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Synthesis of a C^n–C^{n+6} Building Block Common to Important Polyol,Polyene Antibiotics from a Divinylcarbinol by a Desymmetrizing Sharpless Epoxidation

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A stereocontrolled synthesis of the enantiomerically pure epoxide **7b** from propargyl ether **15** has been realized in 15 steps. Epoxide **7b** represents a building block for the "eastern" moieties of the title compounds. Key steps in our approach were a desymmetrizing Sharpless epoxidation (→ *anti*,*cis*-**16**), the selective processing of the bis-enolate of the bis(*tert*-butyl alkoxyacetate) **11** through a diastereoselective [2,3]-Wittig rearrangement (→ *syn*,*syn*-**9**), and a stereo- and chemoselective iodolactonization (→ **35**). The CO_2H groups of dicarboxylic acid **37** were differentiated in a one-pot bis-oxidation reaction. The latter entailed the novel transformation of HO_2CCH_2-*O*-alkyl into $AcOCH_2$-*O*-alkyl.

Introduction

The polyol,polyene macrolides are a family of several hundred secondary metabolites and are produced by bacterial pathogens of the genus *Streptomyces*.[1] Most polyol, polyene macrolides show antifungal activity.[1] From a clinical point of view, the best-known polyol,polyene macrolides are amphotericin B (**1**)[2] and nystatin A_1 (**2**;[3] Scheme 1). The potential to keep fungi from food let pimaricin (**4**)[4,5] become an important food preservative (E235).[6] Candidin (**3**)[7] is structurally closely related to **1** and **2**. Compounds **1**–**4** have a tetrahydropyrancarboxylic acid moiety ("eastern moiety") in common. This structural motif is shared by rimocidin (**5**),[8] genetically engineered nystatin analogues,[9] and a number of other polyol,polyene macrolides.[10] The tetrahydropyrancarboxylic acid moiety of these compounds should assume, and does so[2c] in **1**, a chair conformation with four equatorial substituents and an axially oriented anomeric OH group. Considering this and the abundance of this substructure, it is tempting to suggest that the "eastern" moiety co-defines the 3D structure of said compounds. By extrapolation, one may wonder whether inserting this "eastern" moiety between unnatural polyol and polyene sections interconnected by an ester bond could give rise to modified polyol,polyene macrolides also acting as antibiotics.

The basis for this expectation may be better than standard analogies. This is because the antimycotic activity[11,12] of the polyol,polyene macrolides may not hinge so much upon the exact locations of the functional groups but on shape. For amphotericin B (**1**), such an assessment stems from attributing its bioactivity to the formation of potassium ion channels through membranes.[11] It was suggested that the walls of these channels are a tubular array of 1:1 complexes wherein the hydrophobic backbone of the antibiotic is juxtaposed by a hydrophobic steroid alcohol.[1e,11b] The latter would be ergosterol in fungi or cholesterol in *Homo sapiens*.[13] In these complexes the steroids interact with the membrane, which means that they define the exterior of the channel.[11] The polyol sections of the antibiotics make up the channel's interior. Comparing the ion-channel-forming propensities of amphotericin B (**1**) with designed analogues thereof[14] supported this concept and revealed three facts: 1) Pairs of channels interact with one another longitudinally so that they span the width of the membrane,[14a] 2) the sugar moiety reinforces the binding of the sterol by a hydrogen bridge,[14b,14d,14e] and 3) the carboxylic acid moiety is not essential for antifungal activity.[14b,14e] Smaller-sized polyol,polyene antibiotics like pimaricin (**4**) and rimocidin (**5**) do not make cell membranes permeable for ions.[15] In contrast, specific interactions of pimaricin (**4**) with ergosterol inhibit endocytosis[16] as well as vacuole fusion in fungi.[17]

To obtain (sub)structures that may or may not modify the antifungal activity of the polyol,polyene macrolides, we synthesized the "eastern" moiety of compounds **1**–**5** in a novel fashion. The significant general interest in synthetic polyol,polyene macrolactone antibiotics[18–28] was a further motivation for this work.

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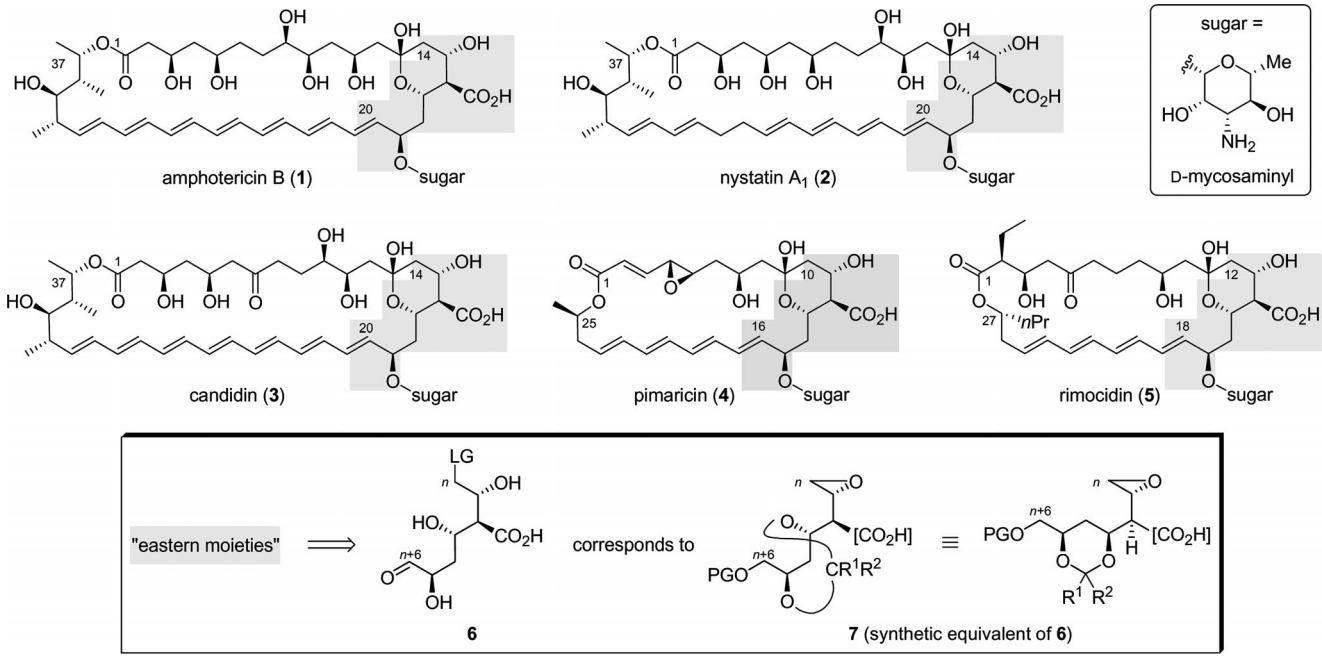


Scheme 1. Top and center: Polyol,polyene macrolides **1**–**5** with a common tetrahydropyrancarboxylic acid, the "eastern moiety". Bottom: Synthon **6** for the "eastern moiety" and synthetic equivalent **7** thereof.

Results and Discussion

Retrosynthetic Analysis

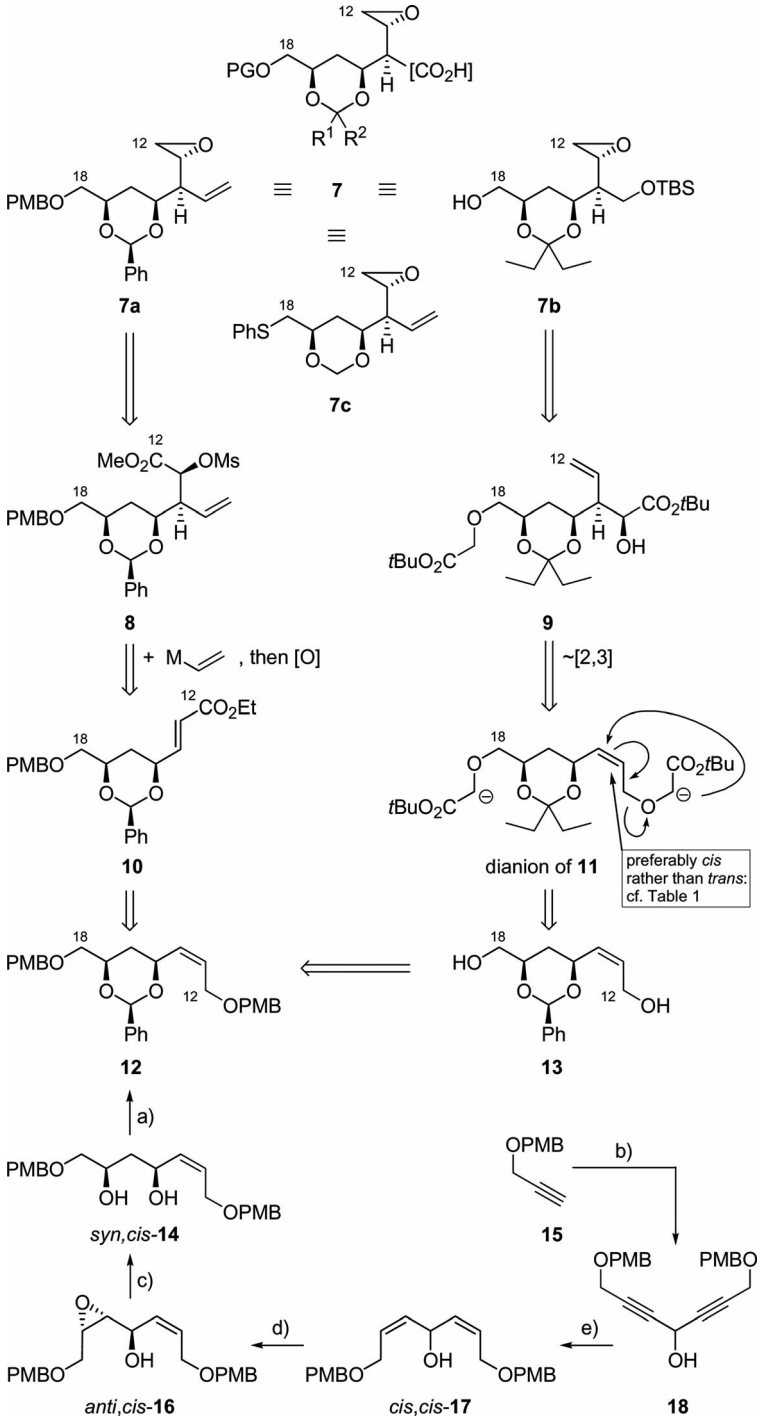
The desired synthetic equivalent **7** of the "eastern" moiety of the polyol,polyene antibiotics **1**–**5** should be incorporable into such compounds, for example, into rimocidin (**5**), or analogues thereof. Accordingly, **7** was equipped with an epoxide ring at one end (i.e., at C^{12}, using the numbering of rimocidin from now on) and a latent OH group at the other (i.e., at C^{18}; Scheme 2). These functional groups should allow combinations with a "northern", that is, polyol fragment (through nucleophilic attack upon C^{12}) and a "southwestern", that is, moderately oxygenated polyene moiety (through olefination of a C^{18} aldehyde). We prepared a similar building block **7c** (Scheme 2) a long time ago,[29] but there were certain deficiencies both in its substitution pattern and in our synthetic route. As a consequence, we have now synthesized two modified "eastern" building blocks **7a**[30] and **7b** (Scheme 2). Their substituents are more adept for further elaboration, there is more stereocontrol, and the use of hexamethylphosphoric triamide (HMPA) is avoided. Both **7a** and **7b** can be prepared from the diol *syn,cis*-**14**, for which we already developed a short synthesis[31,32] (bottom part of Scheme 2[33]). Transacetalization of *syn,cis*-**14** with benzaldehyde dimethyl acetal gave the dioxane **12** uneventfully.[30b] Compound **12** was then converted into both building block **7a** (retrosynthetic sketch: Scheme 2; synthesis: see accompanying paper[30]) and building block **7b**, which is the subject of this paper.

