 1.35–1.75 (m, 2′-H_2) ↔ δ_C = 38.00 (C-2′), δ_H = 1.35–1.75 (m, 1′-H_2) ↔ δ_C = 34.67 (C-1′), δ_H = 3.30 and 3.31 (2× s, OCH_3) ↔ δ_C = 52.02 (OCH_3), δ_H = 4.55 and 4.59 (dq, 2-H) ↔ δ_C = 72.20 and 72.64 (C-2); [B] the indicated nuclei – they are quaternary – were distinguished in an HMBC spectrum ["long-range C,H-COSY spectrum" (125.6 MHz/499.6 MHz) C_6D_6] by their crosspeaks due to ^2J and/or ^3J and/or ^4J couplings to "remote" protons (these had previously been assigned unequivocally): for δ_C = 60.23 and 61.63 (C-3) such a crosspeak was due to $^2J_{5\text{-H,C-3}}$ and $^4J_{OMe,C\text{-}3}$; for δ_C = 72.20 and 72.64 (C-2) such crosspeaks were due to $^2J_{4\text{-H,C-2}}$ and $^2J_{2\text{-Me,C-2}}$; for δ_C = 84.20 and 84.64 (C-5) such crosspeaks were due to $^3J_{4\text{-H,C-5}}$, $^2J_{1'\text{-H,C-5}}$, and $^2J_{5\text{-Me,C-5}}$; for δ_C = 167.58 and 167.61 (C-1′′) such crosspeaks were due to $^3J_{5\text{-H,C-1}''}$, $^3J_{OMe,C\text{-}1''}$, and $^2J_{4\text{-H,C-1}''}$; for δ_C = 210.59 and 211.07 (C-4) such crosspeaks were due to $^3J_{5\text{-H,C-4}}$, $^2J_{4\text{-H,C-4}}$, $^3J_{1'\text{-H,C-4}}$, and $^3J_{5\text{-Me,C-4}}$.

Methyl {(*R*)-5-[(*E*,*E*)-Hexa-1,3-dienyl]-5-methyl-4-oxo-2-[(*E*)-prop-1-enyl]-4,5-dihydrofuran-3-yl}carboxylate [(–)-(*E*,*E*)-(*R*)-2c] = Gregatin A



A mixture (93:7) of (*E*,*E*)-(5*R*,2′′*R*)-**80c** and (1′*E*,3′*Z*)-(5*R*,2′′*R*)-**80c** (155.2 mg, 379.8 μmol) was dissolved in a THF/MeOH/HCl (10%) mixture [4:1:2 (v/v/v), 9.1 mL] and heated at 60 °C for 30 min. A buffered aqueous phosphate solution (pH = 7.0, 10 mL) was added, and the resulting mixture was extracted with EtOAc (4× 10 mL). The combined organic phases were dried with $MgSO_4$. After removal of the solvent under reduced pressure, the residue {= gregatin D [(5*R*,2′′*R*)-**4c**]; 122.9 mg, 417.5 μmol, 1.0 equiv.}, tosyl chloride (199 mg, 1.04 mmol, 2.5 equiv.), NEt_3 (145 μL, 106 mg, 1.04 mmol, 2.5 equiv.), and DMAP (51.1 mg, 418 μmol, 1.0 equiv.) were dissolved in CH_2Cl_2 (2.5 mL). The mixture was stirred at room temp. for 4 h. A buffered aqueous phosphate solution (pH = 7.0, 4.0 mL) was added, and the resulting mixture was extracted with Et_2O (4× 5 mL). After drying with $MgSO_4$, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography[77] (2.0 cm, 20 mL, C_6H_{12}/EtOAc 10:1 → 6:1, #20–36). This provided the title compound (27.9 mg, 27% over the three steps) as a slightly yellow solid. The enantiopurity of product (*E*,*E*)-**2c** corresponded to 91% *ee* and the diastereopurity of the major enantiomer (*R*)-**2c** to an (*E*,*E*)/(1′*E*,3′*Z*) ratio of 93:7, both according to analytical HPLC: Chiralpak AD-H column; *n*-heptane/MeOH 100:1, 1.0 mL min^{-1}; $\lambda_{detector}$ = 230 nm. $t_{r\,(E,E)\text{-}(R)\text{-}\mathbf{2c}}$ = 21.72 min, $t_{r\,(E,E)\text{-}(S)\text{-}\mathbf{2c}}$ = 17.64 min, $t_{r\,(1'E,3'Z)\text{-}(R)\text{-}\mathbf{2c}}$ = 14.42 min [(*E*,*E*)-(*R*)-**2c**/(*E*,*E*)-(*S*)-**2c** = 95.5:4.5 (→ 91% *ee*); (*E*,*E*)-(*R*)-**2c**/(1′*E*,3′*Z*)-(*R*)-**2c** = 93:7]. This mixture of (*E*,*E*)-(*R*)-**2c**, (1′*E*,3′*Z*)-(*R*)-**2c**, and (*E*,*E*)-(*S*)-**2c** was separated into its constituents by preparative HPLC: Chiralpak AD-H column; *n*-heptane/EtOH 200:3, 16 mL min^{-1}; $\lambda_{detector}$ = 230 nm. $t_{r\,(E,E)\text{-}(R)\text{-}\mathbf{2c}}$ = 21.5 min, $t_{r\,(E,E)\text{-}(S)\text{-}\mathbf{2c}}$ = 18.0 min, $t_{r\,(1'E,3'Z)\text{-}(R)\text{-}\mathbf{2c}}$ = 16.0 min. Isomer-free (*E*,*E*)-(*R*)-**2c** (obtained by preparative HPLC) gave the following data: $[\alpha]_D^{20}$ = –165.6 (= first-measurement; *c* = 0.30 in $CHCl_3$). $[\alpha]_D^{20}$ = –166.1 (= second measurement; *c* = 0.31 in $CHCl_3$) {ref.[1a] $[\alpha]_D^{no\ temp.}$ = –140 (*c* = 0.94 in $CHCl_3$); ref.[2] $[\alpha]_D^{20}$ = –144 (*c* = 2.0 in $CHCl_3$)}. ^1H NMR (499.6 MHz, C_6D_6): δ = 0.81 (t, $J_{6',5'}$ = 7.4 Hz, 3 H, 6′-H_3), 1.36 (dd, $J_{3'',2''}$ = 6.9 Hz, $^4J_{3'',1''}$ = 1.6 Hz, 3 H, 3′′-H_3), 1.38 (s, 3 H, 5-CH_3), 1.84 (m_c, possibly interpretable as br. qd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.4 Hz, 2 H, 5′-H_2), 3.53 (s, 3 H, OCH_3), 5.49 (dt, $J_{4',3'}$ = 14.7 Hz, $J_{4',5'}$ = 6.9 Hz, 1 H, 4′-H), 5.56 (d, $J_{1',2'}$ = 15.4 Hz, 1 H, 1′-H), 5.82 (br. dd, $J_{3',4'}$ = 15.3 Hz, $J_{3',2'}$ = 10.6 Hz, 1 H, 3′-H)[A], 6.39 (dd, $J_{2',1'}$ = 15.4 Hz, $J_{2',3'}$ = 10.4 Hz, 1 H, 2′-H)[A], 6.78 (dq, $J_{2'',1''}$ = 15.7 Hz, $J_{2'',3''}$ = 7.1 Hz, 1 H, 2′′-H), 7.52 (dd, $J_{1'',2''}$ = 15.8 Hz, $^4J_{1'',3''}$ = 1.6 Hz, 1 H, 1′′-H) ppm; [A] the indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (499.6 MHz, C_6D_6)] by their crosspeaks with protons that had previously been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 5.82 (dd, 3′-H) ↔ δ = 1.84 (m_c, 5′-H), δ = 5.82 (dd, 3′-H) ↔ δ = 5.49 (dt, 4′-H), and δ = 5.82 (dd, 3′-H) ↔ δ = 6.39 (dd, 2′-H); δ = 6.39 (dd, 2′-H) ↔ δ = 5.56 (d, 1′-H) and δ = 6.39 (dd, 2′-H) ↔ δ = 5.82 (dd, 3′-H). ^{13}C NMR (125.6 MHz, C_6D_6): δ = 13.42 (C-6′)[A], 18.65 (C-3′′)[A], 22.50 (5-CH_3)[A], 25.87 (C-5′)[A], 50.99 (OCH_3)[A], 90.15 (C-5)[B], 104.62 (C-3)[B], 121.23 (C-1′′)[A], 127.38 (C-1′)[A], 128.46 (C-3′)[A], 131.46 (C-2′)[A], 138.66 (C-4′)[A], 143.21 (C-2′′)[A], 163.74 (C-1′′′)[B], 184.69 (C-2)[B], 196.66 (C-4)[B] ppm; [A] the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (125.6/499.6 MHz, C_6D_6)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 0.81 (t, 6′-H_3) ↔ δ_C = 13.42 (C-6′), δ_H = 1.36 (d, 3′′-H_3) ↔ δ_C = 18.65 (C-3′′), δ_H = 1.38 (s, 5-CH_3) ↔ δ_C = 22.50 (5-CH_3), δ_H = 1.84 (m_c, 5′-H_2) ↔ δ_C = 25.87 (C-5′), δ_H = 3.53 (s, OCH_3) ↔ δ_C = 50.99 (OCH_3), δ_H = 5.49 (dt, 4′-H) ↔ δ_C = 138.66 (C-4′), δ_H = 5.56 (d, 1′-H) ↔ δ_C = 127.38 (C-1′), δ_H = 5.82 (dd, 3′-H) ↔ δ_C = 128.46 (C-3′), δ_H = 6.39 (dd, 2′-H) ↔ δ_C = 131.46 (C-2′), δ_H = 6.78 (dq, 2′′-H) ↔ δ_C = 143.21 (C-2′′), δ_H = 7.52 (dd, 1′′-H) ↔ δ_C = 121.23 (C-1′′); [B] the indicated nuclei – they are quaternary – were distinguished in an HMBC spectrum ["long-range C,H-COSY spectrum" (125.6 MHz/499.6 MHz), C_6D_6] by their crosspeaks due to ^2J and/or ^3J and/or ^4J couplings to "remote" protons (these had previously been assigned unequivocally): for δ_C = 90.15 (C-5) such crosspeaks were due to $^3J_{2'\text{-H,C-5}}$, $^2J_{1'\text{-H,C-5}}$, and $^2J_{5\text{-Me,C-5}}$; for δ_C = 163.74 (C-1′′′) such a crosspeak was due to $^3J_{OMe,C\text{-}1'''}$; for δ_C = 184.69 (C-2) such crosspeaks were due to $^2J_{1''\text{-H,C-2}}$, $^3J_{2''\text{-H,C-2}}$, and $^4J_{3''\text{-H,C-2}}$; for δ_C = 196.66 (C-4) such crosspeaks were due to $^3J_{1'\text{-H,C-4}}$ and $^3J_{5\text{-Me,C-4}}$.

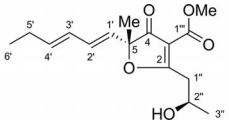
Methyl {(*S*)-5-[(*E*,*E*)-Hexa-1,3-dienyl]-5-methyl-4-oxo-2-[(*E*)-prop-1-enyl]-4,5-dihydrofuran-3-yl}carboxylate [(+)-(*E*,*E*)-(*S*)-2c] = Aspertetronin A



This compound was prepared as described for (–)-(*E*,*E*)-(*R*)-**2c** by starting from a solution of a mixture (93:7) of (*E*,*E*)-(5*S*,2′′*R*)-**80c** and (1′*E*,3′*Z*)-(5*S*,2′′*R*)-**80c** (111 mg, 272 μmol) in a mixture [4:1:2 (v/v/v), 7.0 mL] of THF/MeOH/HCl (10%) and continuing with a solution of the crude product {= antipode of gregatin C [(5*S*,2′′*R*)-**4c**; 85.9 mg, 292 μmol, 1.0 equiv.]}, tosyl chloride (111 mg, 584 μmol, 2.0 equiv.), NEt_3 (81.0 μL, 59.1 mg, 584 μmol, 2.0 equiv.), and 4-(dimethylamino)pyridine (35.7 mg, 292 μmol, 1.0 equiv.) in CH_2Cl_2 (2 mL). Purification by flash chromatography[77] (2.0 cm, 20 mL, C_6H_{12}/EtOAc 6:1, #8–13) provided the title compound (30.8 mg, 41% over the three steps) as a slightly yellow solid. The enantiopurity of product (*E*,*E*)-**2c** corresponded to 93% *ee* and the diastereopurity of the major enantiomer (*S*)-**2c** to an (*E*,*E*)/(1′*E*,3′*Z*) ratio of 93:7, both according to analytical HPLC: Chiralpak AD-H column; *n*-heptane/MeOH 100:1, 1.0 mL min^{-1}; $\lambda_{detector}$ = 230 nm. $t_{r\,(E,E)\text{-}(R)\text{-}\mathbf{2c}}$ = 21.55 min,

$t_{r\,(E,E)\text{-}(S)\text{-}\mathbf{2c}}$ = 17.49 min, $t_{r\,(1'E,3'Z)\text{-}(S)\text{-}\mathbf{2c}}$ = 15.34 min [(*E*,*E*)-(*S*)-**2c**/(*E*,*E*)-(*R*)-**2c** = 96.5:3.5 (→ 93% *ee*); (*E*,*E*)-(*S*)-**2c**/(1′*E*,3′*Z*)-(*S*)-**2c** = 93:7]. This mixture of (*E*,*E*)-(*S*)-**2c**, (1′*E*,3′*Z*)-(*S*)-**2c**, and (*E*,*E*)-(*R*)-**2c** was separated into its constituents by preparative HPLC: Chiralpak AD-H column; *n*-heptane/MeOH 100:1, 16 mL min^{-1}; $\lambda_{detector}$ = 230 nm. $t_{r\,(E,E)\text{-}(S)\text{-}\mathbf{2c}}$ = 23.0 min, $t_{r\,(E,E)\text{-}(R)\text{-}\mathbf{2c}}$ = 31.5 min, $t_{r\,(1'E,3'Z)\text{-}(S)\text{-}\mathbf{2c}}$ = 21.0 min. Isomer-free (*E*,*E*)-(*S*)-**2c** (obtained by preparative HPLC) gave the following data: M.p. 69 °C (ref.[4] 72 °C). $[\alpha]_D^{20}$ = +163.8 (= first measurement; *c* = 0.45 in $CHCl_3$). $[\alpha]_D^{20}$ = +166.1 (= independent second measurement; *c* = 0.55 in $CHCl_3$) {ref.[4] $[\alpha]_D^{no\ temp.}$ = +133 (*c* = 0.30 in $CHCl_3$)}. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.99 (t, $J_{6',5'}$ = 7.5 Hz, 3 H, 6′-H_3), 1.54 (s, 3 H, 5-CH_3), 2.06 (dd, $J_{3'',2''}$ = 6.8, $^4J_{3'',1''}$ = 1.5 Hz, 3 H, 3′′-H_3), superimposed by 2.08 (m_c, possibly interpretable as br. qd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.6 Hz, 2 H, 5′-H_2), 3.83 (s, 3 H, OCH_3), 5.56 (d, $J_{1',2'}$ = 15.4 Hz, 1 H, 1′-H), 5.80 (dt, $J_{4',3'}$ = 15.1, $J_{4',5'}$ = 6.5 Hz, 1 H, 4′-H), 5.97 (br. dd, $J_{3',4'}$ = 15.0, $J_{3',2'}$ = 10.5 Hz, 1 H, 3′-H), 6.26 (dd, $J_{2',1'}$ = 15.4, $J_{2',3'}$ = 10.4 Hz, 1 H, 2′-H), 7.19 (dq, $J_{2'',1''}$ = 15.8, $J_{2'',3''}$ = 6.8 Hz, 1 H, 2′′-H), 7.33 (dq, $J_{1'',2''}$ = 15.7, $^4J_{1'',3''}$ = 1.4 Hz, 1 H, 1′′-H) ppm. (500 MHz, C_6D_6): δ = 0.81 (t, $J_{6',5'}$ = 7.4 Hz, 3 H, 6′-H_3), 1.37 (dd, $J_{3'',2''}$ = 7.1, $^4J_{3'',1''}$ = 1.7 Hz, 3 H, 3′′-H_3), 1.38 (s, 3 H, 5-CH_3), 1.84 (m_c, possibly interpretable as br. qd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.3 Hz, 2 H, 5′-H_2), 3.53 (s, 3 H, OCH_3), 5.49 (dt, $J_{4',3'}$ = 15.0, $J_{4',5'}$ = 6.8 Hz, 1 H, 4′-H), 5.56 (d, $J_{1',2'}$ = 15.4 Hz, 1 H, 1′-H), 5.82 (br. dd, $J_{3',4'}$ = 15.1, $J_{3',2'}$ = 10.4 Hz, 1 H, 3′-H), 6.39 (dd, $J_{2',1'}$ = 15.4, $J_{2',3'}$ = 10.4 Hz, 1 H, 2′-H), 6.79 (dq, $J_{2'',1''}$ = 15.8, $J_{2'',3''}$ = 7.0 Hz, 1 H, 2′′-H), 7.52 (dq, $J_{1'',2''}$ = 15.8, $^4J_{1'',3''}$ = 1.5 Hz, 1 H, 1′′-H) ppm. ^{13}C NMR (125.6 MHz, $CDCl_3$): δ = 13.37 (C-6′), 19.40 (C-3′′), 22.57 (5-CH_3), 25.74 (C-5′), 51.67 (OCH_3), 90.49 (C-5), 103.78 (C-3), 120.86 (C-1′′), 126.23 (C-1′), 127.85 (C-3′), 131.56 (C-2′), 139.35 (C-4′), 144.79 (C-2′′), 163.54 (C-1′′′), 185.28 (C-2), 198.39 (C-4) ppm. ^{13}C NMR (125.6 MHz, C_6D_6): δ = 13.42 (C-6′), 18.66 (C-3′′), 22.50 (5-CH_3), 25.88 (C-5′), 50.99 (OCH_3), 90.15 (C-5), 104.61 (C-3), 121.23 (C-1′′), 127.38 (C-1′), 128.47 (C-3′), 131.46 (C-2′), 138.67 (C-4′), 143.23 (C-2′′), 163.74 (C-1′′′), 184.70 (C-2), 196.67 (C-4) ppm. IR [CH(!)Cl_3]: $\tilde{\nu}$ = 3025, 2960, 2930, 2870, 2840, 1745 (shoulder), 1705, 1645, 1555, 1435, 1395, 1305, 1255, 1200, 1165, 1130, 1050, 990, 975, 920 830, 775, 670 cm^{-1}. HRMS (EI, 70 eV): calcd. for $C_{16}H_{20}O_4$ $[M]^+$ 276.13616; found 276.13590 (Δ = –0.9 ppm). $C_{16}H_{20}O_4$ (276.3): calcd. C 69.55, H 7.30; found C 69.56, H 7.41.

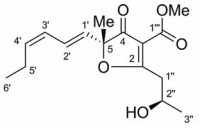
Methyl {(*R*)-5-[(*E*,*E*)-Hexa-1,3-dienyl]-2-[(*R*)-2-hydroxypropyl]-5-methyl-4-oxo-4,5-dihydrofuran-3-yl}carboxylate [(+)-(*E*,*E*)-(5*R*,2′′*R*)-4c] = Gregatin D



A mixture (93:7) of (*E*,*E*)-(5*R*,2′′*R*)-**80c** and (1′*E*,3′*Z*)-(5*R*,2′′*R*)-**80c** (86.0 mg, 210 μmol) was dissolved in a mixture [4:1:2 (v/v/v), 7.0 mL] of THF/MeOH/HCl (10%) and stirred at room temp. for 6 h. A buffered aqueous phosphate solution (pH = 7.0, 7.0 mL) was added, and the resulting mixture was extracted with EtOAc (4× 10 mL). Drying of the combined organic phases with $MgSO_4$, removal of the volatiles under reduced pressure, and purification by flash chromatography[77] (2.5 cm, 20 mL, C_6H_{12}/EtOAc 1:1, #5–6 and #8–18) provided gregatin A [(*E*,*E*)-(*R*)-**2c**; slightly yellow solid, 2.0 mg, 3.4%] in fractions 5–6 and the title compound (54.4 mg, 88%) as a colorless oil in fractions 8–18. The diastereopurity of product (*E*,*E*)-**4c** corresponded to 90% *de* with respect to the stereocenter at C-5 and the diastereopurity of the major diastereomer (5*R*,2′′*R*)-**4c** to an (*E*,*E*)/(1′*E*,3′*Z*) ratio of 94:6 with respect to the stereogenic C=C bonds, both according to analytical HPLC: Chiralpak AD-H column; *n*-heptane/*i*PrOH 9:1, 1.0 mL min^{-1}; $\lambda_{detector}$ = 230 nm. $t_{r\,(E,E)\text{-}(5R,2''R)\text{-}\mathbf{4c}}$ = 11.60 min, $t_{r\,(E,E)\text{-}(5S,2''R)\text{-}\mathbf{4c}}$ = 14.43 min, $t_{r\,(1'E,3'Z)\text{-}(5R,2''R)\text{-}\mathbf{4c}}$ = 9.84 min [(*E*,*E*)-(5*R*,2′′*R*)-**4c**/(*E*,*E*)-(5*S*,2′′*R*)-**4c** = 95:5 (→ 90% *de*); (*E*,*E*)-(5*R*,2′′*R*)-**4c**/(1′*E*,3′*Z*)-(5*R*,2′′*R*)-**4c** = 94:6]. This mixture of (*E*,*E*)-(5*R*,2′′*R*)-**4c**, (1′*E*,3′*Z*)-(5*R*,2′′*R*)-**4c**, and (*E*,*E*)-(5*S*,2′′*R*)-**4c** was separated into its constituents by preparative HPLC: Chiralpak AD-H column; *n*-heptane/*i*PrOH 92:8, 16 mL min^{-1}, $\lambda_{detector}$ = 230 nm. Room temp.; $t_{r\,(E,E)\text{-}(5R,2''R)\text{-}\mathbf{4c}}$ = 17.5 min, $t_{r\,(E,E)\text{-}(5S,2''R)\text{-}\mathbf{4c}}$ = 22.5 min, $t_{r\,(1'E,3'Z)\text{-}(5R,2''R)\text{-}\mathbf{4c}}$ = 15.5 min. Isomer-free (*E*,*E*)-(5*R*,2′′*R*)-**4c** (obtained by preparative HPLC) gave the following data: $[\alpha]_D^{20}$ = +105.8 (= first measurement; *c* = 0.95 in $CHCl_3$). $[\alpha]_D^{20}$ = +105.6 (= independent second measurement; *c* = 0.83 in $CHCl_3$). $[\alpha]_D^{20}$ = +101.5 (= independent third measurement; *c* = 0.68 in $CHCl_3$) {ref.:[1a] $[\alpha]_D^{no\ temp.}$ = +76.9 (*c* = 1.14 in $CHCl_3$); ref.[2] $[\alpha]_D^{20}$ = +72.0 (*c* = 0.10 in $CHCl_3$)}. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ = 0.99 (t, $J_{6',5'}$ = 7.5 Hz, 3 H, 6′-H_3), 1.36 (d, $J_{3'',2''}$ = 6.2 Hz, 3 H, 3′′-H_3), 1.55 (s, 3 H, 5-CH_3), 2.08 (m_c, possibly interpretable as br. qd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.2 Hz, 2 H, 5′-H_2), 2.38 (br. d, $J_{2''\text{-}OH,2''}$ = 5.6 Hz, 1 H, 2′′-OH), AB signal (δ_A = 3.17, δ_B = 3.20, J_{AB} = 13.6 Hz, A part additionally split by $J_{A,2''}$ = 5.1 Hz, B part additionally split by $J_{B,2''}$ = 7.0 Hz, 2 H, 1′′-H_2), 3.84 (s, 3 H, OCH_3), 4.31 (m_c, possibly interpretable as br. ddq, $J_{2'',1''\text{-}H(A)} \approx J_{2'',1''\text{-}H(B)} \approx J_{2'',3''} \approx$ 6.0 Hz, 1 H, 2′′-H), 5.54 (d, $J_{1',2'}$ = 15.5 Hz, 1 H, 1′-H), 5.81 (dt, $J_{4',3'}$ = 15.2 Hz, $J_{4',5'}$ = 6.3 Hz, 1 H, 4′-H), 5.98 (br. dd, $J_{3',4'}$ = 15.2 Hz, $J_{3',2'}$ = 10.2 Hz, 1 H, 3′-H), 6.31 (dd, $J_{2',1'}$ = 15.4 Hz, $J_{2',3'}$ = 10.0 Hz, 1 H, 2′-H) ppm. ^{1}H NMR (499.6 MHz, C_6D_6): δ = 0.82 (t, $J_{6',5'}$ = 7.4 Hz, 3 H, 6′-H_3), 1.03 (d, $J_{3'',2''}$ = 6.0 Hz, 3 H, 3′′-H_3), 1.33 (s, 3 H, 5-CH_3), 1.85 (m_c, possibly interpretable as br. qd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.4 Hz, 2 H, 5′-H_2), 2.07 (br. d, $J_{2''\text{-}OH,2''}$ = 6.0 Hz, 1 H, 2′′-OH), AB signal (δ_A = 2.85, δ_B = 2.91, J_{AB} = 13.2 Hz, A part additionally split by $J_{A,2''}$ = 4.7 Hz, B part additionally split by $J_{B,2''}$ = 7.7 Hz, 2 H, 1′′-H_2), 3.47 (s, 3 H, OCH_3), 4.05 (m_c, 1 H, 2′′-H), 5.52 (d, $J_{1',2'}$ = 15.8 Hz, 1 H, 1′-H), superimposed by 5.56 (dt, $J_{4',3'}$ = 14.9 Hz, $J_{4',5'}$ = 6.9 Hz, 1 H, 4′-H), 5.82 (br. dd, $J_{3',4'}$ = 15.3 Hz, $J_{3',2'}$ = 10.6 Hz, 1 H, 3′-H)^A, 6.42 (dd, $J_{2',1'}$ = 15.4 Hz, $J_{2',3'}$ = 10.4 Hz, 1 H, 2′-H)^A ppm; ^{A} the indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (499.6 MHz, C_6D_6)] by their crosspeaks with protons that had previously been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 5.82 (dd, 3′-H) ↔ δ = 5.56 (dt, 4′-H) and δ = 5.82 (dd, 3′-H) ↔ δ = 6.42 (dd, 2′-H); δ = 6.42 (dd, 2′-H) ↔ δ = 5.52 (d, 1′-H) and δ = 6.42 (dd, 2′-H) ↔ δ = 5.82 (dd, 3′-H). ^{13}C NMR (125.6 MHz, C_6D_6): δ = 13.39 (C-6′)^A, 22.38 (5-CH_3)^A, 23.91 (C-3′′)^A, 25.88 (C-5′)^A, 40.31 (C-1′′)^A, 51.13 (OCH_3)^A, 66.20 (C-2′′)^A, 91.29 (C-5)^B, 108.08 (C-3)^B, 126.53 (C-1′)^A, 128.44 (C-3′)^A, 131.95 (C-2′)^A, 138.91 (C-4′)^A, 164.45 (C-1′′′)^B, 195.57 (C-2)^B, 196.41 (C-4)^B; ^{A} the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ("short-range C,H-COSY spectrum"; 125.6/499.6 MHz, C_6D_6) by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 0.82 (t, 6′-H_3) ↔ δ_C = 13.39 (C-6′), δ_H = 1.03 (d, 3′′-H_3) ↔ δ_C = 23.91 (C-3′′), δ_H = 1.33 (s, 5-CH_3) ↔ δ_C = 22.38 (5-CH_3), δ_H = 1.85 (m_c, 5′-H_2) ↔ δ_C = 25.88 (C-5′), δ_H = 2.85 (dd, 1′′-H^1) and 2.91 (dd, 1′′-H^2) ↔ δ_C = 40.31 (C-1′′), δ_H = 3.47 (s, OCH_3) ↔ δ_C = 51.13 (OCH_3), δ_H = 5.52 (d, 1′-H) ↔ δ_C = 126.5.3 (C-1′), δ_H = 5.56 (dt, 4′-H) ↔ δ_C = 138.91 (C-4′), δ_H = 5.82 (dd, 3′-H) ↔ δ_C = 128.44 (C-3′), δ_H = 6.42 (dd, 2′-H) ↔ δ_C = 131.95 (C-2′); ^{B} the indicated nuclei – they are quaternary – were distinguished in an HMBC spectrum ["long-range C,H-COSY spectrum" (125.6 MHz/499.6 MHz), C_6D_6] by their crosspeaks due to ^2J and/or ^3J and/or ^4J couplings to "remote" protons (these had

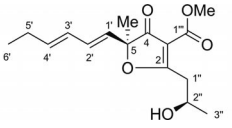
previously been assigned unequivocally): for δ_C = 91.29 (C-5) such crosspeaks were due to $^3J_{2'\text{-H,C-5}}$, $^2J_{1'\text{-H,C-5}}$, and $^2J_{5\text{-Me,C-5}}$; for δ_C = 108.08 (C-3) such crosspeaks were due to $^4J_{\text{OMe,C-3}}$ and $^3J_{1''\text{-H,C-3}}$; for δ_C = 164.45 (C-1‴) such a crosspeak was due to $^3J_{\text{OMe,C-1‴}}$; for δ_C = 195.57 (C-2) such crosspeaks were due to $^3J_{2''\text{-H,C-2}}$ and $^2J_{1''\text{-H,C-2}}$; for δ_C = 196.41 (C-4) such crosspeaks were due to $^3J_{1'\text{-H,C-4}}$ and $^3J_{5\text{-Me,C-4}}$. IR ($CHCl_3$): $\tilde{\nu}$ = 3475, 3020, 2965, 2930, 2875, 1740 (shoulder), 1710, 1655, 1580, 1440, 1390, 1345, 1300, 1205, 1165, 1120, 1070, 1040, 990, 935, 850, 770 cm^{-1}. HRMS (CI): calcd. for $C_{16}H_{22}O_5$ $[M + H]^+$ 295.15455; found 295.15410 (Δ = –1.5 ppm!); $C_{16}H_{22}O_5$ (294.3): calcd. C 65.29, H 7.53; found C 64.99, H 7.56.