Our retrosynthetic analysis revealed the dioxane **12** as an early precursor of building block **7b** and the unsaturated hydroxy ester **9** as the immediate precursor (cf. Scheme 2). The epoxide ring of **7b** should stem from the homoallyl alcohol moiety of **9**. The relative configurations of the stereocenters in **9**[34] suggest that it is a promising substrate for a Mihelich epoxidation.[34a] To achieve **7b**, the hydroxy ester moiety of compound **9** required shortening by an oxidative cleavage. The extra carbon atom and the configuration of its C–OH bond were implemented in **9** for two reasons: 1) To control the steric course of epoxide formation and 2) to be able to obtain **9** by a [2,3]-Wittig rearrangement[35] of the bis-enolate **11**, which is depicted as a dianion in Scheme 2. The transformation **11**→**9** seemed reasonably analogous to its antecessor lithio-*cis*-**19a**→*syn*,*syn*-**20a**, which one of us studied previously (Table 1, entry 1[36]). Related precedents (Table 1, entries 2–4[36]) suggested that we best rearrange a *tert*-butyl ester containing a *cis*-configured C=C double bond.

Closing the gap between the desired rearrangement substrate dilithio-**11** and the already-mentioned dioxane **12** required the following structural changes (Scheme 2): 1) The PMB ether moieties of **12** had to be replaced by (*tert*-butoxycarbonyl)methyl ethers and 2) the underlying 1,3-diol had to be incorporated into a pentanone ketal in lieu of the benzaldehyde acetal, as we discovered later (cf. Table 2).

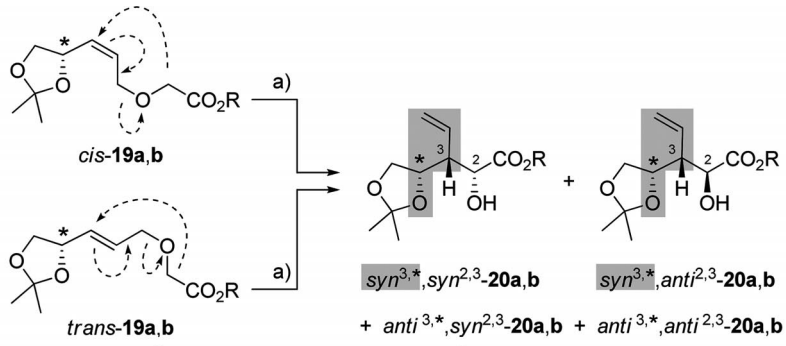
Model Rearrangements, Epoxidations, and Functional Group Modifications

Achieving stereocontrol in the Wittig rearrangement (dilithio-**11**→**9**; Scheme 2), epoxidizing stereoselectively, and



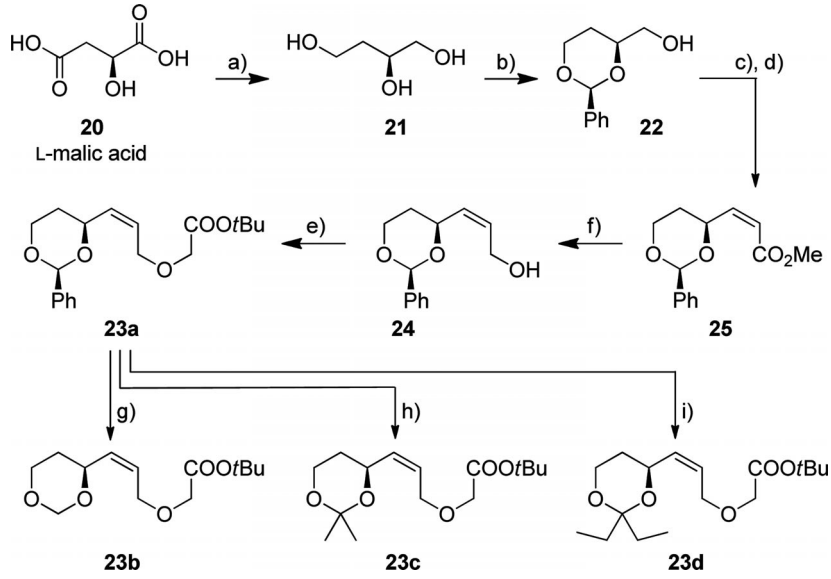
Scheme 2. Retrosynthetic analyses of the synthetic equivalents **7a** (ref.[30]) and **7b** (present study[a]) of the "eastern" moiety **6** [rimocidin (**5**) numbering adopted] of macrolides **1**–**5**. Key building block **12** is a convergence point and emerged from our desymmetrizing route to diol *syn*,*cis*-**14**.[30a,31,32] Reagents and conditions: a) $PhCH(OMe)_2$ (2.0 equiv.), CSA (2.5 mol-%), CH_2Cl_2, room temp., 1 h; 95% [see ref.[30b] for the enantiomeric diol, $PhCH(OMe)_2$, PPTS, DMF, 60 °C, 3 h; 95%]; b) **15** (2.3 equiv.), *n*BuLi (2.1 equiv.), THF, –78 °C, 60 min; addition of HCO_2Et (1.0 equiv.), –35 °C, 17 h; 89% (ref.[31] 94%); c) Red-Al® (10.0 equiv.), toluene, –40 °C, 18 h; 46% over the two steps (ref.[31] 85%); d) $Ti(OiPr)_4$ (1.0 equiv.), D-(–)-DiPT (1.1 equiv.), 4 Å MS, CH_2Cl_2, –25 °C; addition of *cis*,*cis*-**17**, 1 h; addition of *t*BuOOH (2.0 equiv.), 70 h; this mixture (*anti*/*syn* = 78:22; *anti*,*cis*-**16** had >95% *ee*) was used in the next step without purification [ref.[31] 71% (based on recovered starting material) of the diastereomeric mixture; *anti*,*cis*-**16**/*syn*,*cis*-**16** <82:18; *anti*,*cis*-**16** had 94–95% *ee*;[31] ref.[32] 69% of the diastereomeric mixture; *anti*,*cis*-**16**:*syn*,*cis*-**16** <81:19; *anti*,*cis*-**16** had 95% *ee*, *syn*,*cis*-**16** had 39% *ee*[32]]; e) Zn (20 equiv.), $Cu(OAc)_2 \cdot H_2O$ (1 equiv.), H_2O, room temp., 10 min, addition of $AgNO_3$ (1 equiv.), 1 h, filtration, transfer of reductant into $MeOH/H_2O$ (1:1); addition of **18**, 40 °C, 15 h; 76% (ref.[31] 75%, ref.[32] 82%). CSA = camphorsulfonic acid; DiPT = diisopropyl tartrate; MS = molecular sieves; PG = protecting group; PMB = *p*-methoxybenzyl; PPTS = pyridinium *p*-toluenesulfonate; Red-Al® = $NaH_2Al(OCH_2CH_2OMe)_2$; TBS = *tert*-butyldimethylsilyl.[a] The synthesis of building block **7c** is described in ref.[29]

Table 1. [2,3]-Wittig rearrangements of *cis*- vs. *trans*-configured α-(allyloxy)acetates **19a**,**b** under the influence of an oxygenated allylic stereocenter (*), ester dependency of the chemical yield, and geometry dependency of the asymmetric induction.[36]



Entry	Substrate	R	Yield [%]	Product distribution [%]		
				syn^{3},*,*syn*^{2,3}-**20**	*syn*^{3},*,*anti*^{2,3}-**20**	*anti*^{3},*,*syn*^{2,3}-**20** + *anti*^{3},*,*anti*^{2,3}-**20**
1	*cis*-**19a**	Me	40	100	0	0
2	*cis*-**19b**	*t*Bu	79	100	0	0
3	*trans*-**19a**	Me	40	20	63	17
4	*trans*-**19b**	*t*Bu	75	57	32	11

[a] Reagents and conditions: LDA (1.1 equiv.), TMEDA (5.5 equiv.), THF, –78 to –40 °C, 3 h. LDA = lithium diisopropylamide; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

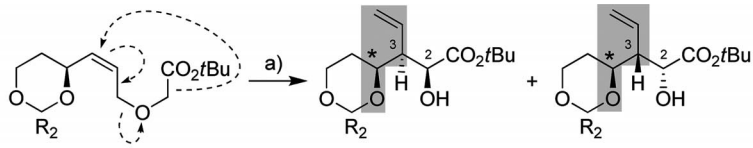


Scheme 3. Conversion of L-malic acid into rearrangement substrate models **23a**–**d**. Reagents and conditions: a) BH_3·Me_2S (3.2 equiv.), $B(OMe)_3$ (3.2 equiv.), THF, 0 °C to room temp., 72 h; 96% (ref.[38] 84% by using this method); b) benzaldehyde dimethyl acetal (1.1 equiv.), CSA (5 mol-% equiv.), CH_2Cl_2, room temp., 20 h; 89%; c) SO_3·pyridine (5 equiv.), NEt_3 (10 equiv.), DMSO, room temp., 2 h; for minimizing the risk of racemization the product was not purified but used in the next step immediately; d) $Ph_3P{=}CHCO_2Me$ (1.5 equiv.), MeOH, room temp., 20 h; 55% *cis*-isomer over two steps (separated from a 90:10 *cis*/*trans* mixture); e) *tert*-butyl bromoacetate (1.2 equiv.), $Bu_4N^+HSO_4^-$, 50% NaOH/CH_2Cl_2 (2:1), room temp., 1 h; 95%; f) DIBAH (2.1 equiv.), THF, 0 °C to room temp., 21 h; 85%; g) dimethoxymethane/toluene 1:2, CSA (0.6 equiv.), 80 °C, 40 h; 55%; h) 2,2-dimethoxypropane (100 equiv.), CSA (0.4 equiv.), 50 °C, 3 h; 66%; i) 3,3-dimethoxypentane (10 equiv.), propan-3-one (200 equiv.), CSA (0.4 equiv.), 85 °C, 1 h; 78%. CSA = camphorsulfonic acid; DIBAH = diisobutylaluminum hydride; DMSO = dimethyl sulfoxide.

removing the (*tert*-butoxycarbonyl)methoxy group, which would withstand the rearrangement step, were three challenges of our approach to building block **7b**. We met the first two challenges in an exploratory study starting from the dioxanones **23a**–**d** (Scheme 3), which model the dioxanone **11**, with which we deal later.

Dioxanone **24** was obtained by a DIBAH reduction of the unsaturated ester **25** (85% yield), which had been obtained from L-(–)-malic acid (**20**) as described previously.[37] Following published procedures, (*S*)-butanetriol (**21**; 96% yield) was obtained from **20**[38] and subsequently the hydroxy acetal **22** (89% yield).[39] This compound was oxidized by using the SO_3·Pyr modification[40] of the activation step of the Swern oxidation[41] as we found this more convenient for large-scale work. Wittig olefination of the resulting aldehyde in methanol[37] gave the *cis*-configured es-

Table 2. Influence of dioxane substituents on the asymmetric induction in ester enolate [2,3]-Wittig rearrangements.[a]



	23a-d		*syn*^{3,*},*syn*^{2,3}-26a-d	*anti*^{3,*},*syn*^{2,3}-26a-d
	CR_2	Yield[b] [%]	*syn*^{3,*},*syn*^{2,3}-**26**[c]	*anti*^{3,*},*syn*^{2,3}-**26**[c]
a	CHPh	39[d] 76[e]	82	18
b	CH_2	37[d]	93	7
c	CMe_2	41[d]	94	6
d	CEt_2	41[d] 79[e]	91	9

[a] Reagents and conditions: a) LDA (1.2 equiv.), TMEDA (5.5 equiv.), THF, –78 °C to –30 °C, 16 h. LDA = Lithium diisopropylamide; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. [b] Combined yield of *syn*^{3,*},*syn*^{2,3}- and *anti*^{3,*},*syn*^{2,3}-**26**. [c] The mol fraction of this diastereomer in the crude product mixture was determined ^{1}H NMR spectroscopically. [d] 0.6–0.8 mmol of **23** were used. [e] 1.7–6.0 mmol of **23** were used.

ter **25** as the major product (55% yield over the two steps). Conversion into **24** (cf. above) and etherification with *tert*-butyl bromoacetate under phase-transfer catalysis conditions[42] rendered the originally desired [2,3]-Wittig rearrangement substrate model, namely (allyloxy)acetate **23a** (95% yield). Shortly we realized that we also needed slightly differently substituted rearrangement substrates. Accordingly, we treated compound **23a**, which is a benzaldehyde acetal, with large excesses of three different dimethyl acetals in the presence of 0.4–0.6 equiv. of camphorsulfonic acid. This induced transacetalizations in yields of 55 (→formaldehyde acetal **23b**), 66 (→acetonide **23c**), and 78% (→pentan-3-one ketal **23d**), respectively; no accompanying transesterification was observed. These transacetalizations increased our stock of rearrangement-prone (allyloxy)acetates from one to four.

[2,3]-Wittig rearrangements of dioxanones **23a**–**d** were induced under conditions similar to those established for the rearrangement of the related dioxolanones *cis*- and *trans*-**19a**,**b** (Table 1[36]): Enolate formation with LDA/TMEDA (ca. 1:4) at –78 °C followed by exposure to –30 °C (rather than –40 °C) for 16 h (Table 2). The rearrangement products **26a**–**d** were isolated in yields of around 40% when we worked on a sub-mmol scale, but the yields almost doubled when mmol quantities of **23** were used. The dioxanone-substituted esters **23a**–**d** rearranged with diastereoselectivities of 82:0:18:0 to 94:0:6:0. In contrast, the dioxolanone-substituted esters *cis*-**19a**,**b** had rearranged with a diastereoselectivity of 100:0:0:0.[36] Each major rearrangement product **26** was assigned the *syn*^{3,*},*syn*^{2,3}-configuration. The major diastereomer of compound **26a** was configured in this manner as determined by X-ray crystal structure analysis[43] (Figure 1), whereas the major isomers of the rearrangement products **26b**–**d** were labeled *syn*^{3,*},*syn*^{2,3} due to their plausible structural similarity to **26a** and *syn*^{3,*},*syn*^{2,3}-**20a**,**b**. The consistency of various ^{1}H NMR chemical shifts and J_{vic} values corroborate the veracity of these assignments.[44]

The X-ray analysis[43] of crystals of the minor rearrangement product **26d** proved that it possesses the *anti*^{3,*},*syn*^{2,3} configuration (Figure 2). The same *anti*^{3,*},*syn*^{2,3} structure was attributed to the minor rearrangement products **26a**–**c** because of their plausible similarity to **26d** and ^{1}H NMR chemical shift and J_{vic} value analogies.[44]

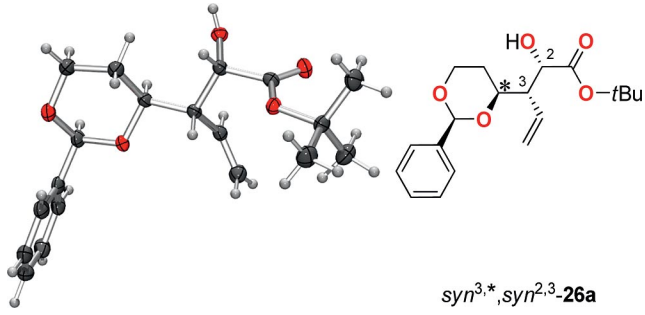


Figure 1. ORTEP plot of the crystal structure of *syn*^{3,*},*syn*^{2,3}-**26a** (at 100 K).[43]

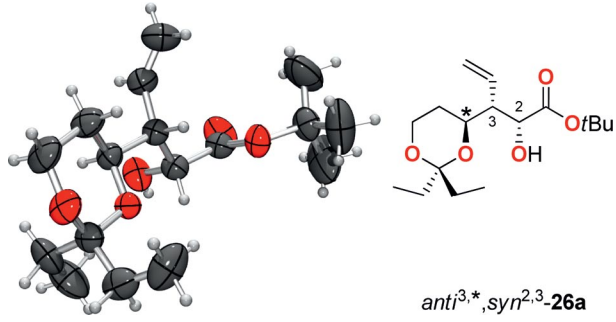
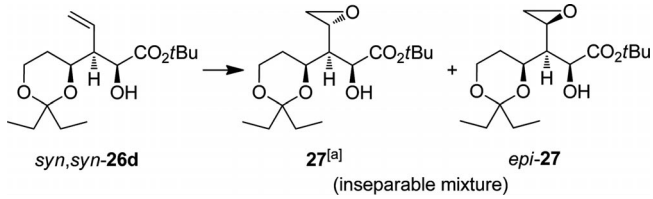


Figure 2. ORTEP plot of the crystal structure of *anti*^{3,*},*syn*^{2,3}-**26d** (at 292 K).[43]

Continuing our investigation of the model systems beyond the rearrangement stage was handicapped by our inability to free the desired *syn*^{3,*},*syn*^{2,3} isomers of compounds **26a**–**c** from between 6 and 18% rel-% of the respective *anti*^{3,*},*syn*^{2,3} isomer by flash chromatography.[45] We

Table 3. Direct epoxidation of the homoallylic alcohol **26d** (CH_2Cl_2, room temp., 66 h for entries 1–3, 24 h for entry 4).