Methyl {(*R*)-5-[(1′*E*,3′*Z*)-Hexa-1,3-dienyl]-2-[(*R*)-2-hydroxypropyl]-5-methyl-4-oxo-4,5-dihydrofuran-3-yl}carboxylate [(1′*E*,3′*Z*)-(5*R*,2′′*R*)-4c] = *cis*-Gregatin D



This product emerged from the HPLC purification of gregatin D [(*E*,*E*)-(5*R*,2′′*R*)-**4c**; cf. above]. The yield of this compound was too small for determination of its $[\alpha]_D^{20}$ value with sufficient precision. ^{1}H NMR (499.6 MHz, C_6D_6): δ = 0.80 (t, $J_{6',5'}$ = 7.6 Hz, 3 H, 6′-H_3), 1.00 (d, $J_{3'',2''}$ = 6.3 Hz, 3 H, 3′′-H_3), 1.31 (s, 3 H, 5-CH_3), 1.85 (br. d, $J_{2''\text{-OH},2''}$ = 5.7 Hz, 1 H, 2′′-OH), 2.04 (m_c, possibly interpretable as qdd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.5 Hz, $J_{5',3'}$ = 1.3 Hz, 2 H, 5′-H_2), AB signal (δ_A = 2.79, δ_B = 2.90, J_{AB} = 13.2 Hz, A part additionally split by $J_{A,2''}$ = 7.9 Hz, B part additionally split by $J_{B,2''}$ = 4.4 Hz, 2 H, 1′′-H_2), 3.44 (s, 3 H, OCH_3), 4.02 (m_c, 1 H, 2′′-H), 5.35 (dt, $J_{4',3'}$ = 10.7 Hz, $J_{4',5'}$ = 7.6 Hz, 1 H, 4′-H), 5.63 (d, $J_{1',2'}$ = 15.1 Hz, 1 H, 1′-H), 5.84 (br. dd, $J_{3',4'} = J_{3',2'}$ = 10.9 Hz, 1 H, 3′-H)^A, 6.83 (dd, $J_{2',1'}$ = 15.4 Hz, $J_{2',3'}$ = 11.0 Hz, 1 H, 2′-H)^A ppm; ^{A} the indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (499.6 MHz, C_6D_6)] by their crosspeaks with protons that had previously been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 5.84 (dd, 3′-H) $\leftrightarrow \delta$ = 5.35 (dt, 4′-H) and δ = 5.84 (dd, 3′-H) $\leftrightarrow \delta$ = 6.83 (dd, 2′-H); δ = 6.83 (dd, 2′-H) $\leftrightarrow \delta$ = 5.63 (d, 1′-H) and δ = 6.83 (dd, 2′-H) $\leftrightarrow \delta$ = 5.84 (dd, 3′-H). ^{13}C NMR (125.6 MHz, C_6D_6): δ = 14.14 (C-6′)^A, 21.38 (C-5′)^A, 22.54 (5-CH_3)^A, 23.92 (C-3′′)^A, 40.29 (C-1′′)^A, 51.11 (OCH_3)^A, 66.29 (C-2′′)^A, 91.31 (C-5)^B, 107.98 (C-3)^B, 126.39 (C-2′)^A, 126.99 (C-3′)^A, 128.74 (C-1′)^A, 136.39 (C-4′)^A, 164.41 (C-1‴)^B, 195.60 (C-2)^B, 196.20 (C-4)^B ppm; ^{A} the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ("short-range C,H-COSY spectrum"; 125.6/499.6 MHz, C_6D_6) by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 0.80 (t, 6′-H_3) $\leftrightarrow \delta_C$ = 14.14 (C-6′), δ_H = 1.00 (d, 3′′-H_3) $\leftrightarrow \delta_C$ = 23.92 (C-3′′), δ_H = 1.31 (s, 5-CH_3) $\leftrightarrow \delta_C$ = 22.54 (5-CH_3), δ_H = 2.04 (m_c, 5′-H_2) $\leftrightarrow \delta_C$ = 21.38 (C-5′), δ_H = 2.79 (dd, 1′′-H^1) and 2.90 (dd, 1′′-H^2) $\leftrightarrow \delta_C$ = 40.29 (C-1′′), δ_H = 3.44 (s, OCH_3) $\leftrightarrow \delta_C$ = 51.11 (OCH_3), δ_H = 5.35 (dt, 4′-H) $\leftrightarrow \delta_C$ = 136.39 (C-4′), δ_H = 5.63 (d, 1′-H) $\leftrightarrow \delta_C$ = 128.74 (C-1′), δ_H = 5.84 (dd, 3′-H) $\leftrightarrow \delta_C$ = 126.99 (C-3′), δ_H = 6.83 (dd, 2′-H) $\leftrightarrow \delta_C$ = 126.39 (C-2′); ^{B} the indicated nuclei – they are quaternary – were distinguished in an HMBC spectrum ["long-range C,H-COSY spectrum" (125.6 MHz/499.6 MHz), C_6D_6] by their crosspeaks due to ^2J and/or ^3J couplings to "remote" protons (these had previously been assigned unequivocally): for δ_C = 91.31 (C-5) such crosspeaks were due to $^3J_{2'\text{-H,C-5}}$, $^2J_{1'\text{-H,C-5}}$, and $^2J_{5\text{-Me,C-5}}$; for δ_C = 107.98 (C-3) such a crosspeak was due to $^3J_{1''\text{-H,C-3}}$; for δ_C = 164.41 (C-1‴) such a crosspeak was due to $^3J_{\text{OMe,C-1‴}}$; for δ_C = 195.60 (C-2) such a crosspeak was due to $^2J_{1''\text{-H,C-2}}$; for δ_C = 196.20 (C-4) such crosspeaks were due to $^3J_{1'\text{-H,C-4}}$ and $^3J_{5\text{-Me,C-4}}$.

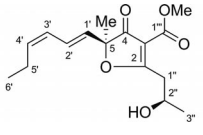
Methyl {(*S*)-5-[(*E*,*E*)-Hexa-1,3-dienyl]-2-[(*R*)-2-hydroxypropyl]-5-methyl-4-oxo-4,5-dihydrofuran-3-yl}carboxylate [(–)-(*E*,*E*)-(5*S*,2′′*R*)-4′c] = Antipode of Gregatin C



A mixture (93:7) of (*E*,*E*)-(5*S*,2′′*R*)-**80c** and (1′*E*,3′*Z*)-(5*S*,2′′*R*)-**80c** (80.0 mg, 196 μmol) was dissolved in a mixture [4:1:2 (v/v/v), 7.0 mL] of THF/MeOH/HCl (10%) and was stirred at room temp. for 6 h. A buffered aqueous phosphate solution (pH = 7.0, 7.0 mL) was added, and the resulting mixture was extracted with EtOAc (4 × 10 mL). Drying of the combined organic phases with $MgSO_4$, removal of the volatiles under reduced pressure, and purification by flash chromatography[77] (2.5 cm, 20 mL, C_6H_{12}/EtOAc 1:1, #4–5 and #7–16) provided aspertetronin A [(*E*,*E*)-(*S*)-**2c**, slightly yellow solid, 1.2 mg, 2.2%] in fractions 4–5 and the title compound (51.9 mg, 90%) as a colorless oil in fractions 7–16. The diastereopurity of product (*E*,*E*)-**4′c** corresponded to 92% *de* with respect to the stereocenter at C-5 and the diastereopurity of the major diastereomer (5*S*,2′′*R*)-**4c** to an (*E*,*E*)/(1′*E*,3′*Z*) ratio of 94:6 with respect to the stereogenic C=C bonds, both according to analytical HPLC: Chiralpak AD-H column; *n*-heptane/MeOH 9:1, 1.0 mL min^{-1}; $\lambda_{detector}$ = 230 nm. $t_{r\,(E,E)\text{-}(5R,2''R)\text{-}4'c}$ = 11.48 min, $t_{r\,(E,E)\text{-}(5S,2''R)\text{-}4'c}$ = 14.25 min, $t_{r\,(1'E,3'Z)\text{-}(5S,2''R)\text{-}4'c}$ = 12.33 min [(*E*,*E*)-(5*S*,2′′*R*)-**4′c**/(*E*,*E*)-(5*R*,2′′*R*)-**4′c** = 96:4 (→ 92% *de*); (*E*,*E*)-(5*S*,2′′*R*)-**4′c**/(1′*E*,3′*Z*)-(5*S*,2′′*R*)-**4′c** = 94:6]. This mixture of (*E*,*E*)-(5*S*,2′′*R*)-**4′c**, (1′*E*,3′*Z*)-(5*S*,2′′*R*)-**4′c**, and (*E*,*E*)-(5*R*,2′′*R*)-**4′c** was separated into the constituents by preparative HPLC: Chiralpak AD-H column; *n*-heptane/*i*PrOH 92:8, 16 mL min^{-1}, $\lambda_{detector}$ = 230 nm. Room temp.; $t_{r\,(E,E)\text{-}(5s,2''R)\text{-}4'c}$ = 21.0 min, $t_{r\,(E,E)\text{-}(5R,2''R)\text{-}4'c}$ = 17.5 min, $t_{r\,(1'E,3'Z)\text{-}(5s,2''R)\text{-}4'c}$ = 19.0 min. Isomer-free (*E*,*E*)-(5*S*,2′′-*R*)-**4′c** (obtained by preparative HPLC) gave the following data: $[\alpha]_D^{20}$ = –169.7 (= first measurement; *c* = 0.54 in $CHCl_3$). $[\alpha]_D^{20}$ = –162.6 (= independent second measurement; *c* = 1.11 in $CHCl_3$). $[\alpha]_D^{20}$ = –163.2 (= independent third measurement; *c* = 1.27 in $CHCl_3$) {ref.[1a] $[\alpha]_D^{\text{no temp.}}$ = +152 (*c* = 0.93 in $CHCl_3$)}. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.99 (t, $J_{6',5'}$ = 7.5 Hz, 3 H, 6′-H_3), 1.35 (d, $J_{3'',2''}$ = 6.2 Hz, 3 H, 3′′-H_3), 1.55 (s, 3 H, 5-CH_3), 2.09 (m_c, possibly interpretable as br. qd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.1 Hz, 2 H, 5′-H_2), 2.44 (br. d, $J_{2''\text{-OH},2''}$ = 5.4 Hz, 1 H, 2′′-OH), AB signal (δ_A = 3.17, δ_B = 3.21, J_{AB} = 13.6 Hz, A part additionally split by $J_{A,2''}$ = 4.8 Hz, B part additionally split by $J_{B,2''}$ = 7.2 Hz, 2 H, 1′′-H_2), 3.84 (s, 3 H, OCH_3), 4.33 (m_c, 1 H, 2′′-H), 5.53 (d, $J_{1',2'}$ = 15.5 Hz, 1 H, 1′-H), 5.82 (dt, $J_{4',3'}$ = 15.0 Hz, $J_{4',5'}$ = 6.4 Hz, 1 H, 4′-H), 5.97 (br. dd, $J_{3',4'}$ = 15.1 Hz, $J_{3',2'}$ = 10.3, 1 H, 3′-H), 6.30 (dd, $J_{2',1'}$ = 15.5 Hz, $J_{2',3'}$ = 10.2 Hz, 1 H, 2′-H) ppm. ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.01 (t, $J_{6',5'}$ = 7.5 Hz, 3 H, 6′-H_3), 1.29 (d, $J_{3'',2''}$ = 6.3 Hz, 3 H, 3′′-H_3), 1.52 (s, 3 H, 5-CH_3), 2.10 (m_c, possibly interpretable as br. qd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.3 Hz, 2 H, 5′-H_2), AB signal (δ_A = 3.14, δ_B = 3.25, J_{AB} = 13.7 Hz, A part additionally split by $J_{A,2''}$ = 5.2 Hz, B part additionally split by $J_{B,2''}$ = 8.1 Hz, 2 H, 1′′-H_2), 3.78 (s, 3 H, OCH_3), 4.29 (m_c, possibly interpretable as qdd, $J_{2'',3''} \approx J_{2'',1''\text{-H(A)}} \approx J_{2'',1''\text{-H(B)}} \approx$ 6.4 Hz, 1 H, 2′′-H), 5.55 (d, $J_{1',2'}$ = 15.4 Hz, 1 H, 1′-H), 5.86 (dt, $J_{4',3'}$ = 15.1 Hz, $J_{4',5'}$ = 6.5 Hz, 1 H, 4′-H), 6.04 (br. dd, $J_{3',4'}$ = 15.2 Hz, $J_{3',2'}$ = 10.3 Hz, 1 H, 3′-H), 6.35 (dd, $J_{2',1'}$ = 15.5 Hz, $J_{2',3'}$ = 10.2 Hz, 1 H, 2′-H) ppm. ^{1}H NMR (499.6 MHz, C_6D_6): δ = 0.81

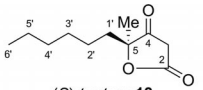
(t, $J_{6',5'}$ = 7.4 Hz, 3 H, 6′-H_3), 1.03 (d, $J_{3'',2''}$ = 6.3 Hz, 3 H, 3′′-H_3), 1.34 (s, 3 H, 5-CH_3), 1.85 (m_c, possibly interpretable as br. qd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.4 Hz, 2 H, 5′-H_2), 2.10 (br. d, $J_{2''\text{-OH},2''}$ = 5.7 Hz, 1 H, 2′′-OH), AB signal (δ_A = 2.81, δ_B = 2.95, J_{AB} = 13.4 Hz, A part additionally split by $J_{A,2''}$ = 4.6 Hz, B part additionally split by $J_{B,2''}$ = 7.7 Hz, 2 H, 1′′-H_2), 3.45 (s, 3 H, OCH_3), 4.07 (m_c, 1 H, 2′′-H), 5.50 (d, $J_{1',2'}$ = 15.4 Hz, 1 H, 1′-H), 5.56 (dt, $J_{4',3'}$ = 14.8 Hz, $J_{4',5'}$ = 6.9 Hz, 1 H, 4′-H), 5.81 (br. dd, $J_{3',4'}$ = 15.1 Hz, $J_{3',2'}$ = 10.4 Hz, 1 H, 3′-H)[A], 6.41 (dd, $J_{2',1'}$ = 15.4 Hz, $J_{2',3'}$ = 10.4 Hz, 1 H, 2′-H)[A] ppm; [A] the indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (499.6 MHz, C_6D_6)] by their crosspeaks with protons that had previously been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 5.81 (dd, 3′-H) ↔ δ = 5.56 (dt, 4′-H) and δ = 5.81 (dd, 3′-H) ↔ δ = 6.41 (dd, 2′-H); δ = 6.41 (dd, 2′-H) ↔ δ = 5.50 (d, 1′-H) and δ = 6.41 (dd, 2′-H) ↔ δ = 5.81 (dd, 3′-H). ^{13}C NMR (125.6 MHz, C_6D_6): δ = 13.36 (C-6′)[A], 22.36 (5-CH_3)[A], 23.74 (C-3′′)[A], 25.87 (C-5′)[A], 40.14 (C-1′′)[A], 51.15 (OCH_3)[A], 66.13 (C-2′′)[A], 91.21 (C-5)[B], 108.23 (C-3)[B], 126.41 (C-1′)[A], 128.38 (C-3′)[A], 132.00 (C-2′)[A], 138.97 (C-4′)[A], 164.53 (C-1′′′)[B], 195.43 (C-2)[B], 196.37 (C-4)[B]; [A] the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ("short-range C,H-COSY spectrum"; 125.6/499.6 MHz, C_6D_6) by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 0.82 (t, 6′-H_3) ↔ δ_C = 13.36 (C-6′), δ_H = 1.03 (d, 3′′-H_3) ↔ δ_C = 23.74 (C-3′′), δ_H = 1.34 (s, 5-CH_3) ↔ δ_C = 22.36 (5-CH_3), δ_H = 1.85 (m_c, 5′-H_2) ↔ δ_C = 25.87 (C-5′), δ_H = 2.81 (dd, 1′′-H^1) and 2.95 (dd, 1′′-H^2) ↔ δ_C = 40.14 (C-1′′), δ_H = 3.45 (s, OCH_3) ↔ δ_C = 51.15 (OCH_3), δ_H = 5.50 (d, 1′-H) ↔ δ_C = 126.41 (C-1′), δ_H = 5.56 (dt, 4′-H) ↔ δ_C = 138.97 (C-4′), δ_H = 5.81 (dd, 3′-H) ↔ δ_C = 128.38 (C-3′), δ_H = 6.41 (dd, 2′-H) ↔ δ_C = 132.00 (C-2′); [B] the indicated nuclei – they are quaternary – were distinguished in an HMBC spectrum ["long-range C,H-COSY spectrum" (125.6 MHz/499.6 MHz), C_6D_6] by their crosspeaks due to ^2J and/or ^3J couplings to "remote" protons (these had previously been assigned unequivocally): for δ_C = 91.21 (C-5) such crosspeaks were due to $^3J_{2'\text{-H},C\text{-}5}$, $^2J_{1'\text{-H},C\text{-}5}$, and $^2J_{5\text{-Me},C\text{-}5}$; for δ_C = 108.23 (C-3) such a crosspeak was due to $^4J_{OMe,C\text{-}3}$ and $^3J_{1''\text{-H},C\text{-}3}$; for δ_C = 164.53 (C-1′′′) such a crosspeak was due to $^3J_{OMe,C\text{-}1'''}$; for δ_C = 195.43 (C-2) such crosspeaks were due to $^3J_{2''\text{-H},C\text{-}2}$ and $^2J_{1''\text{-H},C\text{-}2}$; for δ_C = 196.37 (C-4) such crosspeaks were due to $^3J_{1'\text{-H},C\text{-}4}$ and $^3J_{5\text{-Me},C\text{-}4}$. IR ($CHCl_3$): $\tilde{\nu}$ = 3475, 2965, 2930, 2875, 1740 (shoulder), 1710, 1655, 1580, 1440, 1390, 1345, 1295, 1215, 1200, 1120, 1065, 1040, 990, 935, 920, 850, 775, 670 cm^{-1}. HRMS (EI, 70 eV): calcd. for $C_{16}H_{22}O_5$ $[M]^+$ 294.14672; found 294.14720 (Δ = +1.6 ppm). $C_{16}H_{22}O_5$ (294.3): calcd. C 65.29, H 7.53; found C 65.29, H 7.55.

Methyl {(*S*)-5-[(1′*E*,3′*Z*)-Hexa-1,3-dienyl]-2-[(*R*)-2-hydroxypropyl]-5-methyl-4-oxo-4,5-dihydrofuran-3-yl}carboxylate [(1′*E*,3′*Z*)-(5*S*,2′′-*R*)-4′c**] = Antipode of *cis*-Gregatin C**



This product emerged from the HPLC purification of the antipode [(–)-(*E*,*E*)-(5*S*,2′′-*R*)-**4′c**; cf. above] of gregatin C. The yield of this compound was too small for determination of its $[a]_D^{20}$ value with sufficient precision. ^{1}H NMR (499.6 MHz, C_6D_6): δ = 0.81 (t, $J_{6',5'}$ = 7.4 Hz, 3 H, 6′-H_3), 1.00 (d, $J_{3'',2''}$ = 6.3 Hz, 3 H, 3′′-H_3), 1.33 (s, 3 H, 5-CH_3), 1.94 (br. d, $J_{2''\text{-OH},2''}$ = 5.7 Hz, 1 H, 2′′-OH), 2.04 (m_c, possibly interpretable as qdd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.0 Hz, $J_{5',3'}$ = 1.3 Hz, 2 H, 5′-H_2), 2.73 (dd, J_{gem} = 13.4 Hz, $J_{1''\text{-H}(1),2''}$ = 4.6 Hz, 1 H, 1′′-H^1), 2.99 (dd, J_{gem} = 13.4 Hz, $J_{1''\text{-H}(2),2''}$ = 7.2 Hz, 1 H, 1′′-H^2), 3.44 (s, 3 H, OCH_3), 4.04 (m_c, 1 H, 2′′-H), 5.35 (dt, $J_{4',3'}$ = 10.7 Hz, $J_{4',5'}$ = 7.6 Hz, 1 H, 4′-H), 5.61 (d, $J_{1',2'}$ = 15.4 Hz, 1 H, 1′-H), 5.83 (br. dd, $J_{3',4'}$ = $J_{3',2'}$ = 10.9 Hz, 1 H, 3′-H)[A], 6.82 (ddd, $J_{2',1'}$ = 15.3 Hz, $J_{2',3'}$ = 11.2 Hz, $J_{2',4'}$ = 1.0 Hz, 1 H, 2′-H)[A] ppm; [A] the indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (499.6 MHz, C_6D_6)] by their crosspeaks with protons that had previously been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 5.83 (dd, 3′-H) ↔ δ = 5.35 (dt, 4′-H) and δ = 5.83 (dd, 3′-H) ↔ δ = 6.82 (ddd, 2′-H); δ = 6.82 (ddd, 2′-H) ↔ δ = 5.61 (d, 1′-H) and δ = 6.82 (ddd, 2′-H) ↔ δ = 5.83 (dd, 3′-H). ^{13}C NMR (125.6 MHz, C_6D_6): δ = 14.14 (C-6′)[A], 21.37 (C-5′)[A], 22.46 (5-CH_3)[A], 23.68 (C-3′′)[A], 40.11 (C-1′′)[A], 51.12 (OCH_3)[A], 66.11 (C-2′′)[A], 91.21 (C-5)[B], 108.20 (C-3)[B], 126.46 (C-2′)[A], 126.94 (C-3′)[A], 128.59 (C-1′)[A], 136.48 (C-4′)[A], 164.47 (C-1′′′)[B], 195.40 (C-2)[B], 196.20 (C-4)[B] ppm; [A] the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ("short-range C,H-COSY spectrum"; 125.6/499.6 MHz, C_6D_6) by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 0.81 (t, 6′-H_3) ↔ δ_C = 14.14 (C-6′), δ_H = 1.00 (d, 3′′-H_3) ↔ δ_C = 23.68 (C-3′′), δ_H = 1.33 (s, 5-CH_3) ↔ δ_C = 22.46 (5-CH_3), δ_H = 2.04 (m_c, 5′-H_2) ↔ δ_C = 21.37 (C-5′), δ_H = 2.73 (dd, 1′′-H^1) and 2.99 (dd, 1′′-H^2) ↔ δ_C = 40.11 (C-1′′), δ_H = 3.44 (s, OCH_3) ↔ δ_C = 51.12 (OCH_3), δ_H = 5.35 (dt, 4′-H) ↔ δ_C = 136.48 (C-4′), δ_H = 5.61 (d, 1′-H) ↔ δ_C = 128.59 (C-1′), δ_H = 5.83 (dd, 3′-H) ↔ δ_C = 126.94 (C-3′), δ_H = 6.82 (dd, 2′-H) ↔ δ_C = 126.46 (C-2′); [B] the indicated nuclei – they are quaternary – were distinguished in an HMBC spectrum ["long-range C,H-COSY spectrum" (125.6 MHz/499.6 MHz), C_6D_6] by their crosspeaks due to ^2J and/or ^3J couplings to "remote" protons (these had previously been assigned unequivocally): for δ_C = 91.21 (C-5) such crosspeaks were due to $^3J_{2'\text{-H},C\text{-}5}$, $^2J_{1'\text{-H},C\text{-}5}$, and $^2J_{5\text{-Me},C\text{-}5}$; for δ_C = 108.20 (C-3) such a crosspeak was due to $^3J_{1''\text{-H},C\text{-}3}$; for δ_C = 164.47 (C-1′′′) such a crosspeak was due to $^3J_{OMe,C\text{-}1'''}$; for δ_C = 195.40 (C-2) such a crosspeak was due to $^2J_{1''\text{-H},C\text{-}2}$; for δ_C = 196.20 (C-4) such crosspeaks were due to $^3J_{1'\text{-H},C\text{-}4}$ and $^3J_{5\text{-Me},C\text{-}4}$.

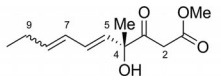
(–)-(*S*)-5-Hexyl-5-methyl-2,4(3*H*,5*H*)-furandione [(–)-(*S*)-*tautom*-18]



(*S*)-*tautom*-**18**

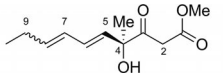
A solution of hydroxy-oxo ester (*S*)-**30** (crude product, 24.7 mg, 107 μmol) in a mixture [4:1:2 (v/v/v), 1.0 mL] of THF/MeOH/HCl (10%) was stirred at room temp. for 2 h. The mixture was extracted with EtOAc (6× 1 mL). The combined organic phases were dried with $MgSO_4$. Removal of the volatiles under reduced pressure and purification by flash chromatography[77] on silica gel, which had been deactivated with 3% (m/m) H_2O (2.0 cm, 10 mL, C_6H_{12}/EtOAc 1:50, #3–14) provided the title compound (1.8 mg, 8.5%) as a colorless solid. $[a]_D^{20}$ = –13.6 (c = 0.18 in $CHCl_3$). ^{1}H NMR (400.1 MHz, $CDCl_3$; pure keto tautomer): δ = 0.87 (t, $J_{6',5'}$ = 6.9 Hz, 3 H, 6′-H_3), 1.17–1.66 (m, 8 H, 2′-H_2, 3′-H_2, 4′-H_2, 5′-H_2), superimposed by 1.47 (s, 3 H, 5-CH_3), 1.74–1.86 (m, 2 H, 1′-H_2) ppm; AB signal (δ_A = 3.14, δ_B = 3.23, J_{AB} = 22.6 Hz, 2 H, 3-H_2).