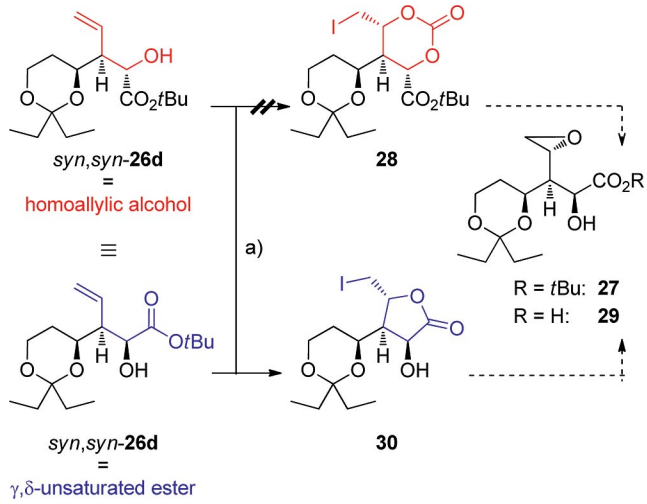
Entry	Oxidant, additive	Conversion [%][b]	Reisolated *syn*,*syn*-**26d** [%]	Isolated **27**+*epi*-**27** [%]	Ratio **27**/*epi*-**27**[b]
1	*t*BuOOH (1.5 equiv.), $VO(acac)_2$ (3 mol-%)	50	42	21[c]	85:15
2	*t*BuOOH (1.5 equiv.), $VO(OEt)_3$ (5 mol-%)	ca. 80	–	29[c]	73:27
3	cumyl-OOH (1.5 equiv.), $VO(OiPr)_3$ (2 mol-%)	35	–	–	82:18
4	*m*CPBA (2 equiv.)	100	0	51[c]	66:34

[a] The configuration of the epoxide ring was inferred from the transition-state model of the Mihelich epoxidation.[34a] [b] Determined by ^{1}H NMR analysis. [c] Yield of the **27**/*epi*-**27** mixture after chromatographic purification. *m*CPBA = *meta*-chloroperoxybenzoic acid.

overcame this obstacle when we included substrate **23d** in our study. Its enolate rearranged to give a 91:9 mixture of *syn*^{3,*},*syn*^{2,3}-**26d** and *anti*^{3,*},*syn*^{2,3}-**26d**. Fortunately, *syn*^{3,*},*syn*^{2,3}-**26d** was readily purified by flash chromatography on silica gel.[45]

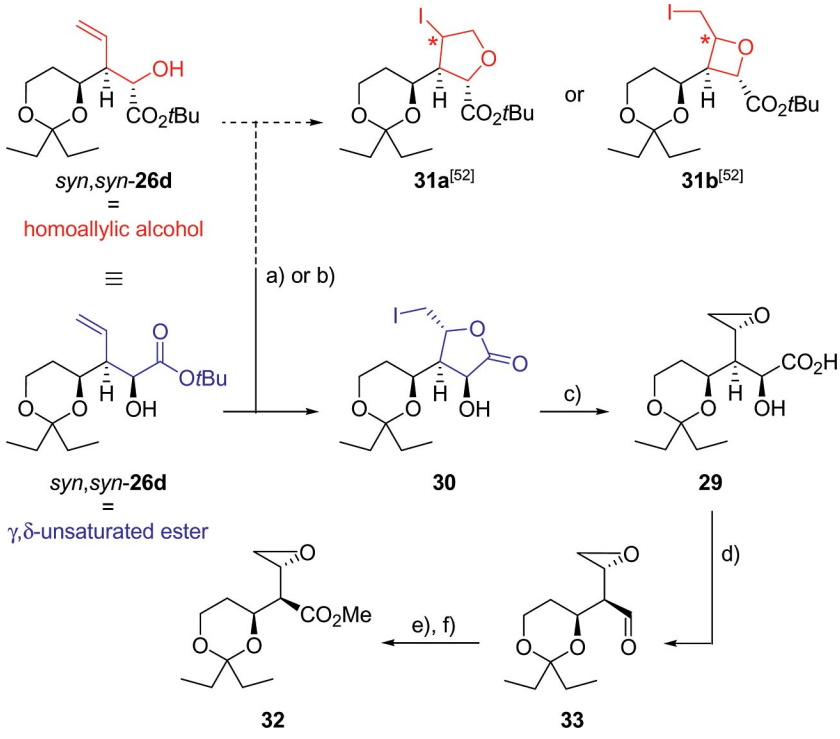
Our next objective was to convert the vinyl group of compound *syn*^{3,*},*syn*^{2,3}-**26d** into an epoxide in a diastereoselective manner. First, we attempted to do this by epoxidation (Table 3). Mihelich epoxidations with *t*BuOOH[34a] or CumylOOH[46] (entries 1–3) were expected to work well, as discussed in the retrosynthetic analysis. Indeed, their diastereoselectivities (85:15–73:27) would have been acceptable except for two aggravating factors: 1) The epoxide diastereomers **27** and *epi*-**27** were inseparable by flash chromatography on silica gel[45] and 2) the epoxidation of *syn*^{3,*},*syn*^{2,3}-**26d** could not be pushed beyond 50% conversion. Replacing Mihelich's additive $VO(acac)_2$ by $VO(OEt)_3$ (which subsists longer under the reaction conditions[47]) or by $VO(OiPr)_3$ had no beneficial effect. Increasing the epoxidation time did not help either because the epoxide started to decompose. *m*CPBA proved to be a better oxidant for *syn*^{3,*},*syn*^{2,3}-**26d**, rendering epoxides **27** and *epi*-**27** in 51% yield (Table 3, entry 4). However, the diastereocontrol was poor (66:34).

To avoid these limitations we attempted to involve a neighboring group effect in the epoxide formation. As a homoallyl alcohol, *syn*^{3,*},*syn*^{2,3}-**26d** might be susceptible to iodo-carbonate formation.[48] The latter would be expected to lead to the isomer **28** with three equatorially oriented substituents (Scheme 4). By using a protocol for a related transformation,[49] we deprotonated the homoallylic alcohol *syn*^{3,*},*syn*^{2,3}-**26d** with *n*BuLi, bubbled dry CO_2 through the solution, added iodine, and allowed the mixture to react at room temp. for 16 h. Disappointingly, we retrieved 48% of the starting material. However, we also isolated about 15% of contaminated iodolactone **30**. Thus, the ester group of *syn*^{3,*},*syn*^{2,3}-**26d** had exerted a neighboring group effect with respect to the iodonium ion intermediate.



Scheme 4. Unintentional iodolactonization of compound *syn*,*syn*-**26d** at the expense of the attempted formation of an iodo-carbonate. Reagents and conditions: a) *n*BuLi (1.05 equiv.), THF, –78 °C, 30 min; dry stream of CO_2, –40 °C, 15 min; addition of I_2 (4.0 equiv.), THF, 0 °C, 16 h, ca. 15% iodolactone **30** (impure) + 48% reisolated *syn*,*syn*-**26d**.

Iodolactonization reactions are an indirect way of epoxidizing unsaturated esters. This is because iodolactones can be cleaved to give iodohydrins, which cyclize to give epoxides.[48] In the case in hand, this epoxide would hopefully be **29**. With this possibility in mind, we deliberately involved the ester group of substrate *syn*^{3,*},*syn*^{2,3}-**26d** in an iodolactonization (Scheme 5) by using Bartlett's "conditions for thermodynamic ring-closure control".[50] Accordingly we treated *syn*^{3,*},*syn*^{2,3}-**26** in acetonitrile with an excess of both iodine and $NaHCO_3$.[51] Our substrate reacted to completion and furnished a 75:25 mixture of diastereomerically pure iodolactone **30** and diastereomerically pure iodo ether **31a** or **31b**.[52] The cyclization of *syn*^{3,*},*syn*^{2,3}-**26d** became chemoselective when we added 1.0 equiv. of LiI to the reaction mixture. Under these conditions, the



Scheme 5. Intentional iodolactonization of compound *syn*,*syn*-**26d** and final steps of our study of a model system towards the C^{12}–C^{18} fragment analogue **32**. Reagents and conditions: a) I_2 (3 equiv.), $NaHCO_3$ (5 equiv.), acetonitrile, –40 °C, 20 h; room temp., 30 h; 75:25 mixture of **30** and **31**[52] (according to ^1H NMR analysis), which was not purified; b) I_2 (6 equiv.), $NaHCO_3$ (5 equiv.), LiI (1 equiv.), acetonitrile, –20 °C, 16 h; 85% **30**; c) LiOH (3.0 equiv.), Ag_2O (0.6-fold molar amount), THF/H_2O (4:1), 0 °C to room temp., 15 min, then dil. HCl, 0 °C; quant. (without purification); d) $Pb(OAc)_4$ (1.5 equiv.), THF, 0 °C to room temp.; 85% (without purification); e) $NaClO_2$ (4.0 equiv.), NaH_2PO_4 (4.5 equiv.), 2-methylbut-2-ene (8.0 equiv.), acetone/H_2O (1:1), 0 °C to room temp., 1 h; f) TMS-diazomethane (excess), benzene/MeOH (7:2), room temp., 10 min; 27% over the four steps from **30**. TMS = trimethylsilyl.

iodo etherification subsided completely and the iodolactonization proceeded to **30** as diastereoselectively as before (85% yield). We have no direct evidence that the newly established stereocenter of iodolactone **30** possesses the configuration indicated in Scheme 5, however, there is good ancillary evidence. We iodolactonized the benzaldehyde-protected rearrangement product *syn*^{3,*},*syn*^{2,3}-**26a** under identical conditions to those used on *syn*^{3,*},*syn*^{2,3}-**26d**, which provided a single iodolactone isomer **30a** (85% yield). Unlike **30** it was crystalline and thus its 3D structure could be determined by X-ray crystallography[43] (Figure 3).

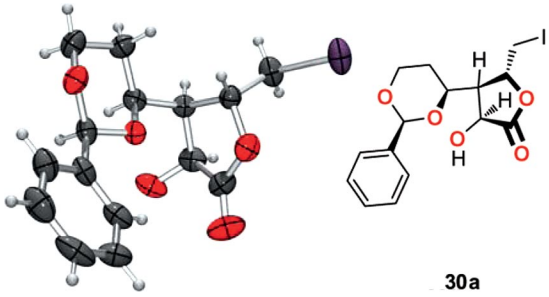


Figure 3. ORTEP plot of the crystal structure of iodolactone **30a** (at 292 K).[43]

Hydrolysis of iodolactone **30** with LiOH in aq. THF furnished the epoxide-containing carboxylic acid **29** in quantitative yield (Scheme 5). The presence of a stoichiometric amount of Ag^I ions, added as Ag_2O, in the hydrolysis mixture was essential for success; they scavenge the iodide ions expelled during epoxide formation. In the absence of Ag^I, the anion of epoxy acid **29** also formed, as revealed by TLC (the TLC spot of iodolactone **30** was replaced by the identical product spot whether Ag_2O was present or not). However, as soon as HCl was added, in preparation of an extractive work-up, this anion was protonated to give the epoxy acid **29**; the latter tended to react with the iodide ions and thereby reverted to the iodolactone **30**.

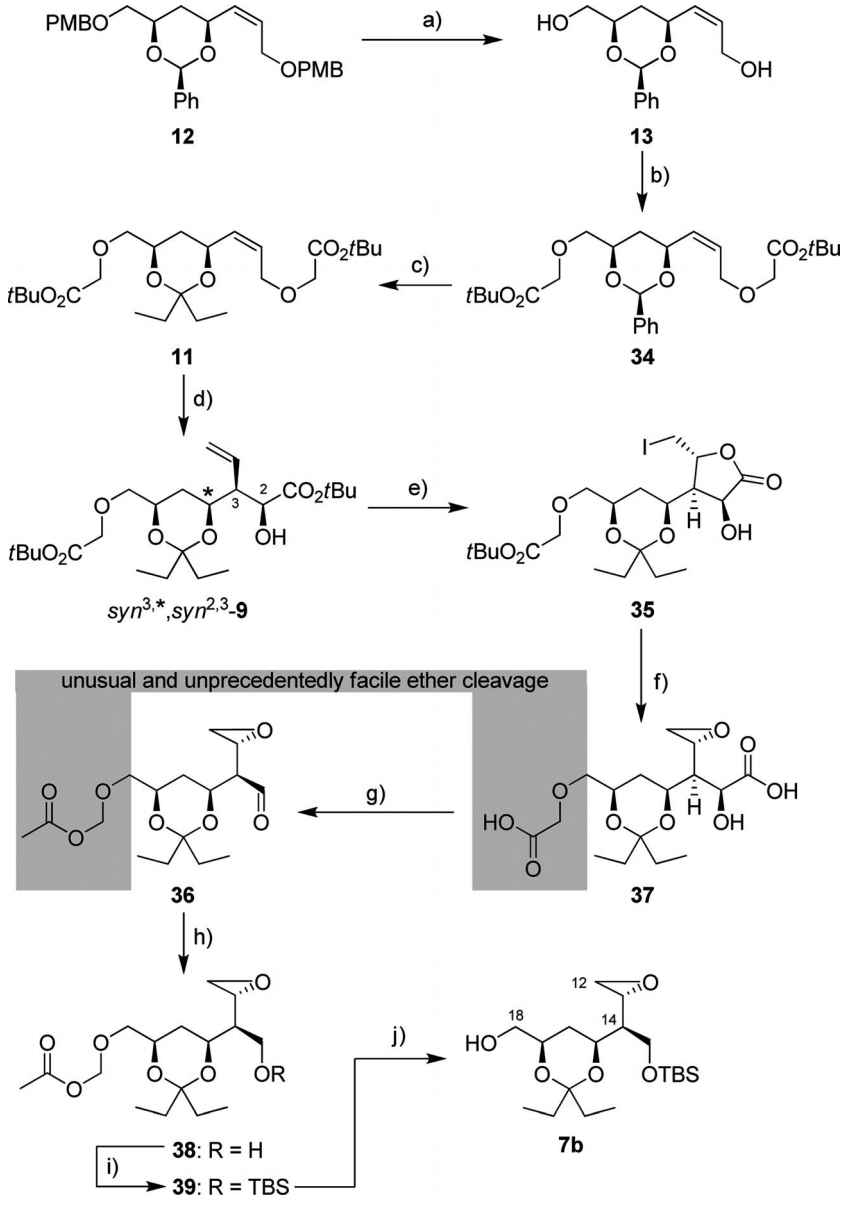
The α-hydroxy acid **29** was cleaved by $Pb(OAc)_4$ (Scheme 5). The resulting aldehyde **33** was very sensitive towards acid and base because its epoxide ring was poised for opening by β-elimination, which probably delivered a formyl-conjugated allylic alcohol. Accordingly, oxidation to the corresponding carboxylic acid had to be effected under neutral conditions. This was achieved by the Lindgren procedure.[53] Without purification the resulting carboxylic acid was methylated with TMS-diazomethane[54] to furnish epoxide **32**.

At this stage we terminated our work on the model system. Having optimized a number of crucial steps, in par-

ticular, the [2,3]-Wittig rearrangement and the iodolactonization, we felt ready to tackle the "eastern" moiety building block **7b**.

Synthesis of the C^{12}–C^{18} Building Block

The PMB ether groups of dioxanone **12** (95.0% *ee*; for its preparation, see Scheme 2) were removed with DDQ in the presence of H_2O[55] to furnish diol **13** (Scheme 6). From here onward until we reached epoxy acid **37** we could employ essentially identical reaction conditions to those used in our model study. Thus, the following steps were performed: Bis(etherification) with *tert*-butyl bromoacetate (→ 80% **34**), transacetalization with 3,3-dimethoxypentane/pentan-3-one (→ 60% **11**), bis(ester enolate) formation and [2,3]-Wittig rearrangement (→ 68% *syn*^{3,*},*syn*^{2,3}-**9** and 17 rel-%[56] of *anti*^{3,*},*syn*^{2,3}-**9** as the only other diastereomer; it proved separable by flash chromatography on



Scheme 6. Synthesis of the C^{12}–C^{18} building block **7b**. Reagents and conditions: a) DDQ (2.5 equiv.), CH_2Cl_2/H_2O (18:1), room temp., 2 h; 85%; b) *tert*-butyl bromoacetate (3.0 equiv.), $Bu_4N^+HSO_4^-$ (0.7 equiv.), 50% NaOH/CH_2Cl_2 (2:1), room temp., 1 h; 80%; c) 3,3-dimethoxypentane (7 equiv.), pentan-3-one (100 equiv.), CSA (0.4 equiv.), 80 °C, 1 h; 60%; d) LDA (2.5 equiv.), TMEDA (10 equiv.), THF, –78 to –30 °C, 15 h; 68% *syn*^{3,*},*syn*^{2,3}-**9** after separation from 17% of *anti*^{3,*},*syn*^{2,3}-**9**, *ds* = 85:15 according to ^{1}H NMR analysis of the crude product; e) I_2 (6.0 equiv.), LiI (1.25 equiv.), $NaHCO_3$ (5.0 equiv.), CH_3CN, –15 °C, 16 h; 71%, *ds* = 100:0; f) LiOH·H_2O (6.0 equiv.), Ag_2O (0.6 equiv.), THF/MeOH/H_2O (10:5:3), room temp., 60 min; 95% crude product, which was neither subjected to chromatography nor characterized by ^{1}H NMR; g) $Pb(OAc)_4$ (3.0 equiv.), $Cu(OAc)_2$ (5 mol-%), visible light (tungsten lamp, 150 W), benzene/THF (1:1), 5 °C, 20 min; h) $NaBH_4$ (5.0 equiv.), MeOH, 0 °C to room temp., 2 h; 46% over the three steps from iodolactone **35**; i) TBSOTf (1.5 equiv.), 2,6-lutidine (2.0 equiv.), CH_2Cl_2, –78 °C, 1 h; j) K_2CO_3 (1.5 equiv.), MeOH, room temp., 30 min; 67% over two steps. CSA = camphorsulfonic acid; DDQ = 2,3-dicyano-5,6-dichlorobenzoquinone; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TBS = *tert*-butyldimethylsilyl; TMS = trimethylsilyl.