Methyl (*E*,*E*)-(*R*)-4-Hydroxy-4-methyl-3-oxodeca-5,7-dienoate [(*E*,*E*)-(*R*)-29, Containing Enol Tautomer (4%)] in a Mixture (92:8) with Methyl (1′*E*,3′*Z*)-(*R*)-4-Hydroxy-4-methyl-3-oxodeca-5,7-dienoate [(1′*E*,3′*Z*)-(*R*)-29]



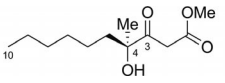
*n*BuLi (2.3 M in hexanes, 15.3 mL, 35.1 mmol, 4.0 equiv.) was added at –78 °C to a solution of diisopropylamine (4.9 mL, 3.6 g, 35 mmol, 4.0 equiv.) in THF (150 mL). After the mixture had been stirred for 15 min, a solution of methyl acetate (2.8 mL, 2.6 g, 35 mmol, 4.0 equiv.) in THF (2 mL) was added over 5 min. After the mixture had been stirred for another 30 min, a solution of a mixture (93:7) of the acetals (*E*,*E*)-(2*S*,5*R*)-**46** and (1′*E*,3′*Z*)-(2*S*,5*R*)-**46** (2.09 g, 8.77 mmol) in THF (2 mL) was added. The mixture was stirred at –78 °C for 30 min, the cooling bath was removed, and the mixture was allowed to gradually reach room temp. After 60 min, a saturated aqueous NH_4Cl solution (100 mL) was added. Extraction with Et_2O (4 × 100 mL), drying of the combined organic phases with $MgSO_4$, and flash chromatography[77] [6.0 cm, 50 mL, petroleum ether (bp. 30–50 °C)/Et_2O 6:1, #25–60] yielded the title compound (1.536 g, 77%) as a colorless oil. The ratio between (*E*,*E*)-(*R*)-**29** and (1′*E*,3′*Z*)-(*R*)-**29** was 92:8 according to the integral ratio of δ = 1.89 [m_c, 2 H of both tautomers of (*E*,*E*)-(*R*)-**29**: 9-H_2] versus δ = 2.04 [m_c, 2 H of (1′*E*,3′*Z*)-(*R*)-**29**: 9-H_2] in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$). Compound (*E*,*E*)-(*R*)-**29** was a mixture (96:4) of the keto and the enol tautomer according to the integral ratio of δ = 3.15 [s, 1 H of the keto tautomer of (*E*,*E*)-(*R*)-**29**: 4-OH] versus δ = 12.80 [s, 1 H of the keto tautomer of (*E*,*E*)-(*R*)-**29**: 3-OH] in the same ^{1}H NMR spectrum (400 MHz, $CDCl_3$). $[a]_D^{20}$ = +29.6 (*c* = 1.1 in $CHCl_3$). ^{1}H NMR [400.1 MHz, C_6D_6; most resonances of (1′*E*,3′*Z*)-(*R*)-**29** are visible, but all resonances (except 3-OH) of enol-(*E*,*E*)-(*R*)-**29** are superimposed]: δ = 0.83 [t, $J_{10,9}$ = 7.5 Hz, 3 H of (1′*E*,3′*Z*)-**29**, 10-H_3], 0.85 [t, $J_{10,9}$ = 7.5 Hz, 3 H of keto-(*E*,*E*)-(*R*)-**29**, 10-H_3], 1.25 [s, 3 H of (1′*E*,3′*Z*)-**29**, 4-CH_3], 1.26 [s, 3 H of keto-(*E*,*E*)-(*R*)-**29**, 4-CH_3], 1.89 [m_c, interpretable as qdd, $J_{9,10} \approx J_{9,8} \approx$ 7.2 Hz, $J_{9,7}$ = 1.2 Hz, 2 H of keto-(*E*,*E*)-(*R*)-**29**, 9-H_2], 2.04 [m_c, interpretable as qdd, $J_{9,10} \approx J_{9,8} \approx$ 7.5 Hz, $J_{9,7}$ = 1.5 Hz, 2 H of (1′*E*,3′*Z*)-**29**, 9-H_2], 3.15 [br. s, 1 H of keto-(*E*,*E*)-(*R*)-**29**, 4-OH], 3.24 [s, 3 H of (1′*E*,3′*Z*)-**29**, OCH_3], 3.25 [s, 3 H of keto-(*E*,*E*)-(*R*)-**29**, OCH_3], superimposed by AB signal [δ_A = 3.25, δ_B = 3.41, J_{AB} = 15.7 Hz, 2 H of keto-(*E*,*E*)-(*R*)-**29**, 2-H_2], superimposed by B-part of AB signal [δ_B = 3.39, J_{AB} = 15.8 Hz, 2 H of (1′*E*,3′*Z*)-**29**, 2-H_2], 5.36 [dt, $J_{8,7}$ = 10.8 Hz, $J_{8,9}$ = 7.6 Hz, 1 H of (1′*E*,3′*Z*)-**29**, 8-H], superimposed by 5.43 [d, $J_{5,6}$ = 15.3 Hz, 1 H of keto-(*E*,*E*)-(*R*)-**29**, 5-H], 5.57 [dt, $J_{8,7}$ = 15.2 Hz, $J_{8,9}$ = 6.6 Hz, 1 H of keto-(*E*,*E*)-(*R*)-**29**, 8-H], 5.76 [d, $J_{5,6}$ = 15.4 Hz, 1 H of (1′*E*,3′*Z*)-**29**, 5-H], 5.88 [ddd, $J_{7,8}$ = 15.2 Hz, $J_{7,6}$ = 10.5 Hz, $J_{7,5}$ = 0.6 Hz, 1 H of keto-(*E*,*E*)-(*R*)-**29**, 7-H]^A, 6.39 [dd, $J_{6,5}$ = 15.3 Hz, $J_{6,7}$ = 10.5 Hz, 1 H of keto-(*E*,*E*)-(*R*)-**29**, 6-H]^A, 6.82 [ddd, $J_{6,5}$ = 15.2 Hz, $J_{6,7}$ = 11.1 Hz, $J_{6,8}$ = 1.1 Hz, 1 H of (1′*E*,3′*Z*)-**29**, 6-H], 12.80 [br. s, 1 H of enol-(*E*,*E*)-(*R*)-**29**, 3-OH] ppm; ^{A} the indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.1 MHz, C_6D_6)] by their crosspeaks with protons that had previously been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 5.88 (ddd, 7-H) ↔ δ = 1.89 (m_c, 9-H_2), δ = 5.88 (ddd, 7-H) ↔ δ = 5.57 (dt, 8-H), and δ = 5.88 (ddd, 7-H) ↔ δ = 6.39 (dd, 6-H); δ = 6.39 (dd, 6-H) ↔ δ = 5.43 (d, 5-H) and δ = 6.39 (dd, 6-H) ↔ δ = 5.88 (ddd, 7-H). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 13.47 (C-10)^A, 25.11 (4-CH_3)^A, 25.91 (C-9)^A, 43.40 (C-2)^A, 51.80 (1-OCH_3)^A, 79.79 (C-4), 128.73 (C-7)^A, 131.37 (C-5)^A, 131.69 (C-6)^A, 137.94 (C-8)^A, 167.82 (C-1), 204.25 (C-3); ^{A} the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.6/400.1 MHz, C_6D_6)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 0.85 (t, 10-H_3) ↔ δ_C = 13.47 (C-10), δ_H = 1.26 (s, 4-CH_3) ↔ δ_C = 25.11 (4-CH_3), δ_H = 1.89 (m_c, 9-H_2) ↔ δ_C = 25.91 (C-9), δ_H = 3.25 (dd, 2-H^1) and 3.41 (dd, 2-H^2) ↔ δ_C = 43.40 (C-2), δ_H = 3.25 (s, 1-OCH_3) ↔ δ_C = 51.80 (1-OCH_3), δ_H = 5.43 (d, 5-H) ↔ δ_C = 131.37 (C-5), δ_H = 5.57 (dt, 8-H) ↔ δ_C = 137.94 (C-8), δ_H = 5.88 (ddd, 7-H) ↔ δ_C = 128.73 (C-7), δ_H = 6.39 (dd, 6-H) ↔ δ_C = 131.69 (C-6). IR ($CHCl_3$): $\tilde{\nu}$ = 3480, 2960, 2935, 2875, 1745, 1715, 1655, 1625, 1435, 1400, 1365, 1320, 1265, 1230, 1205, 1185, 1135, 1110, 1060, 1040, 995, 960, 915, 740, 655 cm^{-1}. $C_{12}H_{18}O_4$ (226.3): calcd. C 63.70, H 8.02; found C 63.46, H 8.23.

Methyl (*E*,*E*)-(*S*)-4-Hydroxy-4-methyl-3-oxodeca-5,7-dienoate [(*E*,*E*)-(*S*)-29, Containing Enol Tautomer (5%)] in a Mixture (92:8) with Methyl (1′*E*,3′*Z*)-(*S*)-4-Hydroxy-4-methyl-3-oxodeca-5,7-dienoate [(1′*E*,3′*Z*)-(*S*)-29]



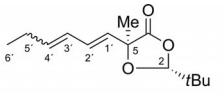
This compound (1.15 g, 76%), a colorless oil, was prepared as described for its enantiomer (*E*,*E*)-(*R*)-**29** from methyl acetate (2.1 mL, 2.0 g, 27 mmol, 4.0 equiv.) and a mixture (93:7) of acetals (*E*,*E*)-(2*R*,5*S*)-**46** and (1′*E*,3′*Z*)-(2*R*,5*S*)-**46** (1.60 g, 6.71 mmol). $[a]_D^{20}$ = –23.4 (*c* = 1.3 in $CHCl_3$). The isomeric and tautomeric compositions were determined in a way analogous to that described for (*E*,*E*)-(*R*)-**29**. The ^{1}H NMR spectrum (400.1 MHz, C_6D_6) was virtually identical with that of (*E*,*E*)-(*R*)-**29**. HRMS (CI): calcd. for $C_{12}H_{22}NO_4$ [M + NH_4]$^+$ 244.15488; found 244.15480 (Δ = –0.3 ppm).

Methyl (*S*)-4-Hydroxy-4-methyl-3-oxodecanoate [(*S*)-30]



A suspension of Pd/C [5% (w/w), 112 mg; contains 5.56 mg of Pd, 53.1 μmol, 10 mol-%] in a solution of the unsaturated hydroxy-oxo ester (*S*)-**29** (120.1 mg, 530.8 μmol) in MeOH (5 mL) was stirred under H_2 (1 bar) at room temp. for 1 h. The reaction mixture was filtered through a glass frit containing a pad of silica gel. The solvent was removed from the filtrate under reduced pressure, and the residue was purified by flash chromatography[77] (2.5 cm, 20 mL, C_6H_{12}/EtOAc 4:1, #12–19) to give the saturated hydroxy-oxo ester (*S*)-**30** (25.9 mg, 21%). This compound was carried on towards (–)-(*S*)-*tautom*-**18** without characterization.

(2*R*,5*S*)-2-*tert*-Butyl-5-[(*E*,*E*)-hexa-1,3-dienyl-5-methyl-1,3-dioxolan-4-one [(*E*,*E*)-(2*R*,5*S*)-46 ("*trans*")] in Mixtures [either 93:7 ("Preparation A") or 98:2 ("Preparation B")] with (2*R*,5*S*)-2-*tert*-Butyl-5-[(1′*E*,3′*Z*)-hexa-1,3-dienyl]-5-methyl-1,3-dioxolan-4-one [(1′*E*,3′*Z*)-(2*R*,5*S*)-46 ("*trans*")]



(*E*,*E*)-(2*R*,5*S*)-**46** ("*trans*")
+ (1′-*E*,3′-*Z*)-isomer

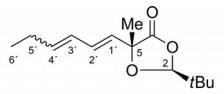
Procedure A: A solution of a mixture (93:7) of (2*R*,5*S*)-**58** ("*trans*") with (2*R*,5*R*)-**58** ("*cis*") (1.0 g, 3.9 mmol), NEt_3 (1.4 mL, 1.0 g, 10 mmol, 2.6 equiv.), and 2,4-dinitrobenzenesulfenyl chloride (2.20 g, 9.36 mmol, 2.4 equiv.) in 1,2-dichloroethane (35 mL) was heated at 85 °C for 5 h. Pentane (25 mL) was added, and the resulting precipitate was removed by filtration. The filtrate was liberated from volatiles under reduced pressure. Flash chromatography[77] [3.0 cm, 20 mL, petroleum ether (bp. 30–50 °C)/Et_2O 85:1, #11–27 and #31–46] provided a mixture (87:13, ref.[16] 100:0) of

the title compounds (735 mg, 79%) (*E*,*E*)-(2*R*,5*S*)-**46** ("*trans*") and (1′*E*,3′*Z*)-(2*R*,5*S*)-**46** ("*trans*") in fractions 11–27 and the diastereomer (*E*,*E*)-(2*R*,5*R*)-**46** ("*cis*"; 45.2 mg, 5%) in fractions 31–46. Treatment of a solution of the mixture (87:13) of the title compounds (*E*,*E*)-(2*R*,5*S*)-**46** ("*trans*") and (1′*E*,3′*Z*)-(2*R*,5*S*)-**46** ("*trans*") (735 mg, 79%) in benzene (2.5 mL) with iodine (cat.) for 12 h at room temp., filtration through silica gel, and concentration delivered a mixture (93:7) of (*E*,*E*)-(2*R*,5*S*)-**46** ("*trans*") and (1′*E*,3′*Z*)-(2*R*,5*S*)-**46** ("*trans*") (733.6 mg, 79%; ref.[16] 87%). The diastereopurity of (2*R*,5*S*)-**46** corresponded to an (*E*,*E*)/(1′*E*,3′*Z*) ratio of 93:7 and the enantiopurity of the major diastereomer (*E*,*E*)-**46** equaled 93% *ee*, both by analytical HPLC: Chiralpak AD-H column; *n*-heptane/*i*PrOH 200:1, 0.8 mL min^{-1}; $\lambda_{detector}$ = 230 nm; $t_{r\,(E,E)\text{-}(2R,5S)\text{-}46}$ = 9.76 min, $t_{r\,(1'E,3'Z)\text{-}(2R,5S)\text{-}46}$ = 7.76 min, $t_{r\,(E,E)\text{-}(2S,5R)\text{-}46}$ = 6.21 min [(*E*,*E*)-(2*R*,5*S*)-**46**/(*E*,*E*)-(2*S*,5*R*)-**46** = 96.5:3.5 (→ 93% *ee*); (*E*,*E*)-(2*R*,5*S*)-**4′c**/(1′*E*,3′*Z*)-(2*R*,5*S*)-**46** = 93:7]. $[\alpha]_D^{20}$ = –100.4 (*c* = 0.97 in MeOH) {ref.[16] $[\alpha]_D^{26}$ = –77.9 (*c* = 0.009 in MeOH)}.

Procedure B: A mixture (95:5) of (2*R*,5*S*)-**64** ("*trans*") and (2*R*,5*R*)-**64** ("*cis*") (100 mg, 299 µmol) in DBU (1.4 mL) was heated at 60 °C for 2 h. HCl [5% (w/w) in H_2O, 2 mL] was added at room temp., and the resulting mixture was extracted with Et_2O (4× 5 mL). After the combined organic phases had been dried with $MgSO_4$ the solvent was removed under reduced pressure and the residue was purified by flash chromatography[77] [2.0 cm, 20 mL, petroleum ether (bp. 30–50 °C)/Et_2O 40:1, #7–12]. This furnished a mixture (98:2) of (*E*,*E*)-(2*R*,5*S*)-**46** ("*trans*") and (1′*E*,3′*Z*)-(2*R*,5*S*)-**46** ("*trans*") (52.11 mg, 73%) as a colorless oil. The diastereopurity of (*E*,*E*)-**46** corresponded to an (*E*,*E*)/(1′*E*,3′*Z*) ratio of 98:2, and the enantiopurity of the major diastereomer (*E*,*E*)-**46** equalled 91% *ee*, both according to analytical HPLC: Chiralpak AD-H column; *n*-heptane/*i*PrOH 600:1, 0.5 mL min^{-1}; $\lambda_{detector}$ = 230 nm; $t_{r\,(E,E)\text{-}(2R,5S)\text{-}46}$ = 17.55 min, $t_{r\,(1'E,3'Z)\text{-}(2R,5S)\text{-}46}$ = 12.67 min, $t_{r\,(E,E)\text{-}(2S,5R)\text{-}46}$ = 13.61 min [(*E*,*E*)-(2*R*,5*S*)-**46**/(*E*,*E*)-(2*S*,5*R*)-**46** = 95.5:4.5 (→ 91% *ee*); (*E*,*E*)-(2*R*,5*S*)-**46**/(1′*E*,3′*Z*)-(2*R*,5*S*)-**46** = 98:2]. $[\alpha]_D^{20}$ = –100.4 (*c* = 0.97 in MeOH) {ref.[16] $[\alpha]_D^{26}$ = –77.9 (*c* = 0.009 in MeOH)}. $[\alpha]_D^{20}$ = –108.2 (*c* = 1.05 in $CDCl_3$).

^{1}H NMR (400.1 MHz, C_6D_6): δ = 0.78 [t, $J_{6',5'}$ = 7.5 Hz, 3 H of (1′*E*,3′*Z*)-(2*R*,5*S*)-**46**, 6′-H_3], superimposed by 0.81 [s, 9 H of (1′*E*,3′*Z*)-(2*R*,5*S*)-**46**, *t*Bu], 0.82 [s, 9 H of (*E*,*E*)-(2*R*,5*S*)-**46**, *t*Bu], superimposed by 0.83 [t, $J_{6',5'}$ = 7.5 Hz, 3 H of (*E*,*E*)-(2*R*,5*S*)-**46**, 6′-H_3], 1.42 [s, 3 H of (1′*E*,3′*Z*)-(2*R*,5*S*)-**46**, 5-CH_3], 1.43 [s, 3 H of (*E*,*E*)-(2*R*,5*S*)-**46**, 5-CH_3], 1.86 [m_c, possibly interpretable as qdd, $J_{5',4'} \approx J_{5',6'} \approx$ 7.2 Hz, $J_{5',3'}$ = 1.1 Hz, 2 H of (*E*,*E*)-(2*R*,5*S*)-**46**, 5′-H_2], 2.00 [m_c, possibly interpretable as qdd, $J_{5',4'} \approx J_{5',6'} \approx$ 7.5 Hz, $J_{5',3'}$ = 1.5 Hz, 2 H of (1′*E*,3′*Z*)-(2*R*,5*S*)-**46**, 5′-H_2], 4.94 [s, 1 H of (1′*E*,3′*Z*)-(2*R*,5*S*)-**46**, 2-H], 4.95 [s, 1 H of (*E*,*E*)-(2*R*,5*S*)-**46**, 2-H], 5.37 [dt, $J_{4',3'}$ = 10.9 Hz, $J_{4',5'}$ = 7.7 Hz, 1 H of (1′*E*,3′*Z*)-(2*R*,5*S*)-**46**, 4′-H], superimposed by 5.43 [d, $J_{1',2'}$ = 15.5 Hz, 1 H of both diastereomers, 1′-H], 5.51 [dt, $J_{4',3'}$ = 15.2 Hz, $J_{4',5'}$ = 6.6 Hz, 1 H of (*E*,*E*)-(2*R*,5*S*)-**46**, 4′-H], 5.85 [ddd, $J_{3',4'}$ = 15.2 Hz, $J_{3',2'}$ = 10.4 Hz, $J_{3',1'}$ = 0.6 Hz, 1 H of both diastereomers, 3′-H]^A, 6.43 [dd, $J_{2',1'}$ = 15.6 Hz, $J_{2',3'}$ = 10.4 Hz, 1 H of (*E*,*E*)-(2*R*,5*S*)-**46**, 2′-H]^A, 6.83 [ddd, $J_{2',1'}$ = 15.4 Hz, $J_{2',3'}$ = 11.1 Hz, $J_{2',4'}$ = 1.1 Hz, 1 H of (1′*E*,3′*Z*)-(2*R*,5*S*)-**46**, 2′-H] ppm; ^{A} the indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.1 MHz, C_6D_6)] by their crosspeaks with protons that had previously been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 5.85 (ddd, 3′-H) ↔ δ = 5.51 (dt, 4′-H), and δ = 5.85 (ddd, 3′-H) ↔ δ = 6.43 (dd, 2′-H); δ = 6.43 (dd, 2′-H) ↔ δ = 5.43 (d, 1′-H) and δ = 6.43 (dd, 2′-H) ↔ δ = 5.85 (ddd, 3′-H).

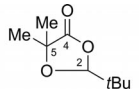
(2*S*,5*R*)-2-*tert*-Butyl-5-[(*E*,*E*)-hexa-1,3-dienyl]-5-methyl-1,3-dioxolan-4-one [(*E*,*E*)-(2*S*,5*R*)-46 ("*trans*")] in a Mixture (93:7) with (2*S*,5*R*)-2-*tert*-Butyl-5-[(1′*E*,3′*Z*)-hexa-1,3-dienyl]-5-methyl-1,3-dioxolan-4-one [(1′*E*,3′*Z*)-(2*S*,5*R*)-46 ("*trans*")]



(*E*,*E*)-(2*S*,5*R*)-**46** ("*trans*") + (1′-*E*,3′-*Z*)-isomer

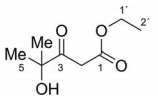
The title mixture was prepared from a mixture (95:5) of (2*S*,5*R*)-**58** ("*trans*") and (2*S*,5*S*)-**58** ("*cis*") (3.42 g, 13.3 mmol) analogously to "Procedure A" in our description of how we prepared the mixture (93:7) of the corresponding enantiomers (*E*,*E*)-(2*R*,5*S*)-**46** ("*trans*") and (1′*E*,3′*Z*)-(2*R*,5*S*)-**46** ("*trans*"). We obtained a mixture (93:7) of (*E*,*E*)-(2*S*,5*R*)-**46** ("*trans*") and (1′*E*,3′*Z*)-(2*S*,5*R*)-**46** ("*trans*") (2.36 g, 74%) as a yellowish oil. The diastereopurity of (2*S*,5*R*)-**46** corresponded to an (*E*,*E*)/(1′*E*,3′*Z*) ratio of 93:7, and the enantiopurity of the major diastereomer (*E*,*E*)-**46** equalled 90% *ee*, both according to analytical HPLC: Chiralpak AD-H column; *n*-heptane/*i*PrOH 200:1, 0.8 mL min^{-1}; $\lambda_{detector}$ = 230 nm; $t_{r\,(E,E)\text{-}(2S,5R)\text{-}46}$ = 5.88 min, $t_{r\,(1'E,3'Z)\text{-}(2S,5R)\text{-}46}$ = 5.50 min, $t_{r\,(E,E)\text{-}(2R,5S)\text{-}46}$ = 8.42 min [(*E*,*E*)-(2*S*,5*R*)-**46**/(*E*,*E*)-(2*R*,5*S*)-**46** = 95:5 (→ 93% *ee*); (*E*,*E*)-(2*S*,5*R*)-**46**/(1′*E*,3′*Z*)-(2*S*,5*R*)-**46** = 93:7]. $[\alpha]_D^{20}$ = +103.8 (*c* = 0.82 in MeOH). The ^{1}H NMR spectrum (400.1 MHz, C_6D_6) was virtually identical with that of the enantiomeric mixture.

2-*tert*-Butyl-5,5-dimethyl-1,3-dioxolan-4-one (49)



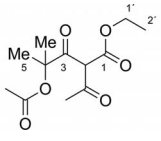
A solution of isobutyric acid (4.05 g, 38.9 mmol) in Et_2O (60 mL) was combined with pivaldehyde (5.00 mL, 3.85 g, 44.7 mmol, 1.15 equiv.) and $BF_3{\cdot}OEt_2$ (7.20 mL, 8.12 g, 57.2 mmol, 1.47 equiv.). The mixture was stirred at room temp. for 4 h, after which a saturated aqueous $NaHCO_3$ solution (150 mL) was added. The organic phase was separated and washed with saturated aqueous $NaHCO_3$ solution (2× 30 mL → pH = 9) and with H_2O (30 mL). The organic phase was dried with $MgSO_4$ and liberated from the solvent under reduced pressure. Distillation (0.5 mbar/30–34 °C) delivered the title compound (5.55 g, 83%) as a colorless oil. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.94 (s, 9 H, *t*Bu), 1.40 and 1.45 [2× s, 2× 3 H, 5-$(CH_3)_2$], 5.16 ppm (s, 1 H, 2-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.67 and 24.30 [5-$(CH_3)_2$]^A, 23.37 [C(CH_3)$_3$]^A, 34.28 [$C(CH_3)_3$], 77.30 (C-5), 107.41 (C-2)^A, 176.09 (C-4) ppm; ^{A} the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ("short-range C,H-COSY spectrum"; 100.6/400.1 MHz, $CDCl_3$) by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 0.94 (s, *t*Bu) ↔ δ_C = 23.37 [C(CH_3)$_3$], δ_H = 1.40 and 1.45 [2× s, 5-$(CH_3)_2$] ↔ δ_C = 21.67 and 24.30 [5-$(CH_3)_2$], δ_H = 5.16 (s, 2-H) ↔ δ_C = 107.41 (C-2). IR ($CHCl_3$): $\tilde{\nu}$ = 2975, 2935, 2875, 2905, 1900, 1485, 1460, 1435, 1405, 1385, 1360, 1345, 1285, 1270, 1210, 1180, 1155, 1080, 1035, 975, 940, 910, 880, 775, 745, 715, 610 cm^{-1}. $C_9H_{16}O_3$ (172.2): calcd. C 62.77, H 9.36; found C 62.52, H 9.26.