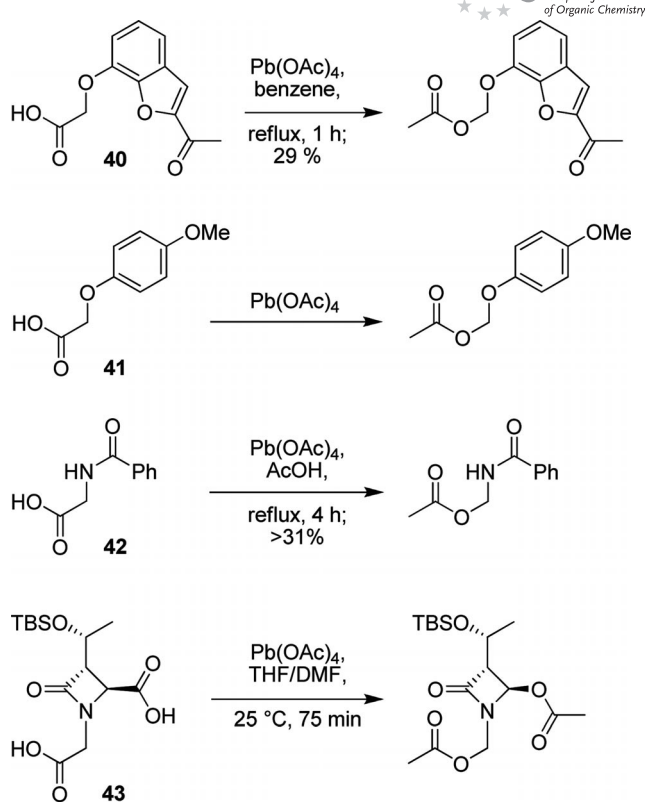
silica gel;[45] note that one ester moiety remained unchanged, as desired), diastereo- and chemoselective iodolactonization in the presence of I_2 and LiI (→ 71% **35**), and LiOH-mediated and Ag_2O-assisted conversion into epoxy acid **37** (95% as a crude product, which was prone to decomposition and too polar to be chromatographed rapidly).

An unusual and novel step in Scheme 6 is the oxidative degradation of the bis(carboxylic acid) **37** by treatment in benzene/THF[57] (1:1) at 5 °C with a mixture of $Pb(OAc)_4$ (stoichiometric) and $Cu(OAc)_2$ (catalytic) while irradiating with a tungsten lamp.[58] Under these conditions, the –$CH(OH)CO_2H$ moiety of **37** rendered a –CH=O group, which represents a routine glycol acid cleavage; concomitantly, the HO_2C–CH_2O– group of **37** was converted into an AcO–CH_2O– moiety. This suggests that this HO_2C–CH_2O– group was decarboxylated oxidatively and the resulting carboxonium ion $CH_2{=}O^+$– scavenged by an acetate ion from one of the heavy metal salts.[59] The degradation of HO_2C–CH_2O– to AcO–CH_2O– in the bis(carboxylic acid) **37** proceeded smoothly and went to completion within 20 min only when the reaction mixture was irradiated.[60] In the absence of light the substrate failed to react during as much as 4 h (at room temp.) or the reaction was sluggish and led to numerous side-products (2 h at 80 °C). The degradation product **36** is an *O*,*O*-acetal and concomitantly a type of acycal. For this reason we skipped purification by flash chromatography until after the next step (→ **38**; see below).

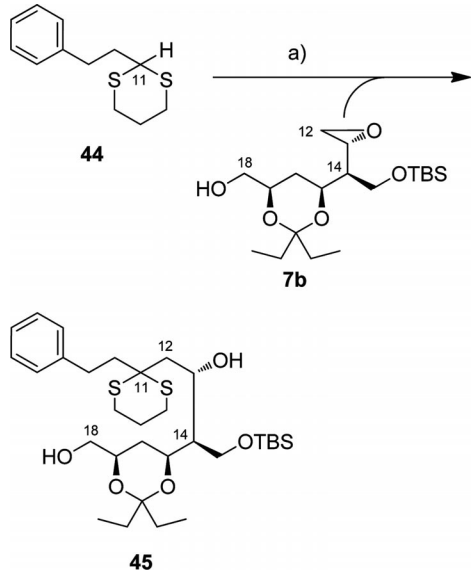
Scheme 7 presents literature precedents for the transformation **37** → **36**. To the best of our knowledge, to date, no α-(alkoxy)acetic acid has been degraded by treatment with $Pb(OAc)_4$ or with a reagent mixture containing $Pb(OAc)_4$. Only two α-(aryloxy)acetic acids (**40** and **41**) have been degraded in this manner delivering formaldehyde *O*,*O*-acetals[61] akin to **36**. More distant analogies to the transformation **37** → **36** are the $Pb(OAc)_4$-mediated degradations of *N*-acylglycins like **41**[62] or **42**,[63] which contains the reactive moiety in duplicate. These substrates provided formaldehyde *N*,*O*-acetals. Some of these oxidation reactions were performed at an elevated temperature, but the assistance of light had not been tested.

With the stereocenters established and the backbone shortened as required, the aldehyde **36** was subjected to the final transformation, starting with a reduction (Scheme 6). The resulting alcohol **38** was protected as the *tert*-butyldimethylsilyl ether **39**. Methanolysis of the (acetoxy)methoxy moiety of this compound provided the C^{12}–C^{18} building block **7b** (31% overall yield over the five steps from the iodolactone **35**).

The C^{12}–C^{18} building block **7b** contains a CH_2OSiR_3 side-chain where the model compound **32** (Scheme 5) bears a CO_2Me group. This change was necessary to suppress the acidity of the 14-H atom, which would have made model **32** but not building block **7b** incompatible with our final transformation: epoxide-opening by treatment with the lithio derivative of model dithiane **44** (Scheme 8). The latter mimics the hypothetical "northern fragment" of any of the polyol/polyene macrolides **1**–**5**, for example, the "northern



Scheme 7. Copper-free Pb^{IV}-mediated degradations of α-(aryloxy)-acetic acids **40** and **41** and of *N*-protected α-amino acids **42** and **43** from refs.[61a,61b,62,63] None of these reactions invoked support by $Cu(OAc)_2$ and/or light, whereas the degradation of our α-(alkyloxy)acetic acid **37** was most effective when both were present (Scheme 6). TBS = *tert*-butyldimethylsilyl.



Scheme 8. Coupling of the C^{12}–C^{18} building block **7b** with the model 1,3-dithiane **44**. Reagents and conditions: a) **44** (4.0 equiv.), *n*BuLi (3.5 equiv.), THF, 0 °C, 30 min; HMPA (4.0 equiv.), –78 °C, 10 min; addition of **7b** (1.0 equiv.), –40 °C, 16 h; 70% **45** separated from recovered **44** (78% of the 3.0 equiv., which we used in excess). HMPA = *N*,*N*,*N*′,*N*′,*N*′′,*N*′′-hexamethylphosphoric triamide.

fragment" of rimocidin (**5**). This dithiane was deprotonated in THF solution with *n*BuLi. After the addition of HMPA, epoxide **7b** was added to the reaction mixture. The hydroxyalkylated dithiane **45** was isolated in 70% yield and separated from 78% of recovered excess dithiane.

Conclusions

A universal C^n–C^{n+6} building block **7b** for the synthesis of macrolide antibiotics **1**–**5** (Scheme 1) has been synthesized from propargyl ether **15**. The route comprises 15 steps in the longest linear sequence. The average yield was 71% per step and the overall yield 2.0%. The enantiopurity was created in a desymmetrizing Sharpless epoxidation of divinylcarbinol *cis*,*cis*-**17** (→ epoxy alcohol *anti*,*cis*-**16**; >95% *ee*). Another key step was the stereocontrolled [2,3]-Wittig rearrangement of the bis(enolate) of diester **11**. This reaction exhibited a diastereoselectivity of 85:15:0:0. The epoxide ring of target molecule **7b** incorporates a stereogenic C–O bond, which was established by a perfectly diastereoselective iodolactonization. The latter only completely dominated over an otherwise competing iodoetherification reaction if iodine and LiI were present. This was concluded from the study of a model system, which gave **31**.

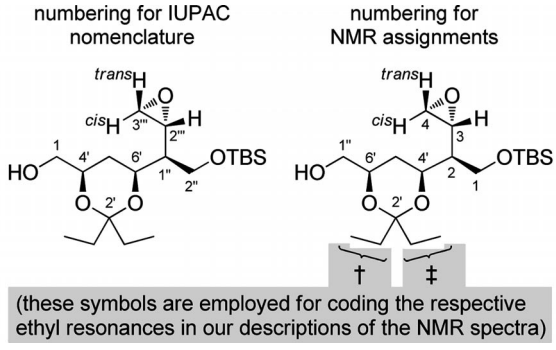
A tBuO$_2$CCH$_2$ ether moiety was carried through the major part of our synthesis, only removing it after cleavage of the tBuO$_2$C group by an innovative two-step procedure: an oxidative degradation (**37**→**36**) and a methanolysis (**39**→**7b**). The oxidative degradation was effected by treatment with Pb(OAc)$_4$ (stoichiometric), Cu(OAc)$_2$ (substoichiometric), and visible light. The functional group interconversion HO$_2$CCH$_2$O-alkyl→AcOCH$_2$O-alkyl, which was induced thereby, seems to be unprecedented. It may warrant further study with respect to developing an orthogonal protecting group.

The viability of building block **7b** for macrolide antibiotic total synthesis was established by combining it in 70% yield with an umpoled aldehyde, namely the lithiated dithiane **44**.

Experimental Section

General: Reactions were performed under N_2 in glassware that had been dried under vacuum at heat-gun temperature. THF was freshly distilled over potassium prior to use and CH_2Cl_2 from CaH_2. Petroleum ether had a boiling range of 30–50 °C. Products were purified by flash chromatography[45] on Merck silica gel 60 (0.040–0.063 mm), yields refer to analytically pure samples. ^{1}H NMR [TMS (δ = 0.00 ppm) as an internal standard in $CDCl_3$; C_6HD_5 (δ = 7.16 ppm) as an internal standard in C_6D_6]: Varian Mercury VX 300, Bruker Avance 400, and Bruker DRX 500. ^{13}C NMR [TMS (δ = 0.00 ppm) as an internal standard in $CDCl_3$; C_6HD_5 (δ = 128.06 ppm) as an internal standard in C_6D_6]: Bruker Avance 400 and Bruker DRX 500. Assignments of ^{1}H and ^{13}C NMR resonances refer to the IUPAC nomenclature except within substituents (where primed numbers are used) or when indicated explicitly. NMR measurements: Dr. M. Keller, F. Reinbold, M. Schonhardt, Institut für Organische Chemie, University of Freiburg. MS measurements: Dr. J. Wörth, C. Warth, Institut für Organische Chemie, University of Freiburg. Combustion analyses: E. Hickl, F. Tönnies, and A. Siegel, Institut für Organische Chemie, University of Freiburg. IR spectra: Perkin–Elmer Paragon 1000. Optical rotations were measured with a Perkin–Elmer 341 polarimeter at 589 nm and 20 °C and calculated by using the Drude equation: $[\alpha]_D = (\alpha_{exp} \times 100)/(c \times d)$; rotational values are the average of five measurements of α_{exp} in a given solution of the corresponding sample. Melting points were measured with a Dr. Tottoli apparatus (Büchi). The *ee* values were determined by chiral HPLC with a Chiralpak AD-H column (0.46×25 cm; Daicel Chemical Ind. Ltd.) by G. Fehrenbach, Institut für Organische Chemie, University of Freiburg.

[(4*R*,6*S*)-6-{(*S*)-2-(*tert*-Butyldimethylsiloxy)-1-[(*R*)-oxiran-2-yl]-ethyl}-2,2-diethyl-1,3-dioxan-4-yl]methanol (7b):

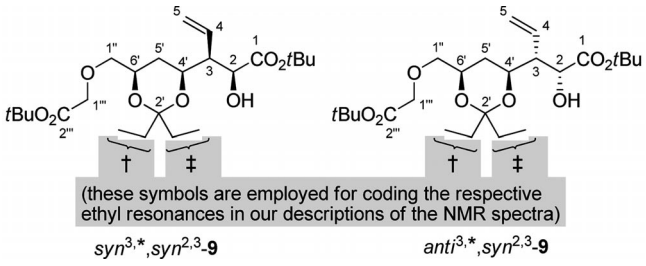


At –78 °C, TBSOTf (40 µL, 181 µmol, 1.5 equiv.) was added dropwise to a solution of alcohol **38** (40 mg, 120 µmol, 1.0 equiv.) and 2,6-lutidine (28 µL, 240 µmol, 2.0 equiv.) in CH_2Cl_2 (2.5 mL). After 1 h, H_2O (3 mL) was added and the temperature was raised to room temp. The mixture was extracted with Et_2O (3×3 mL). The combined organic layers were washed with brine (4 mL), dried with Na_2SO_4, and filtered.

After evaporation of the solvent under reduced pressure, the residue (**39**) was dissolved in MeOH. Powdered K_2CO_3 (25 mg, 180 µmol, 1.5 equiv.) was added. After stirring vigorously for 30 min aqueous phosphate buffer (pH = 7.1, 0.5 M, 10 mL) was added. The resulting mixture was extracted with AcOEt (3×5 mL). The combined organic layers were washed with brine (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography[45] (1.5 cm; petroleum ether/Et_2O, 7:3) to yield **7b** as a colorless wax (fractions 4–13, 30 mg, 67% over the two steps from **38**). $[\alpha]_D^{20}$ = +11.0 (c = 1.20, $CHCl_3$, 10 cm). ^{1}H NMR (400.1 MHz, C_6D_6): δ = 0.06 and 0.08 [2×s, 2×3 H, $Si(CH_3)_2$], 0.79 (t, $^3J_{CH2}$ = 7.5 Hz, 3 H, 2′-CH$_2$-C$H_3^{\dagger}$), 0.96 (dd, $^3J_{CH^AH^B}$ = $^3J_{CH^AH^B}$ = 7.5 Hz, 3 H, 2′-CH$_2$-C$H_3^{\ddagger}$), 0.97 [s, 9 H, $SiC(CH_3)_3$], 1.04 (ddd, $^2J_{5'eq,5'ax}$ = 12.6, $J_{5'eq,4'}$ = $J_{5'eq,6'}$ = 2.5 Hz, 1 H, 5′-H^{eq}), 1.16 (dddd, $J_{2,3}$ = 8.5, $J_{2,1B}$ = 6.7, $J_{2,4'}$ = 5.4, $J_{2,1A}$ = 3.8 Hz, 1 H, 2-H), 1.33 (ddd, $^2J_{5'ax,5'eq}$ = 12.4, $J_{5'ax,4'}$ = $J_{5'ax,6'}$ = 11.9 Hz, 1 H, 5′-H^{ax}), AB signal (δ_A = 1.61, δ_B = 1.65, J_{AB} = 13.9 Hz, in addition split by $J_{A,CH3}$ = $J_{B,CH3}$ = 7.4 Hz, 2 H, 2′-CH_2-CH$_3^{\ddagger}$), 1.71 (q, $^3J_{CH3}$ = 7.5 Hz, 2 H, 2′-CH_2-CH$_3^{\dagger}$), 2.38 (dd, $^2J_{4cis,4trans}$ = 5.4, $J_{4cis,3}$ = 2.6, 1 H, 4-H^{cis}), 2.56 (dd, $^2J_{4trans,4cis}$ = 5.4, $J_{4trans,3}$ = 3.9 Hz, 1 H, 4-H^{trans}), 3.02 (ddd, $J_{3,2}$ = 8.5, $J_{3,4trans}$ = 3.9, $J_{3,4cis}$ = 2.6 Hz, 1 H, 3-H), AB signal (δ_A = 3.35, δ_B = 3.42, J_{AB} = 11.2 Hz, in addition split by $J_{A,6'}$ = 5.8, $J_{B,6'}$ = 3.5 Hz, 2 H, 1′′-H$_2$), 3.62 (dddd, $J_{6',5'ax}$ = 11.7, $J_{6',1''A}$ = 5.8, $J_{6',1''B}$ = 3.5, $J_{6',5'eq}$ = 2.4 Hz, 1 H, 6′-H), AB signal (δ_A = 3.80, δ_B = 3.94, J_{AB} = 9.9 Hz, in addition split by $J_{A,2}$ = 3.8, $J_{B,2}$ = 6.7 Hz, 2 H, 1-CH$_2$), 4.14 (ddd, $J_{4',5'ax}$ = 11.9, $J_{4',2}$ = 5.4, $J_{4',5'eq}$ = 2.5 Hz, 1 H, 4′-H)ppm. ^{13}C NMR (100.6 MHz, C_6D_6): δ = –5.43 and –5.40 [$Si(CH_3)_2$], 7.19 (2′-CH$_2$-$CH_3^{\ddagger}$), 8.25 (2′-CH$_2$-$CH_3^{\dagger}$), 18.42

[Si*C*(CH_3)$_3$], 22.68 (2′-*C*H_2-$CH_3^{\dagger}$), 26.06 [SiC(*C*H_3)$_3$], 30.42 (C-5′), 31.51 (2′-*C*H_2-$CH_3^{\ddagger}$), 47.66 (C-4), 50.39 (C-3), 50.67 (C-2), 60.61 (C-1), 66.18 and 66.24 (C-1′′, C-4′), 69.43 (C-6′), 101.75 (C-2′) ppm. IR (film): $\tilde{\nu}$ = 3455, 2955, 2930, 2880, 2860, 1465, 1380, 1360, 1250, 1165, 1105, 980, 940, 840, 775, 665 cm^{-1}. $C_{19}H_{38}O_5Si$ (374.59): calcd. C 60.92, H 10.22; found C 60.71, H 10.47.

***tert*-Butyl (2*S*,3*S*)-3-{(4*S*,6*R*)-6-[(2-*tert*-Butoxy-2-oxoethoxy)methyl]-2,2-diethyl-1,3-dioxan-4-yl}-2-hydroxypent-4-enoate (*syn*^{3,*},*syn*^{2,3}-9, Major Diastereomer) and *tert*-Butyl (2*R*,3*R*)-3-{(4*S*,6*R*)-6-[(2-*tert*-Butoxy-2-oxoethoxy)methyl]-2,2-diethyl-1,3-dioxan-4-yl}-2-hydroxypent-4-enoate (*anti*^{3,*},*syn*^{2,3}-9, Minor Diastereomer):**

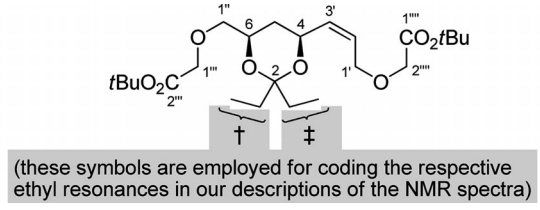


At –78 °C, the allyl ether derivative **11** (2.29 g, 5.00 mmol, 1 equiv.) in THF (25 mL) was added during 20 min to a solution prepared from diisopropylamine (2.25 mL, 16.0 mmol, 3.2 equiv.) and *n*BuLi (2.4 M in hexanes, 5.2 mL, 12.5 mmol, 2.5 equiv.) in THF (25 mL). Tetramethylethylenediamine (7.5 mL, 50.0 mmol, 10 equiv.) was added 20 min later. Another 20 min later the temperature was allowed to rise to –30 °C. After 15 h the reaction was quenched by the addition of half-satd. NH_4Cl (50 mL) and the mixture was extracted with *t*BuOMe (3 × 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product contained an 81:19 mixture of *syn*^{3,*},*syn*^{2,3}-**9** and *anti*^{3,*},*syn*^{2,3}-**9** (determined by ^{1}H NMR signal integration). Purification by flash chromatography[45] (6 cm; petroleum ether/Et_2O, 3:1) afforded the major diastereomer *syn*^{3,*},*syn*^{2,3}-**9** (fractions 14–39, 1.55 g, 68%, colorless oil) pure and the minor diastereomer *anti*^{3,*},*syn*^{2,3}-**9** (fractions 9–13, 319 mg, 17%, colorless oil) also pure.