Ethyl 4-Hydroxy-4-methyl-3-oxopentanoate [50, Containing Enol Tautomer (5%)]



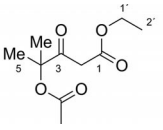
*n*BuLi (2.0 M in hexanes, 15.3 mL, 2.9 mmol, 2.0 equiv.) was added at –78 °C to a solution of diisopropylamine (0.41 mL, 0.29 g, 2.9 mmol, 2.0 equiv.) in THF (7 mL). After the mixture had been stirred for 30 min, a solution of ethyl acetate (0.28 mL, 0.26 g, 2.9 mmol, 2.0 equiv.) in THF (0.6 mL) was added. Stirring was continued for 40 min. A solution of acetal **49** (250 mg, 1.45 mmol) in THF (3 mL) was added. Stirring was continued at –78 °C for 60 min and also after removal of the cooling bath and until the mixture had gradually come to room temp. A saturated aqueous NH_4Cl solution (10 mL) was added. Extraction with Et_2O (4× 10 mL), drying of the combined organic phases with $MgSO_4$, and flash chromatography[77] (2.5 cm, 20 mL, C_6H_{12}/EtOAc 4:1, #10–18) furnished the title compound (186.4 mg, 74%) as a colorless oil and in a mixture (95:5) with the enol tautomer. This ratio was derived from the integrals over the following resonances in the ^1H NMR spectrum (400 MHz, $CDCl_3$): δ = 2.33 (s, 1 H of the enol tautomer, 4-OH) versus δ = 3.38 (s, 1 H of the keto tautomer, 4-OH). ^1H NMR (400.1 MHz, $CDCl_3$): $\delta_{keto\ tautomer}$ = 1.25 (t, $J_{2',1'}$ = 7.2 Hz, 3 H, 2′-H_3), 1.36 [s, 2× 3 H, 4-$(CH_3)_2$], 3.38 (s, 1 H, 4-OH), 3.63 (s, 2 H, 2-H_2), 4.17 (q, $J_{1',2'}$ = 7.2 Hz, 2 H, 1′-H_2) ppm; $\delta_{enol\ tautomer}$ = 1.25 (t, $J_{2',1'}$ = 7.2 Hz, 3 H, 2′-H_3), 1.39 [s, 2× 3 H, 4-$(CH_3)_2$], 2.33 (s, 1 H, 4-OH), 4.18 (q, $J_{1',2'}$ = 7.2 Hz, 2 H, 1′-H_2), 5.32 (s, 1 H, 2-H), 12.26 (s, 1 H, 3-OH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta_{keto\ tautomer}$ = 14.07 (C-2′)[A], 26.37 [4-$(CH_3)_2$][A], 43.68 (C-2)[A], 61.64 (C-1′)[A], 77.24 (C-4), 167.77 (C-1), 207.79 (C-3) ppm; $\delta_{enol\ tautomer}$ = 14.25, 27.72, 60.27, 71.68, 85.79, 173.28, and 182.13 ppm; [A] the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum"] (100.6/400.1 MHz, $CDCl_3$) by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 1.25 (t, 2′-H_3) $\leftrightarrow$ δ_C = 14.07 (C-2′), δ_H = 1.36 [s, 4-$(CH_3)_2$] $\leftrightarrow$ δ_C = 26.37 [4-$(CH_3)_2$], δ_H = 3.63 (s, 2-H_2) $\leftrightarrow$ δ_C = 43.68 (C-2), δ_H = 4.17 (q, 1′-H_2) $\leftrightarrow$ δ_C = 61.64 (C-1′). IR ($CHCl_3$): $\tilde{\nu}$ = 3485, 2980, 2935, 2910, 2875, 1740, 1715, 1645, 1630, 1465, 1445, 1405, 1365, 1320, 1265, 1195, 1160, 1130, 1095, 1055, 1030, 970, 940, 875, 845, 815, 770, 685, 640 cm^{-1}. HRMS (CI): calcd. for $C_8H_{15}O_4$ $[M + H]^+$ 175.09703; found 175.09660 (Δ = –2.5 ppm). $C_8H_{14}O_4$ (174.2): calcd. C 55.16, H 8.10; found C 54.88, H 8.45.

Ethyl 4-Acetoxy-2-acetyl-4-methyl-3-oxopentanoate[78] (51)



A solution of ethyl 4-hydroxy-4-methyl-3-oxopentanoate (**50**, 51.2 mg, 294 µmol) in a mixture (3.0 mL) of Ac_2O and pyridine [2:1 (v/v)] was stirred at 50 °C for 1 h. After cooling to room temp., the mixture was diluted with Et_2O (3 mL) and washed with a saturated aqueous$CuSO_4$ solution (2× 3 mL). Drying of the organic phases with $MgSO_4$, removal of the volatiles under reduced pressure, and purification by flash chromatography[77] (2.0 cm, 10 mL, C_6H_{12}/EtOAc 5:1) led to compound **53** (#5–6, 15.2 mg, 24%) and to the title compound (**51**; #9–11, 49.3 mg, 65%). ^1H NMR (400.1 MHz, $CDCl_3$; the title compound was one tautomer according to this spectrum, but we could not determine which one): δ = 1.25 (t, $J_{2',1'}$ = 7.1 Hz, 3 H, 2′-H_3), 1.59 [s, 2× 3 H, 4-$(CH_3)_2$], 2.02 (s, 3 H, 4-OAc), 2.27 (s, 3 H, 2-$COCH_3$), 4.12 (q, $J_{1',2'}$ = 7.1 Hz, 2 H, 1′-H_2), 5.87 (s, 1 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.22 (C-2′)[A], 21.08 (2-CO*C*H_3)[A], 21.93 (4-OAc)[A], 24.82 [4-$(CH_3)_2$][A], 60.38 (C-1′)[A], 79.85 (C-4), 106.16 (C-2)[A], 161.93 (4-OAc)[B], 164.08 (C-1)[B], 167.58 (2-*C*OCH_3)[B], 169.41 (C-3)[B] ppm; [A] the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ("short-range C,H-COSY spectrum"; 100.6/400.1 MHz, $CDCl_3$) by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 1.25 (t, 2′-H_3) $\leftrightarrow$ δ_C = 14.22 (C-2′), δ_H = 1.59 [s, 4-$(CH_3)_2$] $\leftrightarrow$ δ_C = 24.82 [4-$(CH_3)_2$], δ_H = 2.02 (s, 4-OAc) $\leftrightarrow$ δ_C = 21.93 (4-OAc), δ_H = 2.27 (s, 2-$COCH_3$) $\leftrightarrow$ δ_C = 21.08 (2-CO*C*H_3), δ_H = 4.12 (q, 1′-H_2) $\leftrightarrow$ δ_C = 60.38 (C-1′), δ_H = 5.87 (s, 2-H) $\leftrightarrow$ δ_C = 106.16 (C-2); [B] assignment interchangeable. IR ($CHCl_3$): $\tilde{\nu}$ = 2980, 2940, 1780, 1740, 1720, 1660, 1470, 1435, 1385, 1365, 1330, 1265, 1245, 1205, 1160, 1090, 1035, 1015, 915, 845, 740 cm^{-1}. $C_{12}H_{18}O_6$ (258.3): calcd. C 55.81, H 7.02; found C 55.95, H 7.24.

Ethyl 4-Acetoxy-4-methyl-3-oxopentanoate [53, Containing Enol Tautomer (3%)]

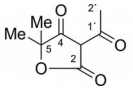


Procedure A: A mixture of the hydroxy-oxo ester **50** (45.8 mg, 263 µmol), Ac_2O (240 µL, 265 mg, 2.6 mmol, 10 equiv.), and $FeCl_3$ (cat.) in CH_2Cl_2 (2 mL) was stirred at room temp. for 1 h. After the addition of an aq. satd. $NaHCO_3$ solution (3.0 mL), the mixture was extracted with Et_2O (4× 3 mL). The combined organic phases were dried with $MgSO_4$. Removal of the volatiles under reduced pressure and purification by flash chromatography[77] (2.0 cm, 10 mL, C_6H_{12}/EtOAc 5:1, #5–9) led to the title compound (52.25 mg, 93%).

Procedure B: A solution of the hydroxy-oxo ester **50** (51.7 mg, 297 µmol), acetic anhydride (280 µL, 303 mg, 2.97 mmol, 10 equiv.), and 4-(dimethylamino)pyridine (3.63 mg, 29.7 µmol, 10 mol-%) in THF (2 mL) was stirred at room temp. for 7 h. After the addition of saturated aqueous $NaHCO_3$ solution (5 mL), the mixture was extracted with Et_2O (4× 5 mL). The combined organic phases were dried with $MgSO_4$. Removal of the volatiles under reduced pressure and purification by flash chromatography[77] (2.0 cm, 20 mL, C_6H_{12}/EtOAc 3:1, #6–9) provided the title compound (48.8 mg, 76%) as a colorless oil. Tautomer **53** was the major constituent of a mixture (97:3) with the enol tautomer. This was indicated by the integrals over the following resonances in the ^1H NMR spectrum (400.1 MHz, $CDCl_3$): δ = 3.49 (s, 2 H of the keto tautomer, 2-H_2) versus δ = 5.16 (s, 1 H of the enol tautomer, 2-H). ^1H NMR (400.1 MHz, $CDCl_3$): $\delta_{keto\ tautomer}$ = 1.25 (t, $J_{2',1'}$ = 7.1 Hz, 3 H, 2′-H_3), 1.50 [s, 6 H, 4-$(CH_3)_2$], 2.07 (s, 3 H, 4-OAc), 3.49 (s, 2 H, 2-H_2), 4.17 (q, $J_{1',2'}$ = 7.2 Hz, 2 H, 1′-H_2) ppm; $\delta_{enol\ tautomer}$ = 1.57 [s, 6 H, 4-$(CH_3)_2$], 2.03 (s, 3 H, 4-OAc), 5.16 (s, 1 H, 2-H), 12.37 (s, 1 H, 3-OH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta_{keto\ tautomer}$ = 14.14 (C-2′)[A], 21.14 (4-OAc)[A], 23.23 [4-$(CH_3)_2$][A], 43.22 (C-2)[A], 61.42 (C-1′)[A], 83.83 (C-4), 167.08 (4-OAc)[B], 170.44 (C-1)[B], 201.25 (C-3) ppm; $\delta_{enol\ tautomer}$ = 14.27, 21.68, 25.32, 60.36, 77.30, 78.87, 86.68, 169.50, 173.07, 178.85 ppm; [A] the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.6/400.1 MHz), $CDCl_3$] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 1.25 (t, 2′-H_3) $\leftrightarrow$ δ_C = 14.14 (C-2′), δ_H = 2.07 (s, 4-OAc) $\leftrightarrow$ δ_C = 21.14 (4-OAc), δ_H = 1.50 [s, 4-$(CH_3)_2$] $\leftrightarrow$ δ_C = 23.23 [4-$(CH_3)_2$], δ_H = 3.49 (s, 2-H_2) $\leftrightarrow$ δ_C = 43.22 (C-2), δ_H = 4.17 (q,

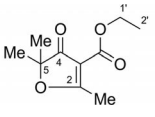
1′-H_2) ↔ δ_C = 61.42 (C-1′); [B] assignment interchangeable. IR ($CHCl_3$): $\tilde{\nu}$ = 2985, 2940, 2905, 2875, 1735, 1465, 1445, 1410, 1370, 1325, 1255, 1150, 1095, 1060, 1025, 970, 940, 890, 840, 770, 695, 665, 615 cm^{-1}. $C_{10}H_{16}O_5$ (216.2): calcd. C 55.55, H 7.46; found C 55.62, H 7.68.

3-Acetyl-5,5-dimethyl-2,4(3*H*,5*H*)-furandione[79] (54)



A solution of acetyl chloride (53.3 µL, 58.6 mg, 0.746 mmol, 2.5 equiv.) and 4-(dimethylamino)pyridine (7.5 mg, 0.12 mmol, 20 mol-%) in CH_2Cl_2 (1 mL) was added dropwise at room temp. to a solution of hydroxy-oxo ester **50** (52.0 mg, 0.299 mmol) and DBU (49 µL, 50 mg, 0.33 mmol, 1.1 equiv.) in CH_2Cl_2 (1 mL). After the mixture had been stirred for 30 min, a buffered phosphate solution (pH = 7.0, 2 mL) was added. The mixture was extracted with Et_2O (4× 5 mL). The combined organic phases were dried with $MgSO_4$. Removal of the volatiles under reduced pressure and purification by flash chromatography[77] (2.0 cm, 20 mL, C_6H_{12}/EtOAc 2:1, #4–5) provided the title compound (15.2 mg, 30%). ^1H NMR (400.1 MHz, $CDCl_3$): δ = 1.49 [s, 6 H, 5-$(CH_3)_2$], 2.32 (s, 3 H, 2′-H_3), 6.03 (s, 1 H, 3-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.17 (C-2′)[A], 24.30 [5-$(CH_3)_2$][A], 82.79 (C-5)[B], 99.45 (C-3)[A], 165.67 (C-1′)[B], 171.14 (C-2)[B], 173.53 (C-4)[B] ppm; [A] the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.6/400.1 MHz), $CDCl_3$] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 1.49 [s, 5-$(CH_3)_2$] ↔ δ_C = 24.30 [5-$(CH_3)_2$], δ_H = 2.32 (s, 2′-H_3) ↔ δ_C = 21.17 (C-2′), δ_H = 6.03 (s, 3-H) ↔ δ_C = 99.45 (C-3); [B] the indicated nuclei – they are quaternary – were distinguished in an HMBC spectrum ["long-range C,H-COSY spectrum" (100.6/400.1 MHz), $CDCl_3$] by their crosspeaks due to ^2J and/or ^3J couplings to "remote" protons (these had previously been assigned unequivocally): for δ_C = 82.79 (C-5) such crosspeaks were due to $^3J_{3\text{-H,C-5}}$ and $^2J_{5\text{-Me,C-5}}$; for δ_C = 165.67 (C-1′) such a crosspeak was due to $^2J_{2'\text{-H,C-1'}}$; for δ_C = 171.14 (C-2) such a crosspeak was due to $^2J_{3\text{-H,C-2}}$; for δ_C = 173.53 (C-4) such a crosspeak was due to $^3J_{5\text{-Me,C-4}}$.

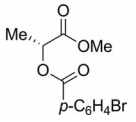
Ethyl (2,5,5-Trimethyl-4-oxo-4,5-dihydrofuran-3-yl)carboxylate (56)



Procedure A: A mixture of acetoxy-oxo ester **53** (73.0 mg, 338 µmol) and $NaHCO_3$ (56.7 mg, 675 µmol, 2.0 equiv.) in EtOH (2 mL) was stirred at room temp. for 2 d. After the addition of H_2O (3.0 mL), the mixture was extracted with Et_2O (4× 5 mL). The combined organic phases were dried with $MgSO_4$. Removal of the volatiles under reduced pressure and purification by flash chromatography[77] (2.0 cm, 20 mL, C_6H_{12}/EtOAc 3:1, #7–18) provided the title compound (64.1 mg, 96%) as a colorless solid (m.p. 56 °C).

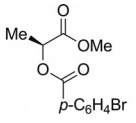
Procedure B: A solution of acetyl chloride (45.1 µL, 49.6 mg, 632 µmol, 2.0 equiv.) in CH_2Cl_2 (0.6 mL) was added at room temp. over the course of 15 min to a stirred solution of the hydroxy-oxo ester **50** (55.0 mg, 316 µmol) and NEt_3 (96.3 µL, 70.3 mg, 695 µmol, 2.2 equiv.) in CH_2Cl_2 (1.0 mL). Stirring was continued for 30 min. A buffered phosphate solution (pH = 7.0, 3 mL) was added, and the resulting mixture was extracted with Et_2O (4× 5 mL). The combined organic phases were dried with $MgSO_4$. Removal of the volatiles under reduced pressure and purification by flash chromatography[77] (2.0 cm, 20 mL, C_6H_{12}/EtOAc 3:1, #8–13) provided the title compound (36.5 mg, 58%) as a colorless solid. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 1.34 (t, $J_{2',1'}$ = 7.1 Hz, 3 H, 2′-H_3), 1.40 [s, 6 H, 5-$(CH_3)_2$], 2.58 (s, 3 H, 2-CH_3), 4.29 (q, $J_{1',2'}$ = 7.1 Hz, 2 H, 1′-H_2) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.37 (C-2′)[A], 18.01 (2-CH_3)[A], 22.94 [5-$(CH_3)_2$][A], 60.48 (C-1′)[A], 90.08 (C-5)[B], 106.79 (C-3)[B], 163.08 (CO_2Et)[B], 194.97 (C-2)[B], 200.41 (C-4)[B] ppm; [A] the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.6/400.1 MHz), $CDCl_3$] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 1.34 (t, 2′-H_3) ↔ δ_C = 14.37 (C-2′), δ_H = 1.40 [s, 5-$(Me)_2$] ↔ δ_C = 22.94 [5-$(Me)_2$], δ_H = 2.58 (s, 5-CH_3) ↔ δ_C = 18.01 (5-CH_3), δ_H = 4.29 (q, 1′-H_2) ↔ δ_C = 60.48 (C-1′); [B] this assignment is based on analogy with compound **78**. IR ($CHCl_3$): $\tilde{\nu}$ = 2990, 2960, 2935, 2910, 2875, 1795, 1705, 1590, 1535, 1440, 1410, 1390, 1365, 1355, 1305, 1285, 1260, 1215, 1185, 1110, 1080, 1030, 1020, 1000, 950, 890, 850, 795, 770, 665 cm^{-1}. $C_{10}H_{14}O_4$ (198.2): calcd. C 60.59, H 7.12; found C 60.51, H 6.96.

Methyl (*R*)-2-[(4-Bromobenzoyl)oxy]propanoate [(*R*)-57]



Methyl D-lactate (173 mg of the crude product described above, ≤1.66 mmol), triethylamine (231 µL, 168 mg, 1.66 mmol, ≥1.0 equiv.), *p*-brombenzoyl chloride (364 mg, 1.66 mmol, ≥1.0 equiv.), and 4-(dimethylamino)pyridine (20.3 mg, 166 µmol, ≥10 mol-%) were dissolved in CH_2Cl_2 (5 mL) at room temp. After 65 min, H_2O (5 mL) was added. The aqueous phase was separated and extracted with Et_2O (4× 5 mL). The combined organic phases were dried with $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography[77] (2.5 cm, 20 mL, C_6H_{12}/EtOAc 20:1, #11–14) provided the title compound (72.1 mg, 15% over the two steps) as a colorless liquid. The enantiopurity of this compound was 99.5% *ee* by analytical HPLC: Chiralpak AD-H column; *n*-heptane/EtOH 9:1, 1.0 mL min^{-1}; $\lambda_{detector}$ = 230 nm; $t_{r\,(R)\text{-}57}$ = 6.35 min, $t_{r\,(S)\text{-}57}$ = 8.77 min. $[\alpha]_D^{20}$ = –23.0 (*c* = 1.04 in $CHCl_3$). ^1H NMR (300.1 MHz, $CDCl_3$): δ = 1.63 (d, $J_{2\text{-Me,2}}$ = 7.0 Hz, 3 H, 2-CH_3), 3.77 (s, 3 H, 1-OCH_3), 5.33 (q, $J_{2,2\text{-Me}}$ = 7.1 Hz, 1 H, 2-H) ppm; AA′BB′ signal centered at δ = 7.59 and 7.94 (4 H, 4× ArH).

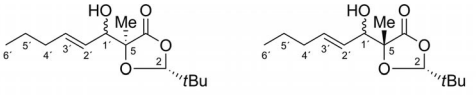
Methyl (*S*)-2-[(4-Bromobenzoyl)oxy]propanoate [(*S*)-57]



This compound was prepared as described for (*R*)-**57**, by starting from a solution of methyl L-lactate (0.10 g, 0.96 mmol), triethylamine (200 µL, 145 mg, 1.44 mmol, 1.5 equiv.), *p*-bromobenzoyl chloride (232 mg, 1.06 mmol, 1.1 equiv.), and 4-(dimethylamino)-pyridine (11.7 mg, 96.0 µmol, 10 mol-%) in CH_2Cl_2 (5 mL). Flash chromatography[77] (2.5 cm, 20 mL, C_6H_{12}/EtOAc 15:1, #7–13) gave the title compound (194.7 mg, 71%) as a colorless liquid. The enantiopurity of this compound was 97.9% *ee* by analytical HPLC: Chiralpak AD-H column; *n*-heptaneEtOH 9:1, 1.0 mL min^{-1}; $\lambda_{detector}$ = 230 nm; $t_{r\,(R)\text{-}57}$ = 6.38 min, $t_{r\,(S)\text{-}57}$ = 8.78 min. $[\alpha]_D^{20}$ = +21.1 (*c* = 0.94 in $CHCl_3$). ^1H NMR (400.1 MHz, $CDCl_3$): δ =

1.62 (d, $J_{2\text{-Me},2}$ = 6.9 Hz, 3 H, 2-CH_3), 3.77 (s, 3 H, 1-OCH_3), 5.33 (q, $J_{2,2\text{-Me}}$ = 7.1 Hz, 1 H, 2-H) ppm; AA′BB′ signal centered at δ = 7.59 and 7.94 (4 H, 4× ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.14 (2-CH_3), 52.51 (1-OCH_3), 69.33 (C-2), 128.44 and 128.60 (2× ArC_{quat}), 131.45 and 131.85 (4× ArCH), 165.27 and 171.13 [C-1, 2-OC(O)Ar] ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2950, 1755, 1725, 1590, 1485, 1450, 1435, 1400, 1380, 1355, 1315, 1270, 1215, 1175, 1115, 1100, 1070, 1045, 1010, 975, 915, 850, 745 cm^{-1}. $C_{11}H_{11}BrO_4$ (287.1): calcd. C 46.02, H 3.86; found C 46.09, H 3.94.

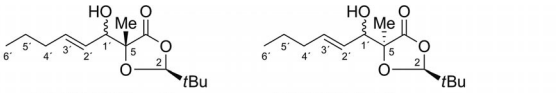
(2*R*,5*S*)-2-*tert*-Butyl-5-[(*E*)-(1-hydroxyhex-2-enyl)-5-methyl-1,3-dioxolan-4-one [(2*R*,5*S*)-58 ("*trans*"; Mixture (52:48) of Unassigned Epimers Defined by the two Possible Configurations at the HO-Substituted Stereocenter)] in a Mixture (93:7) with (2*R*,5*R*)-2-*tert*-Butyl-5-[(*E*)-(1-hydroxyhex-2-enyl)-5-methyl-1,3-dioxolan-4-one [(2*R*,5*R*)-58 ("*cis*"; Pure Epimer with Respect to the Configuration at the HO-Substituted Stereocenter)]



(2*R*,5*S*)-**58** ("*trans*") ($ds_{1'}$ = 52:48) (2*R*,5*R*)-**58** ("*cis*") ($ds_{1'}$ = 100:0)

*n*BuLi (2.4 M in hexane, 16.9 mL, 40.6 mmol, 1.46 equiv.) was added dropwise at –78 °C to a solution of diisopropylamine (5.50 mL, 3.96 g, 39.1 mmol, 1.4 equiv.) in THF (170 mL). Stirring was continued for 15 min. A solution of a mixture (98:2) of (2*R*,5*R*)-**47** and (2*S*,5*R*)-**47** (4.41 g, 27.9 mmol) in THF (22 mL) was added over 10 min. Stirring was continued for 60 min. A solution of *trans*-hex-2-enal (4.60 mL, 3.90 g, 39.7 mmol, 1.42 equiv.) in THF (20 mL) was added. Stirring was continued for 60 min. The temperature was allowed to rise from –78 °C to room temp. over the course of 60 min. A saturated aqueous solution of NH_4Cl (150 mL) was added. Extraction with Et_2O (4× 100 mL), drying of the combined organic phases with $MgSO_4$, and purification by flash chromatography[77] (8.0 cm, 100 mL, C_6H_{12}/EtOAc 12:1 → 10:1, #11–30) provided the title compound [5.41 g, 76%, *ds* = 93(52:48):7(94:6) (2*R*,5*S*)-**58**/(2*R*,5*R*)-**58**; ref.[16] 87%, *ds* = 100(50:50):0] as a yellowish oil. The diastereoselectivity of this reaction was determined by comparing the integrals over the following ^{1}H NMR resonances (400 MHz, $CDCl_3$): δ = 5.38 and 5.41 [2× s, 1 H of the major and the minor 1′-epimer, respectively, of (2*R*,5*S*)-**58**, 2-H] versus δ = 5.18 [s, 1 H of a pure 1′-epimer of (2*R*,5*R*)-**58**, 2-H]. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.89 [t, $J_{6',5'}$ = 7.3 Hz, 3 H of one 1′-epimer of (2*R*,5*S*)-**58**, 6′-H_3], superimposed by 0.91 [t, $J_{6',5'}$ = 7.3 Hz, 3 H of the other 1′-epimer of (2*R*,5*S*)-**58**, 6′-H_3], superimposed by 0.95 (s, 18 H, 2-*t*Bu), 1.28 [s, 3 H of the minor 1′-epimer of (2*R*,5*S*)-**58**, 5-CH_3], 1.36 [s, 3 H of the major 1′-epimer of (2*R*,5*S*)-**58**, 5-CH_3], superimposed by 1.42 (m_c, 4 H, 5′-H_2), 1.97 [br. d, $J_{1'\text{-OH},1'}$ = 3.9 Hz, 1 H of one 1′-epimer of (2*R*,5*S*)-**58**, 1′-OH], superimposed by 1.99 [br. d, $J_{1'\text{-OH},1'}$ = 4.0 Hz, 1 H of the other 1′-epimer of (2*R*,5*S*)-**58**, 1′-OH], 2.06 (m_c, 4 H, 4′-H_2), 4.20 [dd, $J_{1',2'}$ = 7.8 Hz, $J_{1',1'\text{-OH}}$ = 3.0 Hz, 1 H of one 1′-epimer of (2*R*,5*S*)-**58**, 1′-H], superimposed by 4.22 [dd, $J_{1',2'}$ = 8.3 Hz, $J_{1',1'\text{-OH}}$ = 3.0 Hz, 1 H of the other 1′-epimer of (2*R*,5*S*)-**58**, 1′-H], 5.18 [s, 1 H of a pure 1′-epimer of (2*R*,5*R*)-**58**, 2-H], 5.38 [s, 1 H of the major 1′-epimer of (2*R*,5*S*)-**58**, 2-H], 5.41 [s, 1 H of the minor 1′-epimer of (2*R*,5*S*)-**58**, 2-H], 5.59 [dd, $J_{2',3'}$ = 15.4 Hz, $J_{2',1'}$ = 8.3 Hz, 1 H of one 1′-epimer of (2*R*,5*S*)-**58**, 2′-H], superimposed by 5.66 [dd, $J_{2',3'}$ = 15.5 Hz, $J_{2',1'}$ = 8.0 Hz, 1 H of the other 1′-epimer of (2*R*,5*S*)-**58**, 2′-H], 5.77 [dt, $J_{3',2'}$ = 15.3 Hz, $J_{3',4'}$ = 6.2 Hz, 1 H of one 1′-epimer of (2*R*,5*S*)-**58**, 3′-H], 5.78 [dt, $J_{3',2'}$ = 15.2 Hz, $J_{3',4'}$ = 6.2 Hz, 1 H of the other 1′-epimer of (2*R*,5*S*)-**58**, 3′-H] ppm.

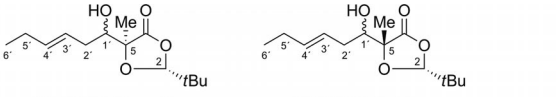
(2*S*,5*R*)-2-*tert*-Butyl-5-[(*E*)-(1-hydroxyhex-2-enyl)-5-methyl-1,3-dioxolan-4-one [(2*S*,5*R*)-58 ("*trans*"; Mixture (60:40) of Unassigned Epimers Defined by the two Possible Configurations at the HO-Substituted Stereocenter)] in a Mixture (95:5) with (2*S*,5*S*)-2-*tert*-Butyl-5-[(*E*)-(1-hydroxyhex-2-enyl)-5-methyl-1,3-dioxolan-4-one [(2*S*,5*S*)-58 ("*cis*"; Pure Epimer with Respect to the Configuration at the HO-Substituted Stereocenter)]



(2*S*,5*R*)-**58** ("*trans*") ($ds_{1'}$ = 60:40) (2*S*,5*S*)-**58** ("*cis*") ($ds_{1'}$ = 100:0)

This mixture was prepared exactly as described for (2*R*,5*S*)-**58**/(2*R*,5*R*)-**58**, from the same amounts of starting materials. Purification by flash chromatography[77] (8.0 cm, 100 mL, C_6H_{12}/EtOAc 12:1 → 10:1, #11–30) provided the title compound [5.06 g, 71%, *ds* = 95(60:40):5(100:0) (2*S*,5*R*)-**58**/(2*S*,5*S*)-**58**] as a yellowish oil. The diastereoselectivity of this reaction was determined by comparing the integrals over the following ^{1}H NMR resonances (300 MHz, $CDCl_3$): δ = 5.39 and 5.41 [2× s, 1 H of the major and the minor 1′-epimer, respectively, of (2*S*,5*R*)-**58**, 2-H] versus δ = 5.19 [s, 1 H of the only 1′-epimer of (2*S*,5*S*)-**58**, 2-H]. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.91 [t, $J_{6',5'}$ = 7.3 Hz, 3 H of the major 1′-epimer of (2*S*,5*R*)-**58**, 6′-H_3], superimposed by 0.92 [t, $J_{6',5'}$ = 7.5 Hz, 3 H of the minor 1′-epimer of (2*S*,5*R*)-**58**, 6′-H_3], superimposed by 0.98 (s, 18 H, 2-*t*Bu), 1.30 [s, 3 H of the minor 1′-epimer of (2*S*,5*R*)-**58**, 5-CH_3], 1.37 [s, 3 H of the major 1′-epimer of (2*S*,5*R*)-**58**, 5-CH_3], superimposed by 1.37–1.48 (m, 4 H, 5′-H_2), 1.84 (br. d, $J_{1'\text{-OH},1'}$ = 4.1 Hz, 2 H, 1′-OH), 2.07 (m_c, 4 H, 4′-H_2), 4.21 [dd, $J_{1',2'}$ = 8.1 Hz, $J_{1',1'\text{-OH}}$ = 4.0 Hz, 1 H of the major 1′-epimer of (2*S*,5*R*)-**58**, 1′-H], superimposed by 4.24 [dd, $J_{1',2'}$ = 8.6 Hz, $J_{1',1'\text{-OH}}$ = 3.9 Hz, 1 H of the minor 1′-epimer of (2*S*,5*R*)-**58**, 1′-H], 5.19 [s, 1 H of the only 1′-epimer of (2*S*,5*S*)-**58**, 2-H], 5.39 [s, 1 H of the major 1′-epimer of (2*S*,5*R*)-**58**, 2-H], 5.41 [s, 1 H of the minor 1′-epimer of (2*S*,5*R*)-**58**, 2-H], 5.60 [dd, $J_{2',3'}$ = 15.5 Hz, $J_{2',1'}$ = 8.3 Hz, 1 H of one 1′-epimer of (2*S*,5*R*)-**58**, 2′-H], superimposed by 5.67 [dd, $J_{2',3'}$ = 15.3 Hz, $J_{2',1'}$ = 7.7 Hz, 1 H of the other 1′-epimer of (2*S*,5*R*)-**58**, 2′-H], 5.74–5.85 (m, 2 H, 3′-H) ppm.

(2*R*,5*S*)-2-*tert*-Butyl-5-[(*E*)-(1-hydroxyhex-3-enyl)-5-methyl-1,3-dioxolan-4-one [(2*R*,5*S*)-59 ("*trans*"; Unknown Ratio of the Epimers Defined by the two Possible Configurations at the HO-Substituted Stereocenter)] in a Mixture (ca. 95:5) with (2*R*,5*R*)-2-*tert*-Butyl-5-[(*E*)-(1-hydroxyhex-3-enyl)-5-methyl-1,3-dioxolan-4-one [(2*R*,5*R*)-59 ("*cis*"; Unknown Ratio of the Epimers Defined by the two Possible Configurations at the HO-Substituted Stereocenter)]

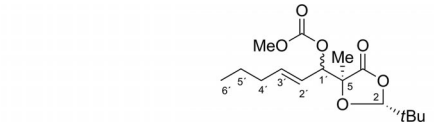


(2*R*,5*S*)-**59** ("*trans*") (2*R*,5*R*)-**59** ("*cis*")

*n*BuLi (2.4 M in hexane, 3.38 mL, 7.82 mmol, 1.41 equiv.) was added dropwise at –78 °C to a solution of diisopropylamine (1.10 mL, 792 mg, 7.82 mmol, 1.41 equiv.) in THF (35 mL). Stirring was continued for 15 min. A solution of a mixture (98:2) of (2*R*,5*R*)-**47** and (2*S*,5*R*)-**47** (880 mg, 5.56 mmol) in THF (4 mL) was added over 10 min. Stirring was continued for 60 min. A solution of freshly prepared (*E*)-hex-3-enal (as a THF solution, ≤2.0 equiv.[57]) was added. Stirring was continued for 60 min. The temperature was allowed to rise from –78 °C to room temp. over the course of 60 min. A saturated aqueous solution of NH_4Cl (150 mL) was added. Extraction with Et_2O (4× 100 mL), drying

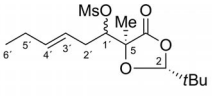
of the combined organic phases with $MgSO_4$, and filtration through silica gel gave the title compound. It was converted without purification into an unspecified mixture of the mesylates (2*R*,5*S*)-**64** and (2*R*,5*R*)-**64**.

(2*R*,5*S*)-2-*tert*-Butyl-5-{(*E*)-1-[(methoxycarbonyl)oxy]hex-2-enyl}-5-methyl-1,3-dioxolan-4-one [(2*R*,5*S*)-62 ("*trans*"; Mixture (60:40) of Unassigned Epimers Defined by the two Possible Configurations at the MeO_2CO-Substituted Stereocenter)] in a Mixture (96:4) with (2*R*,5*R*)-2-*tert*-Butyl-5-{(*E*)-1-[(methoxycarbonyl)oxy]hex-2-enyl}-5-methyl-1,3-dioxolan-4-one [(2*R*,5*R*)-62 ("*cis*"; Pure Epimer with Respect to the Configuration at the MeO_2CO-Substituted Stereocenter)]

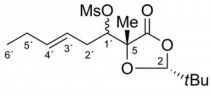


Methyl chloroformate (600 μL, 736 mg, 7.79 mmol, 4.0 equiv.) was added at 0 °C over 45 min to a stirred solution of a mixture (93:7) of aldol adducts (2*R*,5*S*)-**58** ("*trans*") and (2*R*,5*R*)-**58** ("*cis*") (499 mg, 1.95 mmol), pyridine (640 μL, 620 mg, 7.85 mmol, 4.03 equiv.), and 4-(dimethylamino)pyridine (47.5 mg, 389 μmol, 0.2 equiv.) in CH_2Cl_2 (5 mL). Stirring was continued at room temp. for 24 h. H_2O (5 mL) was added, and the resulting mixture was extracted with Et_2O (4× 10 mL). The combined organic extracts were dried with $MgSO_4$. Purification by flash chromatography[77] (2.5 cm, 20 mL, C_6H_{12}/EtOAc 40:1, #12–32) provided the title compound (439 mg, 72%) as a colorless oil. $[\alpha]_D^{20} = -1.2$ (c = 0.98 in $CHCl_3$). The diastereoselectivity of this reaction was determined by comparing the integrals over the following ^{1}H NMR resonances (400 MHz, $CDCl_3$): δ = 3.75 and 3.78 [2× s, 3 H of the minor and the major 1′-epimer, respectively, of (2*R*,5*S*)-**62**, OCH_3] versus δ = 3.76 [s, 3 H of the only 1′-epimer of (2*R*,5*R*)-**62**, OCH_3]. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.886 [t, $J_{6',5'}$ = 7.4 Hz, 3 H of the major 1′-epimer of (2*R*,5*S*)-**62**, 6′-H_3], 0.898 [t, $J_{6',5'}$ = 7.3 Hz, 3 H of the minor 1′-epimer of (2*R*,5*S*)-**62**, 6′-H_3], 0.94 [s, 9 H of the major 1′-epimer of (2*R*,5*S*)-**62**, 2-*t*Bu], 0.96 [s, 9 H of the minor 1′-epimer of (2*R*,5*S*)-**62**, 2-*t*Bu], 1.34 [s, 3 H of the minor 1′-epimer of (2*R*,5*S*)-**62**, 5-CH_3], 1.37–1.49 (m_c, 4 H, 5′-H_2), superimposes 1.39 [s, 3 H of the major 1′-epimer of (2*R*,5*S*)-**62**, 5-CH_3], 1.99–2.13 (m_c, 4 H, 4′-H_2), 3.75 [s, 3 H of the minor 1′-epimer of (2*R*,5*S*)-**62**, 1′-OCO_2CH_3], 3.76 [s, 3 H of the only 1′-epimer of (2*R*,5*R*)-**62**, 1′-OCO_2CH_3], 3.78 [s, 3 H of the major 1′-epimer of (2*R*,5*S*)-**62**, 1′-OCO_2CH_3], 5.14 [br. d, $J_{1',2'}$ = 8.8 Hz, 1 H of the major 1′-epimer of (2*R*,5*S*)-**62**, 1′-H], 5.16 [br. d, $J_{1',2'}$ = 8.8 Hz, 1 H of the minor 1′-epimer of (2*R*,5*S*)-**62**, 1′-H], 5.24 [s, 1 H of the major 1′-epimer of (2*R*,5*S*)-**62**, 2-H], 5.38 [s, 1 H of the minor 1′-epimer of (2*R*,5*S*)-**62**, 2-H], 5.51 [ddt, $J_{2',3'}$ = 15.5 Hz, $J_{2',1'}$ = 8.8 Hz, $J_{2',4'}$ = 1.4 Hz, 1 H of the minor 1′-epimer of (2*R*,5*S*)-**62**, 2′-H], 5.60 [ddt, $J_{2',3'}$ = 15.4 Hz, $J_{2',1'}$ = 8.9 Hz, $J_{2',4'}$ = 1.4 Hz, 1 H of the major 1′-epimer of (2*R*,5*S*)-**62**, 2′-H], 5.70 [ddt, $J_{2',3'}$ = 15.5 Hz, $J_{2',1'}$ = 8.8 Hz, $J_{2',4'}$ = 1.3 Hz, 1 H of the only 1′-epimer of (2*R*,5*R*)-**62**, 2′-H], 5.91 [dt, $J_{3',2'}$ = 15.3 Hz, $J_{3',4'}$ = 6.9, 1 H of one 1′-epimer of (2*R*,5*S*)-**62**, 3′-H], 5.97 [dt, $J_{3',2'}$ = 15.3 Hz, $J_{3',4'}$ = 6.9 Hz, 1 H of the other 1′-epimer of (2*R*,5*S*)-**62**: 3′-H] ppm; [A] the indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.1 MHz, $CDCl_3$)] by their crosspeaks with protons that had previously been assigned unequivocally [δ_H(^{1}H) ↔ δ_H(^{1}H)]: δ = 0.889 and 0.898 (2× t, 6′-H_3) ↔ δ = 1.37–1.49 (m_c, 5′-H_2); δ = 0.889 and 0.898 (2× t, 6′-H_3) ↔ δ = 1.99–2.13 (m_c, 4′-H_2); δ = 1.37–1.49 (m_c, 5′-H) ↔ δ = 1.99–2.13 (m_c, 4′-H_2); δ = 1.99–2.13 (m_c, 4′-H) ↔ 5.91 and 5.97 (2× dt, 3′-H); δ = 5.14 and 5.16 (2× br. d, 1′-H) ↔ δ = 5.51 and 5.60 (2× ddt, 2′-H); δ = 5.51 and 5.60 (ddt, 2′-H) ↔ δ = 5.91 and 5.97 (2× dt, 3′-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.63 (C-6′)[A], 20.42 and 21.06 (5-CH_3)[A], 21.88 and 21.94 (C-5′)[A], 23.35 (2-*t*Bu)[A], 34.35 and 34.49 (C-4′)[A], 34.76 and 34.89 (2-*t*Bu), 54.97 and 55.02 (OCH_3)[A], 80.61 and 81.28 (C-2, C-5), 81.88 and 83.53 (C-1′), 110.28 and 110.37 (C-2)[A], 121.35 and 122.22 (C-2′)[A], 140.20 and 141.20 (C-3′)[A], 154.34 and 154.69 (1′-OCO_2Me), 172.73 and 173.77 (C-4) ppm; [A] the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.6/400.1 MHz), C_6D_6] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [δ_H(^{1}H) ↔ δ_C(^{13}C)]: δ_H = 0.886 and 0.898 (2× t, 6′-H_3) ↔ δ_C = 13.63 (C-6′); δ_H = 0.94 and 0.96 (2× s, 2-*t*Bu) ↔ δ_C = 23.35 (2-*t*Bu); δ_H = 1.34 (s, 5-CH_3) ↔ δ_C = 20.42 and 21.06 (5-CH_3); δ_H = 1.99–2.13 (m_c, 4′-H_2) ↔ δ_C = 34.35 and 34.49 (C-4′); δ_H = 3.75 and 3.78 (2× s, OCH_3) ↔ δ_C = 54.97 and 55.02 (1-OCH_3); δ_H = 5.14 and 5.16 (2× br. d, 1′-H) ↔ δ_C = 81.88 and 83.53 (C-1′); δ_H = 5.24 and 5.38 (2× s, 2-H) ↔ δ_C = 110.28 and 110.37 (C-2); δ_H = 5.51 and 5.60 (2× ddt, 2′-H) ↔ δ_C = 121.35 and 122.22 (C-2′); δ_H = 5.91 and 5.97 (2× dt, 3′-H) ↔ δ_C = 140.20 and 141.20 (C-3′). IR ($CHCl_3$): $\tilde{\nu}$ = 2960, 2935, 2875, 1795, 1755, 1665, 1485, 1440, 1405, 1375, 1350, 1325, 1260, 1180, 1165, 1105, 1075, 1035, 970, 930, 785, 770 cm^{-1}. $C_{16}H_{26}O_6$ (314.4): calcd. C 61.13, H 8.34; found C 61.19, H 8.57.

(2*R*,5*S*)-2-*tert*-Butyl-5-{(*E*)-1-[(methanesulfonyl)oxy]hex-3-enyl}-5-methyl-1,3-dioxolan-4-one [(2*R*,5*S*)-64 ("*trans*"; Unknown Ratio of the Epimers Defined by the two Possible Configurations at the HO-Substituted Stereocenter)], Presumably in a Mixture with (2*R*,5*R*)-2-*tert*-Butyl-5-{(*E*)-1-[(methanesulfonyl)oxy]hex-3-enyl}-5-methyl-1,3-dioxolan-4-one [(2*R*,5*R*)-64 ("*cis*"; Unknown Ratio of the Epimers Defined by the two Possible Configurations at the HO-Substituted Stereocenter)]



(2*R*,5*S*)-**64** ("*trans*")

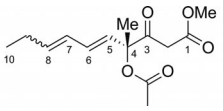


(2*R*,5*R*)-**64** ("*cis*")

Pyridine (1.80 mL, 1.76 g, 22.2 mmol, 4.0 equiv.) and 4-(dimethylamino)pyridine (339 mg, 2.78 mmol, 0.5 equiv.) were added at 0 °C to a solution of an unspecified mixture (≤5.56 mmol) of (2*R*,5*S*)-**59** and (2*R*,5*R*)-**59** in CH_2Cl_2 (27 mL). Neat mesyl chloride (1.72 mL, 2.55 g, 22.2 mmol, 4.0 equiv.) was added dropwise over the course of 30 min. After the mixture had been stirred at room temp. for 15 h, H_2O (5 mL) was added, and the resulting mixture was extracted with Et_2O (4× 10 mL). The combined organic phases were dried with $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography[77] (5.0 cm, 50 mL, C_6H_{12}/EtOAc 15:1, #13–34) provided the title compound (1.04 mg, 56% over the two steps) as a colorless oil. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.96 (s, 9 H, *t*Bu), 0.94–1.03 (m, 3 H, 6′-H_3), 1.46 [s, 3 H of diastereomer-#2 of (2*R*,5*S*)-**64**, 5-CH_3], 1.51 [s, 3 H of diastereomer-#1 of (2*R*,5*S*)-**64**, 5-CH_3], 2.05 (m_c, interpretable as br. dq, $J_{5',4'} \approx J_{5',6'} \approx$ 7.0 Hz, 2 H, 5′-H_2), 2.44–2.68 (m, 2 H, 2′-H_2), 3.02 [s, 3 H of diastereomer-#2 of (2*R*,5*S*)-**64**, 1′-OMs], 3.03 [s, 3 H of diastereomer-#1 of (2*R*,5*S*)-**64**, 1′-OMs], 3.21 [s, 3 H of (2*R*,5*R*)-**64**, 1′-OMs], 4.84 [dd, $J_{1',2'\text{-H}(1)}$ = 8.5 Hz, $J_{1',2'\text{-H}(2)}$ = 4.0 Hz, 1 H of diastereomer-#2 of (2*R*,5*S*)-**64**, 1′-H], 4.87 [dd, $J_{1',2'\text{-H}(1)}$ = 9.7 Hz, $J_{1',2'\text{-H}(2)}$ = 3.8 Hz, 1 H of diastereomer-#1 of (2*R*,5*S*)-**64**, 1′-H], 5.28 [s, 1 H of (2*R*,5*R*)-**64**, 2-H], 5.34–5.49 (m, 1 H, 3′-H), superimposed by 5.35 [s, 1 H of diastereomer-#2 of (2*R*,5*S*)-**64**, 2-H] and 5.49 [s, 1 H of diastereomer-#1 of (2*R*,5*S*)-**64**, 2-H], 5.66 (br. dt, $J_{4',3'}$ = 15.1 Hz, $J_{4',5'}$ = 6.5 Hz, 1 H, 4′-H)

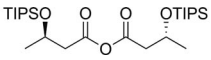
ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2960, 2940, 2875, 1795, 1485, 1460, 1405, 1365, 1285, 1240, 1215, 1185, 1175, 1075, 1035, 965, 910, 830, 790, 775, 725, 650 cm^{-1}. $C_{15}H_{26}O_6S$ (334.4): calcd. C 53.87, H 7.84, S 9.59; found C 54.15, H 8.11, S 9.31.

Methyl (*E*,*E*)-(*R*)-4-Acetoxy-4-methyl-3-oxodeca-5,7-dienoate [(*E*,*E*)-(*R*)-66, Containing Enol Tautomer (3%)] in a Mixture (95:5) with Methyl (5*E*,7*Z*)-(*R*)-4-Acetoxy-4-methyl-3-oxodeca-5,7-dienoate [(5*E*,7*Z*)-(*R*)-66]



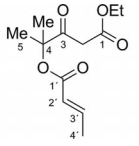
A mixture (92:8) of hydroxy-oxo esters (*E*,*E*)-(*R*)-**29** and (5*E*,7*Z*)-(*R*)-**29** (61.0 mg, 270 µmol), acetic anhydride (253 µL, 275 mg, 2.70 mmol, 10.0 equiv.), and 4-(dimethylamino)pyridine (3.3 mg, 27 µmol, 10 mol-%) in THF (1.3 mL) was stirred at room temp. for 3 h. A saturated aqueous $NaHCO_3$ solution (5 mL) was added, the resulting mixture was extracted with Et_2O (4× 5 mL), and the combined organic phases were dried with $MgSO_4$. Removal of the volatiles under reduced pressure and purification by flash chromatography[77] [2.0 cm, 20 mL, petroleum ether (30:50)/Et_2O 4:1, #19–38] provided the title compound (45.6 mg, 63%) as a colorless oil. The (*E*,*E*)/(5*E*,7*Z*) ratio was 95:5 as concluded from the integrals of the following ^1H NMR resonances (400 MHz, C_6D_6): δ = 6.32 [dd, 1 H of (*E*,*E*) isomer, 6-H] versus δ = 6.72 [ddd, 1 H of (5*E*,7*Z*) isomer, 6-H]. ^1H NMR (400.1 MHz, C_6D_6): δ = 0.82 [t, $J_{10,9}$ = 7.6 Hz, 3 H of (5*E*,7*Z*) isomer, 10-H_3], 0.83 [t, $J_{10,9}$ = 7.5 Hz, 3 H of (*E*,*E*) isomer, 10-H_3], 1.57 [s, 3 H of (5*E*,7*Z*) isomer, 4-CH_3 or 4-OAc], 1.580 and 1.584 [2× s, 2× 3 H of (*E*,*E*) isomer, 4-CH_3, 4-OAc], 1.87 [m_c, interpretable as qdd, $J_{9,10} \approx J_{9,8} \approx$ 7.2 Hz, $J_{9,7}$ = 1.1 Hz, 2 H of (*E*,*E*) isomer, 9-H_2], 2.04 [m_c, interpretable as qdd, $J_{9,10} \approx J_{9,8} \approx$ 7.5 Hz, $J_{9,7}$ = 1.5 Hz, 2 H of (5*E*,7*Z*) isomer, 9-H_2], 3.30 [s, 3 H of (5*E*,7*Z*) isomer, 1-OCH_3], 3.31 [s, 3 H of (*E*,*E*) isomer, 1-OCH_3], AB signal [δ_A = 3.36, δ_B = 3.41, J_{AB} = 15.4 Hz, 2 H of (*E*,*E*) isomer, 2-H_2], superimposed by AB signal [A part superimposed, δ_B = 3.41, J_{AB} = 15.4 Hz, 2 H of (5*E*,7*Z*) isomer, 2-H_2], 5.35 [dt, $J_{8,7}$ = 10.7 Hz, $J_{8,9}$ = 7.6 Hz, 1 H of (5*E*,7*Z*) isomer, 8-H], 5.57 [dt, $J_{8,7}$ = 15.2 Hz, $J_{8,9}$ = 6.6 Hz, 1 H of (*E*,*E*) isomer, 8-H], 5.67 [d, $J_{5,6}$ = 15.7 Hz, 1 H of (*E*,*E*) isomer, 5-H], 5.75 [d, $J_{5,6}$ = 15.5 Hz, 1 H of (5*E*,7*Z*) isomer, 5-H], 5.84 (ddd, $J_{7,8}$ = 15.3 Hz, $J_{7,6}$ = 10.4 Hz, $J_{7,5}$ = 0.6 Hz, 1 H, 7-H)[A], 6.32 [dd, $J_{6,5}$ = 15.7 Hz, $J_{6,7}$ = 10.4 Hz, 1 H of (*E*,*E*) isomer, 6-H][A], 6.72 [ddd, $J_{6,5}$ = 15.5 Hz, $J_{6,7}$ = 11.1 Hz, $J_{6,8}$ = 1.1 Hz, 1 H of (5*E*,7*Z*) isomer, 6-H], 13.03 (br. s, 1 H of enol tautomer, 3-OH) ppm; [A] the indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.1 MHz, C_6D_6)] by their crosspeaks with protons that had previously been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 5.84 (ddd, 7-H) ↔ δ = 1.87 (m_c, 9-H_2); δ = 5.84 (ddd, 7-H) ↔ δ = 5.57 (dt, 8-H); δ = 5.84 (ddd, 7-H) ↔ δ = 6.32 (dd, 6-H); δ = 6.32 (dd, 6-H) ↔ δ = 5.67 (d, 5-H). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 13.36 (C-10)[A], 20.45 and 21.44 (4-CH_3, 4-O_2CCH_3)[A], 25.88 (C-9)[A], 43.68 (C-2)[A], 51.71 (1-OCH_3)[A], 85.66 (C-4), 128.12 (C-5)[A], 128.68 (C-7)[A], 132.79 (C-6)[A], 138.76 (C-8)[A], 167.10 and 169.63 (C-1, 4-OAc), 197.90 (C-3) ppm; [A] the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.6/400.1 MHz), C_6D_6] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 0.83 (t, 10-H_3) ↔ δ_C = 13.36 (C-10), δ_H = 1.580 (s, 4-CH_3 or 4-OAc) ↔ δ_C = 20.45 (4-CH_3 or 4-O_2CCH_3), δ_H = 1.584 (s, 4-CH_3 or 4-OAc) ↔ δ_C = 21.44 (4-CH_3 or 4-O_2CCH_3), δ_H = 1.87 (m_c, 9-H_2) ↔ δ_C = 25.88 (C-9), δ_H = 3.31 (s, 1-OCH_3) ↔ δ_C = 51.71 (1-OCH_3), δ_H = 3.36 (dd, 2-H^1) and 3.41 (dd, 2-H^2) ↔ δ_C = 43.68 (C-2), δ_H = 5.57 (dt, 8-H) ↔ δ_C = 138.76 (C-8), δ_H = 5.67 (d, 5-H) ↔ δ_C = 128.12 (C-5), δ_H = 5.84 (ddd, 7-H) ↔ δ_C = 128.68 (C-7), δ_H = 6.32 (dd, 6-H) ↔ δ_C = 132.79 (C-6). IR ($CHCl_3$): $\tilde{\nu}$ = 2960, 2875, 2850, 1740, 1655, 1460, 1435, 1405, 1370, 1320, 1245, 1220, 1190, 1155, 1090, 1065, 1045, 995, 965, 940, 875, 775, 640, 610 cm^{-1}. $C_{14}H_{20}O_5$ (268.3): calcd. C 62.67, H 7.51; found C 62.44, H 7.64.

(*R*)-3-(Triisopropylsiloxy)butanoic Anhydride (68)



A solution of siloxybutanoic acid **95** (for formula, see ref.[67]) (1.00 g, 3.84 mmol, 2.0 equiv.), NEt_3 (590 µL, 428 mg, 4.23 mmol, 2.2 equiv.), and *p*-toluenesulfonic acid (366 mg, 1.92 mmol, 1.0 equiv.) in CH_2Cl_2 (3 mL) was stirred at 0 °C for 70 min. Hexane was added, and the resulting solution was washed with H_2O (1× 10 mL). Drying with Na_2SO_4 and removal of the solvent under reduced pressure left the title compound (768.4 mg, 80%; ref.[69] 95%). It was not purified by flash chromatography[77] but carried forward as a crude product. ^1H NMR (300.1 MHz, $CDCl_3$): δ = 0.97–1.16 [m, 21 H, Si(*i*Pr)$_3$], 1.29 (d, $J_{4,3}$ = 6.0 Hz, 3 H, 4-H_3), AB signal (δ_A = 2.55, δ_B = 2.69, J_{AB} = 15.7 Hz, A part additionally split by $J_{A,3}$ = 6.7 Hz, B part additionally split by $J_{B,3}$ = 5.8 Hz, 2 H, 2-H_2), 4.41 (m_c, possibly interpretable as ddq, $J_{3,2\text{-}H(A)} \approx J_{3,2\text{-}H(B)} \approx J_{3,4} \approx$ 6.2 Hz, 1 H, 3-H) ppm.

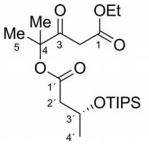
Ethyl 4-[(*E*)-But-2-enoyloxy]-4-methyl-3-oxopentanoate [69, Containing Enol (3%)]



A solution of hydroxy-oxo ester **50** (160.3 mg, 920.8 µmol) crotonic anhydride (205 µL, 213 mg, 1.38 mmol, 2.0 equiv.), and 4-(dimethylamino)pyridine (16.9 mg, 138 µmol, 15 mol-%) in THF (5 mL) was stirred at room temp. for 3 d. A saturated aqueous solution of $NaHCO_3$ (5 mL) was added, and the resulting mixture was extracted with Et_2O (4× 7 mL). The combined organic phases were dried with $MgSO_4$. Removal of the volatiles under reduced pressure and purification by flash chromatography[77] [2.5 cm, 20 mL, petroleum ether (30:50)/Et_2O 5:1, #13–26] provided the title compound (115.2 mg, 52%) as a colorless oil. The keto/enol ratio was 97:3 as concluded from the integrals of the following ^1H NMR resonances (400 MHz, $CDCl_3$): δ = 3.49 (s, 2 H of the keto tautomer, 2-H_2) versus δ = 5.18 (s, 1 H of the enol tautomer, 2-H). ^1H NMR (400.1 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.1 Hz, 3 H, 1-OCH_2CH_3), 1.52 [s, 6 H, 4-$(CH_3)_2$], 1.89 (dd, $J_{4',3'}$ = 6.9 Hz, $J_{4',2'}$ = 1.6 Hz, 3 H, 4′-H_3), 3.49 (s, 2 H, 2-H_2), 4.17 (q, J = 7.2 Hz, 2 H, 1-OCH_2CH_3), 5.18 (s, 1 H of the enol tautomer, 2-H), 5.84 (dq, $J_{2',3'}$ = 15.5 Hz, $J_{2',4'}$ = 1.7 Hz, 1 H, 2′-H), 7.01 (dq, $J_{3',2'}$ = 15.3 Hz, $J_{3',4'}$ = 6.9 Hz, 1 H, 3′-H), 12.39 (br. s, 1 H of the enol tautomer, 3-OH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.14 (1-OCH_2CH_3)[A], 18.13 (C-4′)[A], 23.25 [4-$(CH_3)_2$][A], 43.06 (C-2)[A], 61.36 (1-OCH_2CH_3)[A], 83.62 (C-4), 122.10 (C-2′)[A], 146.66 (C-3′)[A], 165.68 and 167.27 (C-1, C-1′), 201.46 (C-3) ppm; [A] the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.6/400.1 MHz), $CDCl_3$] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 1.25 (t, 1-OCH_2CH_3) ↔ δ_C = 14.14 (1-OCH_2CH_3), δ_H = 1.52 [s, 4-$(CH_3)_2$] ↔ δ_C = 23.25 [4-$(CH_3)_2$], δ_H = 1.89 (dd, 4′-H_3) ↔ δ_C =

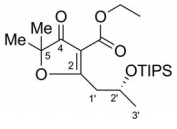
18.13 (C-4′), δ_H = 3.49 (s, 2-H_2) ↔ δ_C = 43.06 (C-2), δ_H = 4.17 (q, 1-OCH_2CH$_3$) ↔ δ_C = 61.36 (1-OCH_2CH$_3$), δ_H = 5.84 (dq, 2′-H) ↔ δ_C = 122.10 (C-2′), δ_H = 7.01 (dq, 3′-H) ↔ δ_C = 146.66 (C-3′). IR ($CHCl_3$): ṽ = 2980, 2940, 2875, 1745, 1720, 1655, 1465, 1445, 1410, 1385, 1365, 1320, 1285, 1270, 1195, 1145, 1105, 1060, 1030, 1015, 995, 965, 925, 840, 755, 685, 640, 620 cm^{-1}. HRMS (CI): calcd. for $C_{12}H_{19}O_5$ [M + H]$^+$ 243.12325; found 243.12320 (Δ = –0.2 ppm).

Ethyl (*R*)-4-Methyl-[3-(triisopropylsiloxy)butanoyloxy]-3-oxopentanoate [70, Containing Enol Tautomer (6%)]



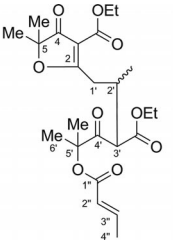
A solution of hydroxy-oxo ester **50** (50.0 mg, 0.297 mmol), the siloxy-butanoic anhydride **68** (346 mg, 0.689 mmol, 2.4 equiv.), and 4-(dimethylamino)pyridine (7.01 mg, 57.4 μmol, 20 mol-%) in THF (1.5 mL) was stirred at room temp. for 24 h. A saturated aqueous solution of $NaHCO_3$ (5 mL) was added, and the mixture was extracted with Et_2O (4× 5 mL). The combined organic phases were dried with $MgSO_4$. Removal of the volatiles under reduced pressure and purification by flash chromatography[77] (2.5 cm, 20 mL, C_6H_{12}/EtOAc 15:1, #6–11) provided the title compound (76.2 mg, 64%) as a colorless oil. The keto/enol ratio was 94:6 as concluded from the integrals of the following ^{1}H NMR resonances (300 MHz, C_6D_6): AB signal (δ_A = 2.27, δ_B = 2.45, 2 H of the keto tautomer, 2-H_2) versus δ = 5.34 (s, 1 H of the enol tautomer, 2-H). ^{1}H NMR (300.1 MHz, C_6D_6): $\delta_{keto\ tautomer}$ = 0.93 (t, J = 7.1 Hz, 3 H, 1-OCH_2CH_3), 1.04–1.12 [m, 21 H, Si(iPr)$_3$], 1.18 (d, $J_{4',3'}$ = 6.0 Hz, 3 H, 4′-H_3), 1.35 and 1.39 [2× s, 2× 3 H, 4-$(CH_3)_2$], AB signal (δ_A = 2.27, δ_B = 2.45, J_{AB} = 15.0 Hz, A part additionally split by $J_{A,3'}$ = 6.7 Hz, B part additionally split by $J_{B,3'}$ = 5.3 Hz, 2 H, 2′-H_2), interlocked AB signal (δ_A = 3.43, δ_B = 3.45, J_{AB} = 15.5 Hz, 2 H, 2-H_2), 3.94 (q, J = 7.1 Hz, 2 H, 1-OCH_2CH$_3$), 4.30 (m$_c$, interpretable as qdd, $J_{3',4'} \approx J_{3',2'\text{-H(A)}} \approx J_{3',2'\text{-H(B)}} \approx$ 6.1 Hz, 1 H, 3′-H) ppm; $\delta_{enol\ tautomer}$ = 1.04–1.12 [m, 21 H, Si(iPr)$_3$], 1.49 and 1.51 [s, 2× 3 H, 4-$(CH_3)_2$], 2.56 [dd, J_{gem} = 14.9 Hz, $J_{2'\text{-H(1)},3'}$ = 5.4 Hz, 1 H, 2′-H^1], 5.34 (s, 1 H, 2-H), 13.10 (s, 1 H, 3-OH) ppm.

Ethyl (*R*)-{5,5-Dimethyl-4-oxo-2-[2-(triisopropylsiloxy)propyl]-4,5-dihydrofuran-3-yl}carboxylate (72)



A solution of the siloxy-acyl chloride **76** (144 mg, 517 μmol, 2.0 equiv.) in CH_2Cl_2 (0.3 mL) was added at room temp. over 15 min to a stirred solution of hydroxy-oxo ester **50** (45 mg, 0.26 mmol) and NEt_3 (80 μL, 58 mg, 57 μmol, 2.2 equiv.) in CH_2Cl_2 (1.2 mL). After 45 min, buffered phosphate solution (pH = 7.0, 2 mL) was added. The mixture was extracted with Et_2O (4× 5 mL). The combined organic phases were dried with $MgSO_4$. Removal of the solvent under reduced pressure and purification by flash chromatography[77] (2.0 cm, 20 mL, C_6H_{12}/EtOAc 12:1, #9–23) yielded the title compound (69.1 mg, 67%) as a colorless oil. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.98–1.12 [m (almost m$_c$), 21 H, Si(iPr)$_3$], 1.25 (d, $J_{3',2'}$ = 6.1 Hz, 3 H, 3′-H_3), 1.34 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.40 and 1.41 [2× s, 2× 3 H, 5-$(CH_3)_2$], AB signal (δ_A = 3.15, δ_B = 3.26, J_{AB} = 13.4 Hz, A part additionally split by $J_{A,2'}$ = 6.7 Hz, B part additionally split by $J_{B,2'}$ = 5.9 Hz, 2 H, 1′-H_2), 4.29 (q, J = 7.1 Hz, 2 H, OCH_2CH$_3$), 4.45 (m$_c$, interpretable as ddq, $J_{2',1'\text{-H(A)}} \approx J_{2',1'\text{-H(B)}} \approx J_{2',3'}$ = 6.2 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (125.6 MHz, C_6D_6): δ = 12.57 {flanked by d, which is an isotope satellite due to $^1J^{13}C,^{29}Si$ = 59.2 Hz, Si[CH-$(CH_3)_2]_3$}^{A}, 14.38 (OCH_2CH_3)^A, 18.14 and 18.17 {Si[CH-$(CH_3)_2]_3$}^{A}, 22.98 and 23.02 [5-$(CH_3)_2$]^A, 24.01 (C-3′)^A, 41.19 (C-1′)^A, 60.51 (OCH_2CH$_3$)^A, 66.70 (C-2′)^A, 89.87 (C-5)^B, 107.62 (C-3)^B, 162.91 (CO_2Et)^B, 195.21 (C-2)^B, 200.80 (C-4)^B ppm; ^{A}the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.6/400.1 MHz), $CDCl_3$] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [δ_H(^{1}H) ↔ δ_C(^{13}C)]: δ_H = 0.98–1.12 [m (almost an m$_c$), Si(iPr)$_3$] ↔ δ_C = 12.57 {Si[CH(CH$_3$)$_2$]$_3$} and 18.14 as well as 18.17 {Si[CH(CH_3)$_2$]$_3$}, δ_H = 1.25 (d, 3′-H_3) ↔ δ_C = 24.01 (C-3′), δ_H = 1.34 (t, OCH$_2$CH_3) ↔ δ_C = 14.38 (OCH_2CH$_3$), δ_H = 1.40 and 1.41 [2× s, 5-$(CH_3)_2$] ↔ δ_C = 22.98 and 23.02 [5-$(CH_3)_2$], δ_H = 3.15 ("A-part", 1′-H^A) and 3.26 ("B-part", 1′-H^B) ↔ δ_C = 41.19 (C-1′), δ_H = 4.29 (q, OCH_2CH$_3$) ↔ δ_C = 60.51 (OCH_2CH$_3$), δ_H = 4.45 (m$_c$, 2′-H) ↔ δ_C = 66.70 (C-2′); ^{B} these resonances were assigned as in the analogous TBDMS ether **78**, in which the assignments were inferred from an HMBC spectrum. IR ($CHCl_3$): ṽ = 2960, 2940, 2865, 2895, 1745 (shoulder), 1720, 1705, 1585, 1465, 1430, 1385, 1365, 1340, 1310, 1250, 1215, 1180, 1110, 1070, 1045, 1000, 920, 880, 780, 770, 720, 685 cm^{-1}. $C_{21}H_{38}O_5Si$ (398.6): calcd. C 63.28, H 9.61; found C 63.10, H 9.85.

Ethyl (2-{5-[(*E*)-But-2-enoyloxy]-3-(ethoxycarbonyl)-2,5-dimethyl-4-oxohexyl}-5,5-dimethyl-4-oxo-4,5-dihydrofuran-3-yl)carboxylate (74) as a Mixture (60:40) of the Two Possible Diastereomers



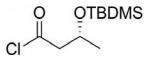
$NaHCO_3$ (49.9 mg, 594 μmol, 2.0 equiv.) was added at 30 °C to a solution of crotonate **69** (71.9 mg, 297 μmol, 2.0 equiv.) in EtOH (2 mL). The suspension was stirred for 3 d. H_2O was added, and the resulting mixture was extracted with Et_2O (4× 5 mL). The combined organic phases were dried with $MgSO_4$. Removal of the volatiles under reduced pressure and purification by flash chromatography[77] (2.5 cm, 20 mL, C_6H_{12}/EtOAc 4:1, #11–22) provided the title compound (40.4 mg, 58%). The diastereomer ratio was 60:40 as concluded from an analysis by chiral (!) HPLC: Chiralpak AD-H column; n-heptane/iPrOH 95:5, 1.0 mL min^{-1}, 23 °C; $\lambda_{detector}$ = 263 nm; $t_{r,\ 2\ enantiomers\ of\ the\ major\ diastereomer}$ = 12.97 and 14.05 min; $t_{r,\ 2\ enantiomers\ of\ the\ minor\ diastereomer}$ = 19.40 and 20.77 min. HRMS of the mixture (CI): calcd. for $C_{24}H_{35}O_9$ [M + H]$^+$ 467.22811; found 467.22830 (Δ = +0.4 ppm). The mixture was separated into the diastereomorphic constituents by preparative HPLC: Chiralpak AD-H column; n-heptane/iPrOH 95:5, 15 mL min^{-1}, $\lambda_{detector}$ = 263 nm, room temp.; $t_{r,\ the\ two\ enanantiomers\ of\ the\ "more\ slowly\ eluting\ diastereomer"}$ ≈ 24 and 25.5 min, $t_{r,\ the\ two\ enanantiomers\ of\ the\ "more\ rapidly\ eluting\ diastereomer"}$ ≈ 17.5 and 18.5 min.

More Rapidly Eluting Diastereomer: ^{1}H NMR (499.6 MHz, $CDCl_3$): δ = 0.98 (d, $J_{2'\text{-Me},2'}$ = 6.9 Hz, 3 H, 2′-CH_3), 1.27 and 1.34 (2× t, 2× 3 H, J = 7.3 Hz, 2× OCH$_2$CH_3), 1.41 and 1.42 [2× s, 2× 3 H, 5-$(CH_3)_2$], 1.54 and 1.59 (2× s, 2× 3 H, 5′-CH_3, 6′-H_3), 1.90 (dd, $J_{4'',3''}$ = 6.9 Hz, $J_{4'',2''}$ = 1.6 Hz, 3 H, 4′′-H_3), 2.87–2.96

(m, 2 H, 1′-H[1], 2′-H), 3.10–3.14 (m, 1 H, 1′-H[2]), 3.85 (d, $J_{3',2'}$ = 7.9 Hz, 1 H, 3′-H), 4.12–4.24 (m, 2 H, OEt), 4.29 (q, J = 7.0 Hz, 2 H, 2× OCH_2CH$_3$), 5.83 (dq, $J_{2'',3''}$ = 15.5 Hz, $J_{2'',4''}$ = 1.5 Hz, 1 H, 2′′-H), 6.98 (dq, $J_{3'',2''}$ = 15.1 Hz, $J_{3'',4''}$ = 7.1 Hz, 1 H, 3′′-H) ppm. ^{13}C NMR (125.6 MHz, $CDCl_3$; these resonances were assigned as in the more slowly eluting diastereomer, where analogous assignments were inferred from 2D spectra): δ = 14.16 and 14.37 (2× OCH$_2$CH_3), 16.57 (2′-CH$_3$), 18.15 (C-4′′), 22.98, 23.81, and 24.28 [three peaks for four potentially distinct nuclei: 5-(CH$_3$)$_2$, 5′-CH$_3$, C-6′], 31.48 and 35.39 (C-1′, C-2′), 58.51 (C-3′), 60.53 and 61.63 (2× OCH$_2$CH$_3$), 84.34 (C-5′), 89.99 (C-5), 107.75 (C-3), 122.45 (C-2′′), 146.28 (C-3′′), 162.87, 165.42, and 167.99 (2× CO$_2$Et, C-1′′), 196.02 (C-2), 200.80 (C-4), 203.13 (C-4′) ppm.

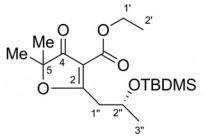
More Slowly Eluting Diastereomer: ^{1}H NMR (499.6 MHz, $CDCl_3$): δ = 0.96 (d, $J_{2'\text{-Me},2'}$ = 6.9 Hz, 3 H, 2′-CH$_3$), 1.28 and 1.35 (2× t, J = 7.3 Hz, 2× 3 H, 2× OCH$_2$CH_3), 1.41 and 1.42 [2× s, 2× 3 H, 5-(CH$_3$)$_2$], 1.57 and 1.59 (2× s, 2× 3 H, 5′-CH$_3$, 6′-H$_3$), 1.90 (dd, $J_{4'',3''}$ = 6.9 Hz, $J_{4'',2''}$ = 1.9 Hz, 3 H, 4′′-H$_3$), 2.90 (m$_c$, 1 H, 2′-H), 2.96 (dd, J_{gem} = 14.3 Hz, $J_{1'\text{-H}(1),2'}$ = 3.9 Hz, 1 H, 1′-H[1]), 3.19 (dd, J_{gem} = 14.2 Hz, $J_{1'\text{-H}(2),2'}$ = 10.4 Hz, 1 H, 1′-H[2]), 3.86 (d, $J_{3',2'}$ = 8.5 Hz, 1 H, 3′-H), 4.13–4.24 [m, 2 H, 3′-CO$_2$CH_2CH$_3$; this assignment follows from the HMBC spectrum (see below)], 4.29 [q, J = 7.0 Hz, 2 H, 3-CO$_2$CH_2CH$_3$; this assignment follows from the HMBC spectrum (see below)], 5.84 (dq, $J_{2'',3''}$ = 15.5 Hz, $J_{2'',4''}$ = 1.5 Hz, 1 H, 2′′-H), 6.99 (dq, $J_{3'',2''}$ = 15.4 Hz, $J_{3'',4''}$ = 7.1 Hz, 1 H, 3′′-H) ppm. ^{13}C NMR (125.6 MHz, $CDCl_3$): δ = 14.15 and 14.36 (2× OCH$_2$CH_3)^A, 17.89 (2′-CH$_3$)^A, 18.14 (C-4′′)^A, 22.91, 23.00, 23.64, and 24.18 [5-(CH$_3$)$_2$, 5′-CH$_3$, C-6′]^A, 32.14 (C-2′)^A, 34.40 (C-1′)^A, 58.59 (C-3′)^A, 60.56 and 61.71 (2× OCH$_2$CH$_3$)^A, 84.46 (C-5′)^B, 90.02 (C-5)^B, 107.77 (C-3)^B, 122.54 (C-2′′)^A, 146.13 (C-3′′)^A, 162.89 (3-CO$_2$Et)^B, 168.03 (3′-CO$_2$Et)^B, 165.40 (C-1′′)^B, 196.05 (C-2)^B, 200.76 (C-4)^B, 202.95 (C-4′)^B ppm; ^{A} the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (125.6/499.6 MHz), $CDCl_3$] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [δ_H(^{1}H) ↔ δ_C(^{13}C)]: δ_H = 0.96 (d, 2′-CH$_3$) ↔ δ_C = 17.89 (2′-CH$_3$), 1.28 and 1.35 (2× t, 2× OCH$_2$CH_3) ↔ δ_C = 14.15 and 14.36 (2× OCH$_2$CH_3), δ_H = 1.41 and 1.42 [2× s, 5-(CH$_3$)$_2$] and 1.57 and 1.59 (2× s, 5′-CH$_3$, 6′-H$_3$) ↔ δ_C = 22.91, 23.00, 23.64, and 24.18 [5-(CH$_3$)$_2$, 5′-CH$_3$, C-6′], δ_H = 1.90 (dd, 4′′-H$_3$) ↔ δ_C = 18.14 (C-4′′), δ_H = 2.96 (dd, 1′-H[1]) and 3.19 (dd, 1′-H[2]) ↔ δ_C = 34.40 (C-1′), δ_H = 3.86 (d, 3′-H) ↔ δ_C = 58.59 (C-3′), δ_H = 4.13–4.24 and 4.29 (m and q, 2× OCH_2CH$_3$) ↔ δ_C = 60.56 and 61.71 (2× OCH$_2$CH$_3$), δ_H = 5.84 (dq, 2′′-H) ↔ δ_C = 122.54 (C-2′′), δ_H = 6.99 (dq, 3′′-H) ↔ δ_C = 146.13 (C-3′′); ^{B} the indicated nuclei – they are quaternary – were distinguished in an HMBC spectrum ["long-range C,H-COSY spectrum"] (125.6 MHz/499.6 MHz, $CDCl_3$) by their crosspeaks due to ^2J, ^3J, and/or ^4J couplings to "remote" protons (these had previously been assigned unequivocally): (1) for δ_C = 84.46 (C-5′) such a crosspeak was due to $^2J_{5'\text{-Me},C\text{-}5'}$; for δ_C = 90.02 (C-5) such crosspeaks were due to $^2J_{5\text{-Me},C\text{-}5}$; (2) for δ_C = 107.77 (C-3) such a crosspeak was due to $^3J_{1'\text{-H},C\text{-}3}$; (3) for δ_C = 162.89 (3-CO$_2$Et) such a crosspeak was due to ^3J3-CO$_2$CH_2CH$_3$,3-CO$_2$Et; (4) for δ_C = 165.40 (C-1′′) such crosspeaks were due to $^3J_{3'',1''\text{-H},C\text{-}1''}$ and $^4J_{4''\text{-H},C\text{-}1''}$; (5) for δ_C = 168.03 (3′-CO$_2$Et) such crosspeaks were due to ^2J3′-H,3′-CO$_2$Et and to ^3J3′-CO$_2$CH_2CH$_3$,3′-CO$_2$Et; (6) for δ_C = 196.05 (C-2) such a crosspeak was due to $^2J_{1'\text{-H},C\text{-}2}$; (7) for δ_C = 200.76 (C-4) such crosspeaks were due to $^3J_{5\text{-Me},C\text{-}4}$; (8) for δ_C = 202.95 (C-4′) such crosspeaks were due to $^2J_{3'\text{-H},C\text{-}4'}$ and $^3J_{5'\text{-Me},C\text{-}4'}$.

(*R*)-3-(*tert*-Butyldimethylsiloxy)butanoyl Chloride (77)



Me_2C=C(NMe_2)Cl (734 mg, 5.50 mmol, 1.2 equiv.) was added at 0 °C with stirring to a solution of siloxybutanoic acid **97** (for formula, see ref.[71]) (1.00 g, 4.58 mmol) in CH_2Cl_2 (33 mL). The cooling bath was removed, and the mixture was stirred for 2 d. After removal of the solvent under reduced pressure, the title compound (599 mg, 55%) was obtained by distillation (bp. 0.5 mbar/55 °C). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.08 [s, 6 H, Si(CH$_3$)$_2$], 0.87 (s, 9 H, tBu), 1.23 (d, $J_{4,3}$ = 6.2 Hz, 3 H, 4-H$_3$), AB signal (δ_A = 2.91, δ_B = 2.99, J_{AB} = 15.3 Hz, A part additionally split by $J_{A,3}$ = 4.8 Hz, B part additionally split by $J_{B,3}$ = 7.7 Hz, 2 H, 2-H$_2$), 4.36 (m$_c$, possibly interpretable as ddq, $J_{3,2\text{-H(A)}} \approx J_{3,2\text{-H(B)}} \approx J_{3,4}$ ≈ 6.2 Hz, 1 H, 3-H) ppm.

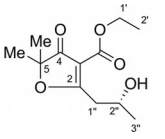
Ethyl (*R*)-{2-[2-(*tert*-Butyldimethylsiloxy)propyl]-5,5-dimethyl-4-oxo-4,5-dihydrofuran-3-yl}carboxylate (78)



NEt_3 (140 μL, 102 mg, 1.01 mmol, 2.2 equiv.) was added at room temp. to a solution of hydroxy-oxo ester **50** (80 mg, 0.46 mmol) in CH_2Cl_2 (2.0 mL). A solution of siloxy-butanoyl chloride **77** (217 mg, 919 μmol, 2.0 equiv.) in CH_2Cl_2 (0.5 mL) was added over the course of 15 min. Stirring was continued for 45 min. Buffered phosphate solution (pH = 7.0, 3 mL) was added. The resulting mixture was extracted with Et_2O (4× 10 mL). The organic phases were combined and dried with $MgSO_4$. Removal of the volatiles under reduced pressure and purification by flash chromatography[77] (2.0 cm, 20 mL, C_6H_{12}/EtOAc 12:1, #14–36) gave the title compound (107.7 mg, 66%) as a colorless oil. ^{1}H NMR (499.6 MHz, C_6D_6): δ = 0.05 and 0.06 [2× s, 2× 3 H, Si(CH$_3$)$_2$], 0.93 (s, 9 H, tBu), 1.09 (t, $J_{2',1'}$ = 6.3 Hz, 3 H, 2′-H$_3$), superimposed by 1.10 (d, $J_{3'',2''}$ = 6.0 Hz, 3 H, 3′′-H$_3$), 1.13 [s, 6 H, 5-(CH$_3$)$_2$], 2.89 (dd, J_{gem} = 12.9 Hz, $J_{1''\text{-H}(1),2''}$ = 6.0 Hz, 1 H, 1′′-H[1]), 3.25 (dd, J_{gem} = 12.9 Hz, $J_{1''\text{-H}(2),2''}$ = 6.6 Hz, 1 H, 1′′-H[2]), 4.15 (q, $J_{1',2'}$ = 7.1 Hz, 2 H, 1′-H$_2$), 4.29 (m$_c$, interpretable as ddq, $J_{2'',1''\text{-H}(1)} \approx J_{2'',1''\text{-H}(2)} \approx J_{2'',3''} \approx$ 6.2 Hz, 1 H, 2′′-H) ppm. ^{13}C NMR (125.6 MHz, C_6D_6;): δ = –4.66 and –4.43 [Si(CH$_3$)$_2$]^A, 14.15 (C-2′)^A, 18.10 [C(CH$_3$)$_3$], 22.78 and 22.82 [5-(CH$_3$)$_2$]^A, 24.02 (C-3′′)^A, 25.94 [C(CH$_3$)$_3$]^A, 41.00 (C-1′′)^A, 60.19 (C-1′)^A, 66.84 (C-2′′)^A, 89.26 (C-5)^B, 108.06 (C-3)^B, 163.34 (CO$_2$Et)^B, 194.55 (C-2)^B, 198.79 (C-4)^B ppm; ^{A} the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (125.6/499.6 MHz), C_6D_6] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [δ_H(^{1}H) ↔ δ_C(^{13}C)]: δ_H = 0.05 and 0.06 [2× s, Si(CH$_3$)$_2$] ↔ δ_C = –4.66 and –4.43 [Si(CH$_3$)$_2$]; δ_H = 0.93 (s, tBu) ↔ δ_C = 25.94 [C(CH$_3$)$_3$]; δ_H = 1.09 (t, 2′-H$_3$) ↔ δ_C = 14.15 (C-2′); δ_H = 1.10 (d, 3′′-H$_3$) ↔ δ_C = 24.02 (C-3′′); δ_H = 1.13 [s, 5-(CH$_3$)$_2$] ↔ δ_C = 22.78 and 22.82 [5-(CH$_3$)$_2$]; δ_H = 2.89 (dd, 1′′-H[2]) and 3.25 (dd, 1′′-H[1]) ↔ δ_C = 41.00 (C-1′′); δ_H = 4.15 (q, 1′-H$_2$) ↔ δ_C = 60.19 (C-1′); δ_H = 4.29 (m$_c$, 2′′-H) ↔ δ_C = 66.84 (C-2′′); ^{B} the indicated nuclei – they are quaternary – were distinguished in an HMBC spectrum ["long-range C,H-COSY spectrum" (125.6 MHz/499.6 MHz) C_6D_6] by their crosspeaks due to ^2J and/or ^3J couplings to "remote" protons (these had previously been assigned unequivocally): (1) for δ_C = 89.26 (C-5) such crosspeaks were due to $^2J_{5\text{-Me},C\text{-}5}$; (2) for δ_C = 108.06 (C-3) such a crosspeak was due to $^3J_{1''\text{-H},C\text{-}3}$; (3) for δ_C = 163.34 (CO$_2$Et) such a crosspeak was due to ^3JCO_2CH$_2$CH$_3$,CO$_2$Et; (4) for δ_C = 194.55 (C-2) such crosspeaks

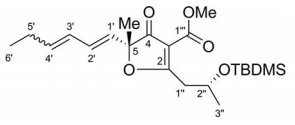
were due to $^2J_{1''\text{-H},C\text{-}2}$ and $^3J_{2''\text{-H},C\text{-}2}$; (5) for δ_C = 198.79 (C-4) such crosspeaks were due to $^3J_{5\text{-Me},C\text{-}4}$. IR ($CHCl_3$): $\tilde{\nu}$ = 2975, 2955, 2930, 2900, 2850, 1745 (shoulder), 1720, 1705, 1585, 1565, 1470, 1430, 1385, 1360, 1310, 1255, 1215, 1180, 1110, 1045, 995, 925, 835, 770 cm^{-1}. $C_{18}H_{32}O_5Si$ (356.5): calcd. C 60.64, H 9.05; found C 60.59, H 9.29.

Ethyl (*R*)-2-(2-Hydroxy-5,5-dimethyl-4-oxo-4,5-dihydrofuran-3-yl)-carboxylate (79)



A solution of the siloxylated furanone **78** (93 mg, 0.26 mmol) in a THF/EtOH/HCl (10%) mixture [4:1:2 (v/v), 7 mL] was stirred at 70 °C for 20 min. After the mixture had cooled to room temp., buffered phosphate solution (pH = 7.0, 5 mL) was added. Extraction with EtOAc (4× 10 mL), drying of the combined organic phases with $MgSO_4$, removal of the volatiles under reduced pressure, and flash chromatography[77] (2.0 cm, 20 mL, C_6H_{12}/EtOAc 1:1, #12–24) furnished the title compound (42.6 mg, 68%) as a colorless solid (m.p. 35–36 °C). ^{1}H NMR (400.1 MHz, C_6D_6): δ = 1.05 (d, $J_{3'',2''}$ = 6.3 Hz, 3 H, 3''-H_3), superimposed by 1.07 (t, $J_{2',1'}$ = 7.1 Hz, 3 H, 2'-H_3), 1.085 and 1.095 [2× s, 2× 3 H, 2-$(CH_3)_2$], 2.41 (br s, 1 H, 2''-OH), AB signal (δ_A = 2.82, δ_B = 2.93, J_{AB} = 13.2 Hz, A part additionally split by $J_{A,2''}$ = 4.7 Hz, B part additionally split by $J_{B,2''}$ = 7.5 Hz, 2 H, 1''-H_2), 4.02–4.12 (m, 1 H, 2''-H), superimposed by 4.10 (q, $J_{1',2'}$ = 7.1 Hz, 2 H, 1'-H_2) ppm. ^{13}C NMR (125.6 MHz, C_6D_6): δ = 14.25 (C-2')^A, 22.65 and 22.72 [5-$(CH_3)_2$]^A, 23.76 (C-3'')^A, 40.16 (C-1'')^A, 60.54 (C-1')^A, 66.17 (C-2'')^A, 89.59 (C-5)^B, 108.28 (C-3)^B, 164.33 [*C*(=O)OEt]^B, 194.97 (C-2)^B, 198.63 (C-4)^B ppm; ^{A} the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.6/400.1 MHz), $CDCl_3$] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 1.05 (d, 3''-H_3) $\leftrightarrow \delta_C$ = 23.76 (C-3''), δ_H = 1.05 (t, 2'-H_3) $\leftrightarrow \delta_C$ = 14.25 (C-2'), δ_H = 1.085 and 1.095 [s, 5-$(CH_3)_2$] $\leftrightarrow \delta_C$ = 22.65 and 22.72 [5-$(CH_3)_2$], δ_H = 2.82 (dd, 1''-H^A) and 2.93 (dd, 1''-H^B) $\leftrightarrow \delta_C$ = 40.16 (C-1''), δ_H = 4.02–4.12 (m, 2''-H) $\leftrightarrow \delta_C$ = 66.17 (C-2''), δ_H = 4.10 (t, 1'-H_2) $\leftrightarrow \delta_C$ = 60.54 (C-1'); ^{B} these resonances were assigned as in the corresponding TBDMS ether **78**, where the assignments were inferred from an HMBC spectrum IR ($CHCl_3$): $\tilde{\nu}$ = 3470, 2975, 2930, 1735 (shoulder), 1705, 1580, 1460, 1435, 1410, 1385, 1295, 1255, 1215, 1185, 1110, 1075, 1040, 935, 920, 880, 850, 795, 770 cm^{-1}. $C_{12}H_{18}O_5$ (242.3): calcd. C 59.49, H 7.49; found C 59.40, H 7.68.

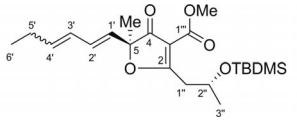
Methyl {(*R*)-2-[(*R*)-2-(*tert*-Butyldimethylsiloxy)propyl]-5-[(*E*,*E*)-hexa-1,3-dienyl]-5-methyl-4-oxo-4,5-dihydrofuran-3-yl}carboxylate [(*E*,*E*)-(5*R*,2''*R*)-80c] in a Mixture (93:7) with Methyl {(*R*)-2-[(*R*)-2-(*tert*-Butyldimethylsiloxy)propyl]-5-[(1'*E*,3'*Z*)-hexa-1,3-dienyl]-5-methyl-4-oxo-4,5-dihydrofuran-3-yl}carboxylate [(1'*E*,3'*Z*)-(5*R*,2''*R*)-80c]



NEt_3 (220 µL, 158 mg, 1.56 mmol, 2.2 equiv.) was added at room temp. to a solution of a mixture (92:8) of hydroxy-oxo esters (*E*,*E*)-(*R*)-**29** and (1'*E*,3'*Z*)-(*R*)-**29** (160 mg, 707 µmol) in CH_2Cl_2 (3.5 mL). After 5 min, a solution of siloxy-butanoyl chloride **77** (334 mg, 1.41 mmol, 2.0 equiv.) in CH_2Cl_2 (0.5 mL) was added over the course of 15 min. Stirring was continued for 30 min. Buffered phosphate solution (pH = 7.0, 5 mL) was added. The resulting mixture was extracted with Et_2O (4× 10 mL). The organic phases were combined and dried with $MgSO_4$. Removal of the volatiles under reduced pressure and purification by flash chromatography[77] (2.5 cm, 20 mL, C_6H_{12}/EtOAc 15:1, #15–34) gave the title compound (194.3 mg, 67%) as a colorless oil. The (*E*,*E*)/(1'*E*,3'*Z*) ratio was 93:7 according to the integrals of the following resonances in a ^{1}H NMR spectrum (400 MHz, C_6D_6): δ = 1.85 [m_c, 2 H of (*E*,*E*) isomer, 5'-H_2] versus δ = 2.01 [m_c, 2 H of (1'*E*,3'*Z*) isomer, 5'-H_2]. $[\alpha]_D^{20}$ = +58.8 (*c* = 0.99 in $CHCl_3$). ^{1}H NMR (400.1 MHz, C_6D_6): δ = 0.04 and 0.06 [2× s, 2× 3 H of (1'*E*,3'*Z*) isomer, $Si(CH_3)_2$], 0.05 and 0.07 [2× s, 2× 3 H of (*E*,*E*) isomer, $Si(CH_3)_2$], 0.79 [t, $J_{6',5'}$ = 7.5 Hz, 3 H of (1'*E*,3'*Z*) isomer, 6'-H_3], 0.82 [t, $J_{6',5'}$ = 7.5 Hz, 3 H of (*E*,*E*) isomer, 6'-H_3], 0.93 [s, 9 H of (1'*E*,3'*Z*) isomer, *t*Bu], 0.94 [s, 9 H of (*E*,*E*) isomer, *t*Bu], 1.11 (d, $J_{3'',2''}$ = 6.2 Hz, 3 H, 3''-H_3), 1.35 [s, 3 H of (1'*E*,3'*Z*) isomer, 5-CH_3], 1.37 [s, 3 H of (*E*,*E*) isomer, 5-CH_3], 1.85 [m_c, possibly interpretable as qdd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.2 Hz, $J_{5',3'}$ = 1.0 Hz, 2 H of (*E*,*E*) isomer, 5'-H_2], 2.01 [m_c, possibly interpretable as qdd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.5 Hz, $J_{5',3'}$ = 1.5 Hz, 2 H of (1'*E*,3'*Z*) isomer, 5'-H_2], 2.87 [dd, J_{gem} = 12.9 Hz, $J_{1''\text{-H}(1),2''}$ = 6.4 Hz, 1 H of (*E*,*E*) isomer, 1''-H^1], 2.95 [dd, J_{gem} = 12.9 Hz, $J_{1''\text{-H}(1),2''}$ = 6.7 Hz, 1 H of (1'*E*,3'*Z*) isomer, 1''-H^1], 3.24 [dd, J_{gem} = 12.8 Hz, $J_{1''\text{-H}(2),2''}$ = 6.3 Hz, 1 H of (1'*E*,3'*Z*) isomer, 1''-H^2], 3.30 [dd, J_{gem} = 12.9 Hz, $J_{1''\text{-H}(2),2''}$ = 6.3 Hz, 1 H of (*E*,*E*) isomer, 1''-H^2], 3.49 [s, 3 H of (1'*E*,3'*Z*) isomer, OCH_3], 3.51 [s, 3 H of (*E*,*E*) isomer, OCH_3], 4.31 (m_c, possibly interpretable as qdd, $J_{2'',3''} \approx J_{2'',1''\text{-H}(1)} \approx J_{2'',1''\text{-H}(2)} \approx$ 6.2 Hz, 1 H, 2''-H), 5.35 [dt, $J_{4',3'}$ = 10.8 Hz, $J_{4',5'}$ = 7.6 Hz, 1 H of (1'*E*,3'*Z*) isomer, 4'-H], 5.54 [d, $J_{1',2'}$ = 15.5 Hz, 1 H of (*E*,*E*) isomer, 1'-H], signal superimposed by 5.55 [dt, $J_{4',3'}$ = 15.1 Hz, $J_{4',5'}$ = 6.3 Hz, 1 H of (*E*,*E*) isomer, 4'-H], 5.64 [d, $J_{1',2'}$ = 15.4 Hz, 1 H of (1'*E*,3'*Z*) isomer, 1'-H], 5.84 [ddd, $J_{3',4'}$ = 15.2 Hz, $J_{3',2'}$ = 10.5 Hz, $J_{3',5'}$ = 0.6 Hz, 1 H of (*E*,*E*) isomer, 3'-H]^A, 6.41 [dd, $J_{2',1'}$ = 15.5 Hz, $J_{2',3'}$ = 10.5 Hz, 1 H of (*E*,*E*) isomer, 2'-H]^A, 6.80 [dd, $J_{2',1'}$ = 15.4 Hz, $J_{2',3'}$ = 11.1 Hz, $J_{2',4'}$ = 1.0 Hz, 1 H of (1'*E*,3'*Z*) isomer, 2'-H] ppm; ^{A} the indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.1 MHz), C_6D_6] by their crosspeaks with protons that had previously been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 5.84 (ddd, 3'-H) $\leftrightarrow \delta$ = 5.55 (dt, 4'-H) and δ = 5.84 (ddd, 3'-H) $\leftrightarrow \delta$ = 6.41 (dd, 2'-H); δ = 6.41 (dd, 2'-H) $\leftrightarrow \delta$ = 5.54 (d, 1'-H) and δ = 6.41 (dd, 2'-H) $\leftrightarrow \delta$ = 5.84 (ddd, 3'-H). ^{13}C NMR (100.6 MHz, C_6D_6): δ = –4.63 and-4.47 [$Si(CH_3)_2$]^A, 13.40 (C-6')^A, 18.11 [$C(CH_3)_3$], 22.58 (5-CH_3)^A, 23.99 (C-3'')^A, 25.89 (C-5')^A, 25.95 [$C(CH_3)_3$], 41.03 (C-1'')^A, 50.94 (OCH_3)^A, 66.81 (C-2'')^A, 90.95 (C-5), 108.22 (C-3), 126.69 (C-1')^A, 128.40 (C-3')^A, 132.04 (C-2')^A, 138.98 (C-4')^A, 163.57 (C-1'''), 194.87 (C-2), 196.49 (C-4) ppm; ^{A} the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.6/400.1 MHz), C_6D_6] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 0.05 and 0.07 (s, $SiCH_3$) $\leftrightarrow \delta_C$ = –4.63 and –4.47 [$Si(CH_3)_2$], δ_H = 0.82 (t, 6'-H_3) $\leftrightarrow \delta_C$ = 13.40 (C-6'), δ_H = 0.94 (s, *t*Bu) $\leftrightarrow \delta_C$ = 25.95 [$C(CH_3)_3$], δ_H = 1.11 (d, 3''-H_3) $\leftrightarrow \delta_C$ = 23.99 (C-3''), δ_H = 1.37 (s, 5-CH_3) $\leftrightarrow \delta_C$ = 22.58 (5-CH_3), δ_H = 1.85 (m_c, 5'-H_2) $\leftrightarrow \delta_C$ = 25.89 (C-5'), δ_H = 2.87 (dd, 1''-H^1) and 3.30 (dd, 1''-H^2) $\leftrightarrow \delta_C$ = 41.03 (C-1''), δ_H = 3.51 (s, OCH_3) $\leftrightarrow \delta_C$ = 50.94 (OCH_3), δ_H = 5.54 (d, 1'-H) $\leftrightarrow \delta_C$ = 126.69 (C-1'), δ_H = 5.55 (dt, 4'-H) $\leftrightarrow \delta_C$ = 138.98 (C-4'), δ_H = 5.84 (ddd, 3'-H) $\leftrightarrow \delta_C$ = 128.40 (C-3'), δ_H = 6.41 (dd, 2'-H) $\leftrightarrow \delta_C$ = 132.04 (C-2'). IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2955, 2930, 2885, 2855, 1750 (shoulder), 1715,

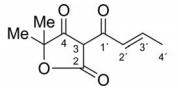
1655, 1585, 1470, 1460, 1435, 1385, 1340, 1305, 1255, 1195, 1125, 1040, 995, 940, 920, 840, 810, 775 cm^{-1}. $C_{22}H_{36}O_5Si$ (408.6): calcd. C 64.67, H 8.88; found C 64.48, H 8.78.

Methyl {(*S*)-2-[(*R*)-2-(*tert*-Butyldimethylsiloxy)propyl]-5-[(*E*,*E*)-hexa-1,3-dienyl]-5-methyl-4-oxo-4,5-dihydrofuran-3-yl}carboxylate [(*E*,*E*)-(5*S*,2′′*R*)-80c] in a Mixture (93:7) with Methyl {(*S*)-2-[(*R*)-2-(*tert*-Butyldimethylsiloxy)propyl]-5-[(1′*E*,3′*Z*)-hexa-1,3-dienyl]-5-methyl-4-oxo-4,5-dihydrofuran-3-yl}carboxylate [(1′*E*,3′*Z*)-(5*S*,2′′*R*)-80c]



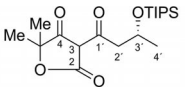
NEt_3 (162 µL, 118 mg, 1.17 mmol, 2.2 equiv.) was added at room temp. to a solution of a mixture (92:8) of hydroxy-oxo esters (*E*,*E*)-(*S*)-**29** and (1′*E*,3′*Z*)-(*S*)-**29** (120 mg, 530 µmol) in CH_2Cl_2 (2.5 mL). After 5 min, a solution of the siloxybutanoyl chloride **77** (251 mg, 1.06 mmol, 2.0 equiv.) in CH_2Cl_2 (0.5 mL) was added over the course of 15 min. Stirring was continued for 45 min, buffered phosphate solution (pH = 7.0, 5 mL) was added, and the resulting mixture was extracted with Et_2O (4× 10 mL). The organic phases were combined and dried with $MgSO_4$. Removal of the volatiles under reduced pressure and purification by flash chromatography[77] (2.5 cm, 20 mL, C_6H_{12}/EtOAc 15:1, #13–32) provided the title compound (151.8 mg, 70%) as a colorless oil. The (*E*,*E*)/(1′*E*,3′*Z*) ratio was 93:7 according to the integrals of the following resonances in a ^1H NMR spectrum (400 MHz, C_6D_6): δ = 1.85 [m_c, 2 H of (*E*,*E*) isomer, 5′-H_2] versus δ = 2.01 [m_c, 2 H of (1′*E*,3′*Z*) isomer, 5′-H_2]. $[\alpha]_D^{20}$ = –105.3 (*c* = 0.97 in $CHCl_3$). ^1H NMR (400.1 MHz, C_6D_6): δ = 0.04 and 0.06 [2× s, 2× 3 H, $Si(CH_3)_2$], 0.82 (t, $J_{6',5'}$ = 7.5 Hz, 3 H, 6′-H_3), 0.93 (s, 9 H, *t*Bu), 1.13 (d, $J_{3'',2''}$ = 6.1 Hz, 3 H, 3′′-H_3), 1.35 [s, 3 H of (1′*E*,3′*Z*) isomer, 5-CH_3], 1.37 [s, 3 H of (*E*,*E*) isomer, 5-CH_3], 1.85 [m_c, possibly interpretable as qdd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.2 Hz, $J_{5',3'}$ = 1.1 Hz, 2 H of (*E*,*E*) isomer, 5′-H_2], 2.01 [m_c, possibly interpretable as qdd, $J_{5',6'} \approx J_{5',4'} \approx$ 7.5 Hz, $J_{5',3'}$ = 1.4, 2 H of (1′*E*,3′*Z*) isomer, 5′-H_2], 2.84 [dd, J_{gem} = 13.1 Hz, $J_{1''\text{-H}(1),2''}$ = 6.5 Hz, 1 H of (1′*E*,3′*Z*) isomer, 1′′-H^1], 2.89 [dd, J_{gem} = 12.9 Hz, $J_{1''\text{-H}(1),2''}$ = 6.1 Hz, 1 H of (*E*,*E*) isomer, 1′′-H^1], 3.27 [dd, J_{gem} = 12.9 Hz, $J_{1''\text{-H}(2),2''}$ = 6.4 Hz, 1 H of (*E*,*E*) isomer, 1′′-H^2], 3.31 [dd, J_{gem} = 13.4 Hz, $J_{1''\text{-H}(2),2''}$ = 6.2 Hz, 1 H of (1′*E*,3′*Z*) isomer, 1′′-H^2], 3.50 [s, 3 H of (1′*E*,3′*Z*) isomer, OCH_3], 3.51 [s, 3 H of (*E*,*E*) isomer, OCH_3], 4.30 (m_c, possibly interpretable as qdd, $J_{2'',3''} \approx J_{2'',1''\text{H}(1)} \approx J_{2'',1''\text{H}(2)} \approx$ 6.2 Hz, 1 H, 2′′-H), 5.35 [dt, $J_{4',3'}$ = 10.8 Hz, $J_{4',5'}$ = 7.6 Hz, 1 H of (1′*E*,3′*Z*) isomer, 4′-H], 5.54 [d, $J_{1',2'}$ = 15.5 Hz, 1 H of (*E*,*E*) isomer, 1′-H], signal superimposed by 5.55 [dt, $J_{4',3'}$ = 15.0 Hz, $J_{4',5'}$ = 6.2 Hz, 1 H of (*E*,*E*) isomer, 4′-H], 5.64 [d, $J_{1',2'}$ = 15.4 Hz, 1 H of (1′*E*,3′*Z*) isomer, 1′-H], 5.83 [ddd, $J_{3',4'}$ = 15.2 Hz, $J_{3',2'}$ = 10.4 Hz, $J_{3',5'}$ = 0.6 Hz, 1 H of (*E*,*E*) isomer, 3′-H][A], 6.42 [dd, $J_{2',1'}$ = 15.5 Hz, $J_{2',3'}$ = 10.7 Hz, 1 H of (*E*,*E*) isomer, 2′-H][A], 6.81 [dd, $J_{2',1'}$ = 15.4 Hz, $J_{2',3'}$ = 11.1 Hz, $J_{2',4'}$ = 1.0 Hz, 1 H, of (1′*E*,3′*Z*) isomer, 2′-H] ppm; [A] the indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.1 MHz, C_6D_6)] by their crosspeaks with protons that had previously been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 5.83 (ddd, 3′-H) ↔ δ = 5.55 (dt, 4′-H); δ = 5.83 (ddd, 3′-H) ↔ δ = 6.42 (dd, 2′-H); δ = 6.42 (dd, 2′-H) ↔ δ = 5.54 (d, 1′-H). ^{13}C NMR (100.6 MHz, C_6D_6): δ = –4.65 and –4.45 [$Si(CH_3)_2$][A], 13.41 (C-6′)[A], 18.11 [$C(CH_3)_3$], 22.66 (5-CH_3)[A], 24.08 (C-3′′)[A], 25.89 (C-5′)[A], 25.94 [$C(CH_3)_3$], 41.02 (C-1′′)[A], 50.94 (OCH_3)[A], 66.96 (C-2′′)[A], 91.00 (C-5), 108.21 (C-3), 126.71 (C-1′)[A], 128.41 (C-3′)[A], 132.04 (C-2′)[A], 138.94 (C-4′)[A], 163.60 (C-1′′′), 195.00 (C-2), 196.52 (C-4) ppm; [A] the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.6/400.1 MHz), C_6D_6] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 0.04 and 0.06 (s, $SiCH_3$) ↔ δ_C = –4.65 and –4.45 [$Si(CH_3)_2$]; δ_H = 0.82 (t, 6′-H_3) ↔ δ_C = 13.41 (C-6′); δ_H = 0.93 (s, *t*Bu) ↔ δ_C = 25.94 [$C(CH_3)_3$]; δ_H = 1.13 (d, 3′′-H_3) ↔ δ_C = 24.08 (C-3′′); δ_H = 1.37 (s, 5-CH_3) ↔ δ_C = 22.66 (5-CH_3); δ_H = 1.85 (m_c, 5′-H_2) ↔ δ_C = 25.89 (C-5′); δ_H = 2.89 (dd, 1′′-H^1) and 3.27 (dd, 1′′-H^2) ↔ δ_C = 41.02 (C-1′′); δ_H = 3.51 (s, OCH_3) ↔ δ_C = 50.94 (OCH_3); δ_H = 5.54 (d, 1′-H) ↔ δ_C = 126.71 (C-1′); δ_H = 5.55 (dt, 4′-H) ↔ δ_C = 138.94 (C-4′); δ_H = 5.83 (ddd, 3′-H) ↔ δ_C = 128.41 (C-3′); δ_H = 6.42 (dd, 2′-H) ↔ δ_C = 132.04 (C-2′). IR ($CHCl_3$): $\tilde{\nu}$ = 2955, 2930, 2885, 2855, 1750 (shoulder), 1715, 1655, 1585, 1470, 1460, 1435, 1385, 1340, 1305, 1255, 1215, 1195, 1125, 1095, 1040, 995, 940, 915, 835, 810, 775 cm^{-1}. $C_{22}H_{36}O_5Si$ (408.6): calcd. C 64.67, H 8.88; found C 64.94, H 9.14.

3-[(*E*)-But-2-enoyl]-5,5-dimethyl-2,4(3*H*,5*H*)-furandione[80] (98)



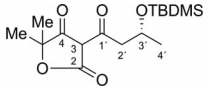
A solution of *trans*-crotonoyl chloride (56 µL, 61 mg, 0.59 mmol, 2.0 equiv.) in CH_2Cl_2 (1 mL) was added dropwise at room temp. to a stirred solution of hydroxy-oxo ester **50** (51.1 mg, 294 µmol), DBU (50 µL, 51 mg, 0.32 mmol, 1.1 equiv.), and 4-(dimethylamino) pyridine (7.2 mg, 59 µmol, 20 mol-%) in CH_2Cl_2 (1 mL). Stirring was continued for 30 min. Buffered phosphate solution (pH = 7.0, 2 mL) was added. Extraction with Et_2O (4× 5 mL), drying of the combined organic phases with $MgSO_4$, removal of the volatiles under reduced pressure, and purification by flash chromatography[77] (2.0 cm, 20 mL, C_6H_{12}/EtOAc 3:1, #4–6) provided the title compound (38.3 mg, 66%) as a colorless solid (m.p. 84–85 °C). ^1H NMR (499.6 MHz, C_6D_6): δ = 1.09 [s, 6 H, 5-$(CH_3)_2$], 1.23 (br. d, $J_{4',3'}$ = 6.9 Hz, 3 H, 4′-H_3), 5.37 (br. d, $J_{2',3'}$ = 15.8 Hz, 1 H, 2′-H), 6.25 (s, 1 H, 3-H), 6.70 (dq, $J_{3',2'}$ = 14.8 Hz, $J_{3',4'}$ = 7.3 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (125.6 MHz, C_6D_6): δ = 17.84 (C-4′)[A], 24.13 [5-$(CH_3)_2$][A], 81.80 (C-5)[B], 99.62 (C-3)[A], 120.22 (C-2′)[A], 149.84 (C-3′)[A], 160.86 (C-1′)[B], 170.03 (C-2)[B], 173.26 (C-4)[B] ppm; [A] the indicated ^{13}C nuclei are primary, secondary, or tertiary and were distinguished in an HMBC (!) spectrum ["long-range C,H-COSY spectrum" (125.7 MHz/ 499.7 MHz), C_6D_6] by their crosspeaks due to a ^1J (!) coupling to the directly bound proton(s), previously assigned unequivocally: [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 1.09 [s, 5-$(CH_3)_2$] ↔ δ_C = 24.13 [5-$(CH_3)_2$], δ_H = 1.23 (br. d, 4′-H_3) ↔ δ_C = 17.84 (C-4′), δ_H = 5.37 (br. d, 2′-H) ↔ δ_C = 120.22 (C-2′), δ_H = 6.25 (s, 3-H) ↔ δ_C = 99.62 (C-3), δ_H = 6.70 (dq, 3′-H) ↔ δ_C = 149.84 (C-3′); [B] the indicated nuclei – they are quaternary – were distinguished in the already discussed HMBC spectrum ["long-range C,H-COSY spectrum" (125.6 MHz/499.6 MHz) C_6D_6] by their crosspeaks due to ^2J, ^3J, and/or ^4J couplings to "remote" protons (these had previously been assigned unequivocally: (1) for δ_C = 81.80 (C-5) such crosspeaks were due to $^3J_{3\text{-H},C\text{-}5}$; (2) for δ_C = 160.86 (C-1′) such crosspeaks were due to $^2J_{2'\text{-H},C\text{-}1'}$, $^3J_{3'\text{-H},C\text{-}1'}$, and $^4J_{4'\text{-H},C\text{-}1'}$; (3) for δ_C = 170.03 (C-2) such a crosspeak was due to $^2J_{3\text{-H},C\text{-}2}$; (4) for δ_C = 173.26 (C-4) such crosspeaks were due to $^3J_{5\text{-}Me,C\text{-}4}$. IR ($CHCl_3$): $\tilde{\nu}$ = 3015, 2985, 2935, 1875, 1825, 1805, 1755, 1650, 1630, 1470, 1440, 1365, 1340, 1310, 1290, 1265, 1215, 1180, 1150, 1110, 1090, 1045, 980, 970, 940, 900, 885, 830, 795, 755, 685, 660, 635 cm^{-1}. $C_{10}H_{12}O_4$ (196.2): calcd. C 61.22, H 6.16; found C 61.13, H 6.07.

3-[(*R*)-2-(Triisopropylsiloxy)butyl]-5,5-dimethyl-2,4(3*H*,5*H*)-furandione[80] (99)



A solution of acyl chloride **76** (187 µL, 670 µmol, 2.0 equiv.) in CH_2Cl_2 (1 mL) was added dropwise at room temp. to a solution of hydroxy-oxo ester **50** (58.3 mg, 335 µmol), DBU (55 µL, 56 mg, 0.37 mmol, 1.1 equiv.), and 4-(dimethylamino)pyridine (8.2 mg, 67 µmol, 20 mol-%) in CH_2Cl_2 (1 mL). Stirring was continued for 30 min. Buffered phosphate solution (pH = 7.0, 2 mL) was added. Extraction with Et_2O (4× 5 mL), drying of the combined organic phases with $MgSO_4$, removal of the volatiles under reduced pressure, and purification by flash chromatography[77] (2.0 cm, 20 mL, C_6H_{12}/EtOAc 5:1, #5–11) provided the title compound (79.45 mg, 64%). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.95–1.12 [m, 21 H, Si(*i*Pr)$_3$], 1.33 (d, $J_{4',3'}$ = 6.1 Hz, 3 H, 4′-H$_3$), 1.50 [s, 6 H, 5-(CH$_3$)$_2$], AB signal (δ_A = 2.69, δ_B = 2.76, J_{AB} = 14.9 Hz, A part additionally split by $J_{A,3'}$ = 5.7, B part additionally split by $J_{B,3'}$ = 6.6 Hz, 2 H, 2′-H$_2$), 4.48 (m$_c$, possibly interpretable as qdd, $J_{3',4'} \approx J_{3',2'\text{-H(A)}} \approx J_{3',2'\text{-H(B)}} \approx$ 6.1 Hz, 1 H, 3′-H), 6.07 (s, 1 H, 3-H) ppm.

3-[(*R*)-2-(*tert*-Butyldimethylsiloxy)butyl]-5,5-dimethyl-2,4(3*H*,5*H*)-furandione[80] (100)



A solution of acyl chloride **77** (142 mg, 0.604 mmol, 2.0 equiv.) in CH_2Cl_2 (1 mL) was added dropwise at room temp. to a solution of hydroxy-oxo ester **50** (52.6 mg, 0.302 mmol), DBU (50 µL, 51 mg, 0.33 mmol, 1.1 equiv.), and 4-(dimethylamino)pyridine (7.4 mg, 60 µmol, 20 mol-%) in CH_2Cl_2 (1 mL). Stirring was continued for 30 min. Buffered phosphate solution (pH = 7.0, 2 mL) was added. Extraction with Et_2O (4× 5 mL), drying of the combined organic phases with $MgSO_4$, removal of the volatiles under reduced pressure, and purification by flash chromatography[77] (2.0 cm, 20 mL, C_6H_{12}/EtOAc 4:1, #3–6) provided the title compound (59.9 mg, 60%). ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.03 and 0.07 ppm [2× s, 2× 3 H, Si(CH$_3$)$_2$], 0.84 (s, 9 H, *t*Bu), 1.26 (d, $J_{4',3'}$ = 6.2 Hz, 3 H, 4′-H$_3$), 1.50 [s, 6 H, 5-(CH$_3$)$_2$], AB signal (δ_A = 2.65, δ_B = 2.68, J_{AB} = 14.8 Hz, A part additionally split by $J_{A,3'}$ = 5.3 Hz, B part additionally split by $J_{B,3'}$ = 7.3 Hz, 2 H, 2′-H$_2$), 4.29–4.39 (m, 1 H, 3′-H), 6.07 (s, 3-H) ppm.

Supporting Information (see footnote on the first page of this article): Compilations of specific rotations of natural products vs. synthetic samples (Table S1) and comparisons between NMR data of natural products vs. synthetic samples (Tables S2–S4); experimental procedures and spectroscopic details for compounds (2*R*,5*R*)-**47**, (2*S*,5*S*)-**47**, D-lactic acid, methyl D-lactate, **76**, **86**–**89**, and **93**–**97**, which were already described in the literature yet also prepared in the course of our study and characterized spectroscopically.

Acknowledgments

We express our gratitude to the International Research Training Group 1038 "Catalysts and Catalytic Reactions for Organic Synthesis" of the Deutsche Forschungsgemeinschaft for support of H. B.-S. by a scholarship. We are indebted to Professor Klaus Ditrich (BASF AG) for supplying us with isobutyl D-lactate and to Dipl.-Chem. Thomas Hampel (University of Freiburg) for suggesting the (*E*)-hex-3-enal route to (*E*,*E*)-**46**. R. B. thanks Professor Clemens Richert (University of Stuttgart) for an inspiring discussion about the transformations shown in Scheme 9.

[1] a) First isolation of this compound (from *Cephalosporium gregatum*): K. Kobayashi, T. Ui, *Tetrahedron Lett.* **1975**, *16*, 4119–4122; b) naming of this compound: K. Kobayashi, T. Ui, *Physiol. Plant Pathol.* **1977**, *11*, 55–60.

[2] Second isolation of this compound (from *Aspergillus panamensis*): H. Anke, H. Schwab, H. Achenbach, *J. Antibiot.* **1980**, *33*, 931–939.

[3] Third isolation (from *Phialophora gregata*): S. L. Taylor, R. E. Peterson, L. E. Gray, *Appl. Environ. Microbiol.* **1985**, *50*, 1328–1329.

[4] J. A. Ballantine, V. Ferrito, C. H. Hassall, V. I. P. Jones, *J. Chem. Soc. C* **1969**, 56–61. Note added in proof: Aspertetronine A was also isolated from *Aspergillus* sp. XW-12.[81]

[5] Isolation of this compound (from *Cephalosporium gramineum*): K. Kobayashi, T. Ui, *J. Chem. Soc., Chem. Commun.* **1977**, 774–774.

[6] First isolation of this compound (from *Aspergillus panamensis*): Ref.[2]

[7] K. Yamashita, A. Takaiwa, H. Nakada, *Agric. Biol. Chem.* **1980**, *44*, 2931–2935.

[8] See, however, our conclusions, as shown in Scheme 4, that (*S*)-*tautom*-**18**[29] must be levorotatory and (+)-*tautom*-**18** must be (*R*)-configured.

[9] a) N. G. Clemo, G. Pattenden, *Tetrahedron Lett.* **1982**, *23*, 585–588; b) N. G. Clemo, G. Pattenden, *J. Chem. Soc. Perkin Trans. 1* **1985**, 2407–2411.

[10] K. Takeda, H. Kubo, T. Koizumi, E. Yoshii, *Tetrahedron Lett.* **1982**, *23*, 3175–3178.

[11] O. Miyata, R. R. Schmidt, *Tetrahedron Lett.* **1982**, *23*, 1793–1796.

[12] H. Anke, I. Casser, M. Schrage, W. Steglich, *J. Antibiot.* **1988**, *17*, 1681–1684.

[13] Isolation of this compound (from *Penicillium daleae*): T. Kimura, T. Takeuchi, Y. Kumamoto-Yonezawa, E. Ohashi, H. Ohmori, C. Masutani, F. Hanaoka, F. Sugawara, H. Yoshida, Y. Mizushina, *Bioorg. Med. Chem.* **2009**, *17*, 1811–1816.

[14] Footnote a of Table 1 in ref.[12] states that "in a second isolation [of (+)-cyclogregatin] a doubling of the signals of H-8, H-9, H-10, H-11, and H-12 was observed which indicates the presence of two diastereomers." In our opinion this might mean that "the (+)-cyclogregatins" are isolation artifacts formed from (+)-gregatin C and/or (+)-gregatin D.

[15] A. Takaiwa, K. Yamashita, *Agric. Biol. Chem.* **1984**, *48*, 2061–2065.

[16] K. Matsuo, M. Kanayama, J. Y. Xu, R. Takeuchi, K. Nishiwaki, Y. Asaka, *Heterocycles* **2005**, *65*, 1609–1614.

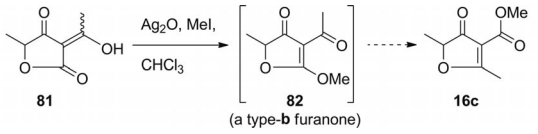
[17] H. Burghart-Stoll, R. Brückner, *Org. Lett.* **2011**, *13*, 2730–2733.

[18] The uniform way in which the second-generation structures **2b**–**9b** and the third-generation structures **2c**–**9c** are presented in this paper entails diverging ways for numbering their furanone cores: in order to comply with IUPAC nomenclature the second-generation furanones must be numbered clockwise and the third-generation furanones counterclockwise. The swapping of positional numbers on moving from a second-generation to a third-generation structure diverts attention from the realization that, structurally speaking, something else swaps: namely the substituents R′ and OMe. To emphasize the appearance of swapped substituents in identical furanones, NMR discussions and NMR assignments refer to IUPAC numbers in the third-generation furanone cores and to identical but non-IUPAC numbers in the second-generation furanones.

[19] Cyclogregatin [(+)-**7**[12]] eludes this statement except when one takes its ^{13}C NMR spectrum into consideration (Table 3). This exhibits indisputable chemical shift analogies with type-**c** compounds.

[20] K. Kato, H. Nouchi, K. Ishikura, S. Takaishi, S. Motodate, H. Tanaka, K. Okudaira, T. Mochida, R. Nishigaki, K. Shigenobu, H. Akita, *Tetrahedron* **2006**, *62*, 2545–2554.

[21] Compound **16c** was prepared by Takaiwa and Yamashita (ref.[22]) by a methylation of **81**, which they believed to deliver **82** but in fact delivered **16c** as we conclude on grounds of ^{1}H (cf. Table 1) and ^{13}C NMR analogies (cf. Table 3):



It is plausible that **82** was the primary product under the authors' conditions but subsequently isomerized to give **16c**. This isomerization would have been promoted by Ag_2O (or Ag_2O and trace impurities of H_2O) assuming a role akin to that of MnO_2 (or MnO_2 and trace impurities of H_2O) in the isomerization (–)-**1b** → (–)-**1c**, which we described recently[17] (Scheme 7, bottom).

[22] A. Takaiwa, K. Yamashita, *Agric. Biol. Chem.* **1982**, *46*, 1721–1722.

[23] In an E-mail dated 11 April 2011, co-author T. Takeuchi (ref.[13]) confirmed to R. B. on behalf of Y. Mizushina that $CDCl_3$ was the solvent and not CD_3OD as suggested in ref.[13]

[24] The ^{1}H NMR spectrum of this compound in $CDCl_3$ was reported in our earlier study.[17]

[25] These data were published in the Supporting Information section of ref.[17]

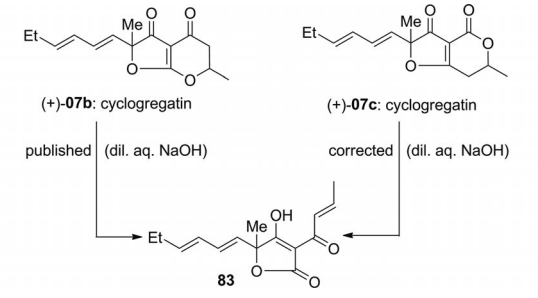
[26] Table 3shows that these variations are largely due to $\Delta\delta_{4\text{-C=O}}$ and $\Delta\delta_{C\text{-}5}$ and only marginally to $\Delta\delta_{C\text{-}3}$. These resonances may not be readily individually assigned for any newcomer structure. In contrast, the discussed sum value would be unequivocally accessible.

[27] The structures obtained by application of reaction conditions (f) and (g) were not specified.

[28] In $CDCl_3$ solution both (+)- and (–)-*tautom*-**10** are keto/enol mixtures (82:18) according to our observations.

[29] A. Svendsen, P. M. Boll, *Tetrahedron Lett.* **1974**, *15*, 2821–2822.

[30] Ref.[12] states that compound **83** resulted "within a few seconds" upon treatment of the then surmised structure (+)-**7b** with NaOH (0.1 M):



Because of ^{1}H (cf. Table 1) and ^{13}C NMR analogies (cf. Table 3) we suggest that structure (+)-**7b** must be replaced by structure (+)-**7c**. Accordingly, the authors' conversion **7c** → **83** is another reaction analogous to **17c** → **19**; the difference is that the 2-hydroxypropyl group is concomitantly dehydrated, delivering a prop-1-enyl group.

[31] a) Compound (–)-**27** was first prepared by K. Mori, *Tetrahedron* **1975**, *31*, 1381–1384. Its stereocenter was considered to be (*S*), because (–)-**27** exhibited a positive Cotton effect ($\Delta\varepsilon$ = +1.80 at 215 nm), *and* the analogous lactone-based acid, which contained H instead of Me and which was known to be (*S*)-configured for independent reasons exhibited a very similar Cotton effect ($\Delta\varepsilon$ = +1.72 at 213 nm). b) Mori converted (–)-**27** into (–)-frontalin in the same study. If (–)-**27** was (*S*)-configured the resulting (–)-frontalin was (1*S*)-configured.

[32] The identity of (–)-frontalin with (1*S*,5*R*)-frontalin became irrefutably clear in 1983 when (1*R*,5*S*)-frontalin was synthesized from (+)-(*S*)-lactic acid and turned out to be dextrorotatory.[33] Since then several other total syntheses of optically active frontalin have served as independent confirmation for (–)- = (1*S*,5*R*)-frontalin and (+)- = (1*R*,5*S*)-frontalin (e.g., ref.[34]).

[33] R. Naef, D. Seebach, *Liebigs Ann. Chem.* **1983**, 1930–1936.

[34] a) J. A. Turpin, L. O. Weigel, *Tetrahedron Lett.* **1992**, *33*, 6563–6564; b) C. Kouklovsky, O. Dirat, T. Berranger, Y. Langlois, M. E. Tran-Huu-Dau, C. Riche, *J. Org. Chem.* **1998**, *63*, 5123–5128; c) B. List, D. Shabat, G. Zhong, J. M. Turner, A. Li, T. Bui, J. Anderson, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **1999**, *121*, 7283–7291.

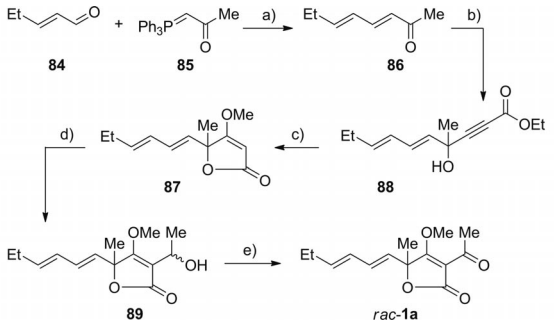
[35] A higher yield for our correlation (*S*)-**29** → (*S*)-**30** → (*S*)-*tautom*-**18** would have been desirable. However, when the lactonization (*S*)-**30** → (*S*)-*tautom*-**18** was performed we had not yet optimized the corresponding protocol. After having achieved that (cf. Scheme 9, Scheme 12), we failed to return to the sequence (*S*)-**29** → (*S*)-**30** → (*S*)-*tautom*-**18**: our total syntheses sufficed to make the various structural reassignments unquestionable.

[36] Method: a) N. G. Clemo, G. Pattenden, *Tetrahedron Lett.* **1982**, *23*, 581–584; b) ref.[11]

[37] N. G. Clemo, G. Pattenden, *Tetrahedron Lett.* **1982**, *23*, 589–592.

[38] R. Muntwyler, W. Keller-Schierlein, *Helv. Chim. Acta* **1972**, *55*, 2071–2094.

[39] This compound was prepared via dienone **86** and from then onward by the method of Pattenden and Clemo:[9b]



Reagents and conditions: (a) Compound **85** (1.6 equiv.), room temp., 5 d (72%). (b) Ethyl propiolate (1.5 equiv.), THF/pentane/Et_2O (4:1:1), –110 °C; addition of *n*BuLi (1.8 M in hexanes, 1.5 equiv.), 15 min; addition of **84**, –100 °C, 4 h; removal of cold bath, addition of buffered phosphate solution (pH = 7.0) (43%, ref.[9b] 52%). (c) NaOMe (0.43 equiv.), MeOH, room temp., 2 d (15%, ref.[9b] 43%). (d) LDA (1.5 equiv.), THF, 30 min; addition of acetaldehyde, 20 min; → room temp. (71%, ref.[9b] 84%). (e) MnO_2 (20 equiv.), CH_2Cl_2, room temp., 3.5 h (47%, ref.[9b] 62%).

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[51] a) Original report: D. Seebach, R. Naef, *Helv. Chim. Acta* **1981**, *64*, 2704–2708; b) detailed study: D. Seebach, R. Naef, G. Calderari, *Tetrahedron* **1984**, *40*, 1313–1324; c) review: D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem.* **1996**, *108*, 2881–2921; D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem.* **1996**, *108*, 2881; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708–2748.
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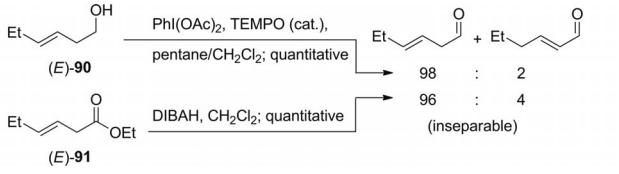
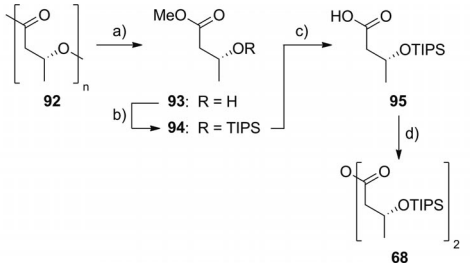
[56] We obtained a slightly purer sample of (*E*)-hex-3-enal by oxidizing the alcohol (*E*)-**90** (by modifying the procedure from ref.[57]) than by reducing the ester (*E*)-**91**. The contaminant was (*E*)-hex-2-enal and the (*E*)-hex-3-enal/(*E*)-hex-2-enal ratios were determined from the integral ratios of the corresponding aldehyde protons in the ^{1}H NMR spectra (300 MHz, C_6D_6): δ = 9.21 (t) for (*E*)-hex-3-enal versus δ = 9.38 (d) for (*E*)-hex-2-enal.

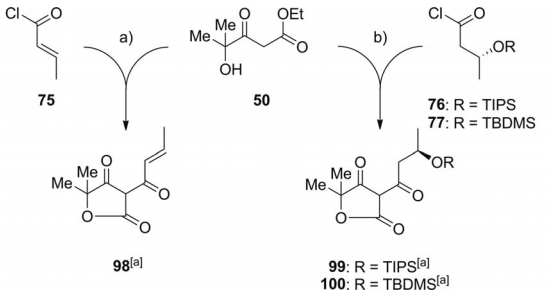


[57] D. J. Vugts, L. Veum, K. al-Mafraji, R. Lemmens, R. F. Schmitz, F. J. J. de Kanter, M. B. Groen, U. Hanefeld, R. V. A. Orru, *Eur. J. Org. Chem.* **2006**, 1672–1677. We modified this procedure as follows: A solution of (*E*)-hex-3-en-1-ol [(*E*)-**90**, 1.25 mL, 1.11 g, 11.1 mmol, 2.0 equiv. relative to the amount of lactone **58**, which was used for converting the resulting (*E*)-hex-3-enal into **59** (Scheme 11)] in a mixture [9:2 (v/v)] of pentane and dichloromethane (34 mL), $PhI(OAc)_2$ (4.64 g, 14.4 mmol, 1.30 equiv.), and TEMPO (0.347 g, 2.22 mmol, 0.20 equiv.) was stirred at room temp. for 3.5 h. The reaction was quenched by the addition of a solution of $NaHCO_3$ (0.29 M in H_2O, 10 mL, 2.9 mmol, 2.6 equiv.) and phosphate buffer (pH = 7, 30 mL). The resulting mixture was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were dried with $MgSO_4$, and the solvents were removed under reduced pressure. The crude product was immediately subjected to the next step.
[58] The addition of the lithium enolate of acetal (2*R*,5*R*)-**47** to *trans*-dodec-2-enal showed complete *trans* selectivity according to: K. Matsuo, M. Kanayama, K. Nishiwaki, *Heterocycles* **2006**, *68*, 1401–1407. Treatment with 2,4-$(O_2N)_2C_6H_3SCl$ and NEt_3 in CH_2Cl_2 at reflux for 4 h furnished an 82% yield of a 1,3-diene analogue to compound (2*R*,5*S*)-**46** as an inseparable 88:12 (*E*,*E*)/(1′*E*,3′*Z*)-mixture (ibid.).
[59] These reaction conditions were adopted from an analogous 1,4-elimination described by: T. Mandai, T. Matsumoto, J. Tsuji, *Tetrahedron Lett.* **1993**, *34*, 2513–2516.
[60] Protocol: A. Palmgren, A. L. E. Larsson, J.-E. Bäckvall, *J. Org. Chem.* **1999**, *64*, 836–842.
[61] These reaction conditions were taken from an analogous 1,4-elimination described by: E. C. Hansen, D. Lee, *Tetrahedron Lett.* **2004**, *45*, 7151–7155.
[62] H. J. Reich, I. L. Reich, S. Wollowitz, *J. Am. Chem. Soc.* **1978**, *100*, 5981–5982; these authors first developed such sulfenylation/rearrangement/β-elimination reactions by converting more than 20 allylic alcohols into 1,3-dienes, which were obtained as 95:5 to 60:40 (*E*,*E*)/(*E*,*Z*) mixtures.
[63] Pyrolysis of an *isolated* (*E*)-allyl phenyl sulfoxide in THF at reflux produced a 1,3-diene as an 87:13 (*E*,*E*)/(*E*,*Z*) mixture: J. D. Ha, J. K. Cha, *J. Am. Chem. Soc.* **1999**, *121*, 10012–10020.
[64] The aldol adduct obtained from the lithium enolate of a δ-unsubstituted δ-valerolactam and (*E*)-hex-2-enal was treated with PhSCl and NEt_3, and the resulting allyl sulfoxide was thermolyzed in THF at reflux. This produced a 1,3-diene as a 90:10 (*E*,*E*)/(*E*,*Z*) mixture: A. G. Waterson, A. I. Meyers, *J. Org. Chem.* **2000**, *65*, 7240–7243.
[65] At 90 °C the O,S-acetal analogue of O,O-acetal (2*R*,5*S*)-**58**, 2,4-$(O_2N)_2C_6H_3SCl$, and NEt_3 furnished the O,S-acetal analogue of O,O-acetal (2*R*,5*S*)-**46** as a 4:1 (*E*,*E*)/(1′*E*,3′*Z*) mixture: J. M. McFadden, S. M. Medghalchi, J. N. Thupari, M. L. Pinn, A. Vadlamudi, K. I. Miller, F. P. Kuhajda, C. A. Townsend, *J. Med. Chem.* **2005**, *48*, 946–961.
[66] The minor enantiomer of the undesired diastereomer (1′*E*,3′*Z*)-(*R*)-**1c** should also have been a contaminant of our synthetic "(+)-gregatin B". However, the quantities expected should have been so small (ca. 0.35 rel-%) as to elude detection.
[67]



Reagents and conditions: (a) Compound **92**, 1,2-dichloroethane/MeOH (12:5), conc. H_2SO_4 (0.3 equiv.), reflux, 3 d (76%, ref.[68] 79%). (b) Lutidine (1.6 equiv.), iPr_3SiOTf (1.0 equiv.), CH_2Cl_2, 0 °C; 0 °C → room temp., 2 h (95%, ref.[69] 100%). (c) $LiOH·H_2O$ (1.5 equiv.), THF/H_2O (1:1.3), room temp., 3 d (91%, ref.[69] 98%). (d) CH_2Cl_2, 0 °C; addition of NEt_3 (1.1 equiv.) and *p*TsOH (0.5 equiv.), 70 min (80%, ref.[69] 95%). Tf = F_3CSO_2O.

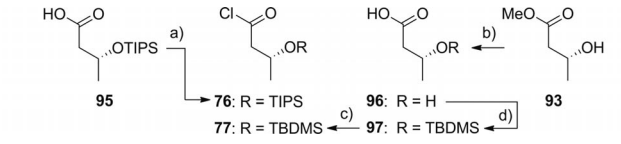
[68] A. Griesbeck, D. Seebach, *Helv. Chim. Acta* **1987**, *70*, 1320–1325.
[69] J. E. Lynch, S. M. Riseman, W. L. Laswell, D. M. Tschaen, R. P. Volante, G. B. Smith, I. Shinkai, *J. Org. Chem.* **1989**, *54*, 3792–3796.
[70]



Reagents and conditions: (a) DBU (1.1 equiv.), CH_2Cl_2, room temp., 5 min; DMAP (20 mol-%), **75** (2.0 equiv.), 30–45 min (66%). (b) Same as (a), but with **76** [→ **99** (64%)] or **77** [→ **100** (60%)].

[a] Cf. ref.[80] We first encountered this ambiguity with respect to the analogous "acyltetronic acid" **54** (Scheme 9).

[71]



Reagents and conditions: (a) Oxalyl chloride (1.5 equiv.), CH_2Cl_2, room temp., 3 h (81%, ref.[69] 89%). (b) KOH (1.5 equiv.), H_2O, 0 °C; room temp., 2 d (94%, ref.[72] 93%). (c) 1-(Dimethylamino)-2-methylprop-1-ene (1.2 equiv.), CH_2Cl_2, 0 °C; room temp., 2 d (55%, cf. ref.[74]). (d) *t*$BuMe_2$SiCl (2.2 equiv.), NEt_3 (2.2 equiv.), DMAP (1.0 equiv.), CH_2Cl_2, 0 °C; room temp., 2 d (100%, ref.[73] 84%).

[72] D. Seebach, U. Brändli, P. Schnurrenberger, M. Przybylski, *Helv. Chim. Acta* **1988**, *71*, 155–167.

[73] D. Seebach, U. Brändli, P. Schnurrenberger, M. Przybylski, *Helv. Chim. Acta* **1988**, *71*, 155–167.

[74] D. Seebach, U. Brändli, P. Schnurrenberger, M. Przybylski, *Helv. Chim. Acta* **1988**, *71*, 155–167.

[75] Ref.[1a] reported a 90 MHz ^{1}H NMR spectrum of (–)-gregatin A in CCl_4. Instead of specifying the data the authors described them collectively as being identical with those for the antipode [i.e., (+)-aspertetronin A].

[76] Reviews: a) K. C. Nicolaou, S. A: Snyder, *Angew. Chem.* **2005**, *117*, 1036–1069, corrigendum 2086–2086; *Angew. Chem. Int. Ed.* **2005**, *44*, 1012–1044, corrigendum 2050–2050; b) M. Elyashberg, A. J. Williams, K. Blinov, *Nat. Prod. Rep.* **2010**, *27*, 1296–1328.

[77] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

[78] There is the same uncertainty about the tautomeric nature of compound **51** as discussed in ref.[79] and ref.[80] for related compounds.

[79] As indicated in footnote [d] of Scheme 9, we cannot assign a tautomeric formula to compound **54**. Ref.[80] discusses the analogous ambiguity in compounds **98**–**100**. With respect to the tautomeric nature of compound **98**, ref.[80] presents a C,H correlation argument, upon which we base the diketone formula given for compound **98**. The analogous argument *for* a diketone formula given for compound **54** stems from its edHSQC spectrum ["short-range C,H-COSY spectrum" (100.6/400.1 MHz), $CDCl_3$] and the following crosspeak, which ought to be caused by a $^1J_{C,H}$ *and not a* $^2J_{C,H}$ *coupling* [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 6.03 (s, 3-H) ↔ δ_C = 99.45 (C-3). The key argument *against* a diketone formula is – exactly as for compound **98**[80] – the fact that the low-field ^{13}C nuclei (δ = 165.67, 171.14, and 173.53) are relatively little deshielded.

[80] Compounds **98**–**100** were single tautomers according to their ^{1}H NMR spectra, but we could not determine which ones. ^{13}C NMR and H,H-correlation data were recorded only for compound **98**. In the HMBC (!) spectrum ["long-range C,H-COSY spectrum" (125.7 MHz/499.7 MHz), C_6D_6] of **98** the following crosspeak was attributed to a $^1J_{C,H}$ (!) coupling [$\delta_H(^1H) \leftrightarrow \delta_C(^{13}C)$]: δ_H = 6.25 (s, 3-H) ↔ δ_C = 99.62 (C-3). We do not consider the deshielding of δ_H = 6.25 a reliable basis for distinguishing the underlying proton (sp^3-bonded in the diketone tautomer **98**) from an enol proton (in whatever enol tautomer of **98**). However, attribution of the cited HMBC crosspeak to $^1J_{C,H}$ *rather than to* $^2J_{C,H}$ makes such a distinction possible. Unfortunately, we do not feel up to deciding whether the interpretation of the underlying coupling constant as $^1J_{C,H}$ is reliable. In any case, the low-field ^{13}C-resonances of compound **98** (δ_C = 160.86, 170.03, and 173.26) appear to be less deshielded as if **98** was the diketone tautomer, as which it is drawn. It should be noted that the structurally related compound (–)-**19** in $CDCl_3$ was reported as an enol on the basis of the deshielding of δ_H = 10.25 (at 60 MHz).[4]

[81] Z.-J. Zhan, J.-P. Jin, Y.-M. Ying, W.-G. Shan, *Helv. Chim. Acta* **2011**, *94*, 1454–1458.

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Structure Elucidation by Synthesis

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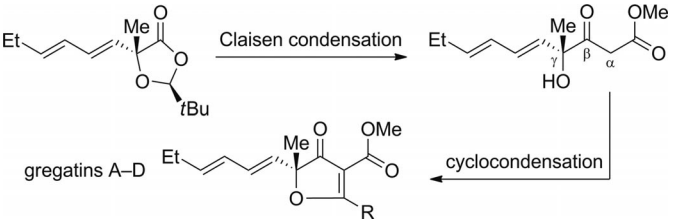

Our recent discovery of the correct structure of gregatin B was an incentive for developing straightforward and (stereo)structure-revising syntheses of the gregatins A–D from L-lactic acid. An unprecedented α-acylation of a γ-hydroxy-β-oxo ester allowed furanone formation through a nucleophilic vinylic substitution.