Major Diastereomer (*syn*^{3,*},*syn*^{2,3}-9): $[\alpha]_D^{20}$ = –3.7 (*c* = 0.80, $CHCl_3$, 10 cm). ^{1}H NMR (400.1 MHz, $CDCl_3$/TMS): δ = 0.83 (dd, $^3J_{CH^AH^B}$ = $^3J_{CH^AH^B}$ = 7.4 Hz, 3 H, 2′-CH_2-C$H_3^{\dagger}$), 0.88 (dd, $^3J_{CH^AH^B}$ = $^3J_{CH^AH^B}$ = 7.4 Hz, 3 H, 2′-CH_2-C$H_3^{\ddagger}$), 1.41 (ddd, $^2J_{5'ax,5'eq}$ = $J_{5'ax,4'}$ = $J_{5'ax,6'}$ = 12.0 Hz, 1 H, 5′-H^{ax}), 1.46 [s, 9 H, C(CH_3)$_3$], 1.48 [s, 9 H, C(CH_3)$_3$], 1.55–1.65 (2 × m, 3 H, 2′-CH_2-$CH_3^{\ddagger}$ and 5′-H^{eq}), AB signal (δ_A = 1.83, δ_B = 1.85, J_{AB} = 9.1 Hz, in addition split by $J_{A,CH3}$ = $J_{B,CH3}$ = 7.4 Hz, 2 H, 2′-CH_2-$CH_3^{\dagger}$), 2.47 (ddd, $J_{3,4}$ = 9.4, $J_{3,4'}$ = 6.2, $J_{3,2}$ = 3.0 Hz, 1 H, 3-H), 3.23 (d, $J_{2\text{-}OH,2}$ = 3.8 Hz, 1 H, 2-OH), AB signal (δ_A = 3.50, δ_B = 3.56, J_{AB} = 10.2 Hz, in addition split by $J_{A,4'}$ = 4.6, $J_{B,4'}$ = 5.7 Hz, 2 H, 1′′-H_2), AB signal (δ_A = 4.01, δ_B = 4.06, J_{AB} = 16.4 Hz, 2 H, 1′′′-H_2), 4.08–4.16 (m, 2 H, 4′-H, 6′-H), 4.30 (dd, $J_{2,2\text{-}OH}$ = 3.7, $J_{2,3}$ = 2.8 Hz, 1 H, 2-H), 5.13 (ddd, $J_{5cis,4}$ = 17.2, $^2J_{5cis,5trans}$ = 2.1, $^4J_{5cis,3}$ = 0.6 Hz, 1 H, 5-H^{cis}), 5.19 (dd, $J_{5trans,4}$ = 10.3, $^2J_{5trans,5cis}$ = 2.1 Hz, 1 H, 5-H^{trans}), 5.85 (ddd, $J_{4,5cis}$ = 17.2, $J_{4,5trans}$ = 10.3, $J_{4,3}$ = 9.7 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 7.00 (2′-CH_2-*C*$H_3^{\ddagger}$), 8.14 (2′-CH_2-*C*$H_3^{\dagger}$), 22.33 (2′-*C*H_2-$CH_3^{\dagger}$), 28.18 and 28.18 [2 × C(*C*H_3)$_3$], 30.85 (C-5′), 31.13 (2′-*C*H_2-$CH_3^{\ddagger}$), 52.55 (C-3), 68.05 and 69.05 (C-4′, C-6′), 69.39 (C-1′′′), 71.66 (C-2), 74.86 (C-1′′), 81.59 and 82.48 [2 × *C*(CH_3)$_3$], 102.07 (C-2′), 119.52 (C-5), 132.86 (C-4), 169.77 and 172.7 (C-1, C-2′′′) ppm. IR (film): $\tilde{\nu}$ = 3490, 2975, 2940, 1750, 1730, 1460, 1395, 1370, 1255, 1225, 1160, 1135, 915, 745 cm^{-1}. $C_{24}H_{42}O_8$ (458.59): calcd. C 62.86, H 9.23; found C 63.01, H 9.26.

Minor Diastereomer (*anti*^{3,*},*syn*^{2,3}-9): $[\alpha]_D^{20}$ = –1.10 (*c* = 1.09, $CHCl_3$, 10 cm). ^{1}H NMR (400.1 MHz, $CDCl_3$/TMS): δ = 0.87 (dd, ^3J = 7.5 Hz, 3 H, 2′-CH_2-C$H_3^{\dagger}$), 0.91 (dd, ^3J = 7.5 Hz, 3 H, 2′-CH_2-C$H_3^{\ddagger}$), 1.12 (ddd, $^2J_{5'ax,5'eq}$ = 12.8, $J_{5'ax,4'}$ = $J_{5'ax,6'}$ = 11.8 Hz, 1 H, 5′-H^{ax}), 1.46 [s, 9 H, C(CH_3)$_3$], 1.47 (s, 9 H, *tert*-butyl), 1.53 (ddd, $^2J_{5'eq,5'ax}$ = 13.0, $J_{5'eq,4'}$ = $J_{5'eq,6'}$ = 2.5 Hz, 1 H, 5′-H^{äq}), AB signal (δ_A = 1.61, δ_B = 1.66, J_{AB} = 14.2 Hz, in addition split by $J_{A,CH3}$ = $J_{B,CH3}$ = 7.4 Hz, 2 H, 2′-CH_2-$CH_3^{\ddagger}$), AB signal (δ_A = 1.78, δ_B = 1.94, J_{AB} = 14.9 Hz, in addition split by $J_{A,CH3}$ = $J_{B,CH3}$ = 7.3 Hz, 2 H, 2′-CH_2-$CH_3^{\dagger}$), 2.40 (ddd, $J_{3\text{-}4}$ = $J_{3,4'}$ = 9.8, $J_{3,2}$ = 2.2 Hz, 1 H, 3-H), 2.90 (d, $J_{2\text{-}OH,2}$ = 3.8 Hz, 1 H, 2-OH), AB signal (δ_A = 3.50, δ_B = 3.54, J_{AB} = 10.2 Hz, in addition split by $J_{A,4'}$ = 4.5, $J_{B,4'}$ = 5.6 Hz, 2 H, 1′′-H_2), AB signal (δ_A = 4.01, δ_B = 4.06, J_{AB} = 16.4 Hz, 2 H, 1′′′-H_2), 3.98–4.12 (m, 2 H, 4′-H, 6′-H), 4.51 (dd, $J_{2,2\text{-}OH}$ = 5.1, $J_{2,3}$ = 2.2 Hz, 1 H, 2-H), 5.11 (ddd, $J_{5cis,4}$ = 17.1, $^2J_{5cis,5trans}$ = 2.2, $^4J_{5cis,3}$ = 0.6 Hz, 1 H, 5-H^{cis}), 5.15 (dd, $J_{5trans,4}$ = 10.4, $^2J_{5trans,5cis}$ = 2.2 Hz, 1 H, 5-H^{trans}), 5.62 (ddd, $J_{4,5cis}$ = 17.1, $J_{4,5trans}$ = $J_{4,3}$ = 10.2 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS): δ = 7.13 (2′-CH_2-*C*$H_3^{\ddagger}$), 7.89 (2′-CH_2-*C*$H_3^{\dagger}$), 22.16 (2′-*C*H_2-$CH_3^{\dagger}$), 28.13 and 28.17 [2 × C(*C*H_3)$_3$], 31.15 (C-5′), 32.13 (2′-*C*H_2-$CH_3^{\ddagger}$), 54.12 (C-3), 66.06 (C-6′), 68.29 (C-4′), 69.10 (C-2), 69.40 (C-1′′′), 74.94 (C-1′′), 81.49 and 82.37 [2 × *C*(CH_3)$_3$], 102.15 (C-2′), 119.97 (C-5), 132.13 (C-4), 169.76 and 174.18 (C-1, C-2′′′) ppm. IR (film): $\tilde{\nu}$ = 3505, 2980, 2940, 2885, 1750, 1725, 1460, 1395, 1370, 1280, 1255, 1225, 1165, 1135, 995, 970, 930, 850, 755 cm^{-1}. $C_{24}H_{42}O_8$ (458.59): calcd. C 62.86, H 9.23; found C 62.94, H 9.30.

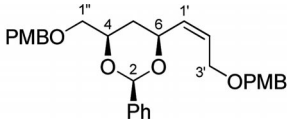
***tert*-Butyl 2-{(*Z*)-3-[(4*S*,6*R*)-6-{(2-*tert*-Butoxy-2-oxoethoxy)methyl}-2,2-diethyl-1,3-dioxan-4-yl]allyloxy}acetate (11):**



At 80 °C, a mixture of benzylidene derivative **34** (1.31 g, 2.73 mmol, 1 equiv.), camphorsulfonic acid (253 mg, 1.09 mmol, 0.4 equiv.), 3-pentanone (30 mL, 80 mmol, 100 equiv.), and 3,3-dimethoxypentane (2 mL, excess) was stirred for 1 h. The brown solution was neutralized by adding half-satd. aqueous $NaHCO_3$ (50 mL). After extraction with *t*BuOMe (2 × 50 mL), the combined organic layers were washed with brine (50 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography[45] (5 cm; cyclohexane/AcOEt, 9:1) to yield the title compound as a yellowish oil (741 mg, 60%). $[\alpha]_D^{20}$ = +4.23 and $[\alpha]_{365}^{20}$ = +14.5 (in both instances *c* = 1.12 in $CDCl_3$, 10 cm). ^{1}H NMR (400.1 MHz, $CDCl_3$/TMS): δ = 0.85 (t, ^3J = 7.5 Hz, 3 H, CH_3), 0.85 (dd, $^3J_{CH^AH^B}$ = $^3J_{CH^AH^B}$ = 7.5 Hz, 3 H, 2-CH_2-C$H_3^{\dagger}$), 0.90 (t, $^3J_{CH2}$ = 7.4 Hz, 3 H, 2-CH_2-C$H_3^{\ddagger}$), 1.33 (ddd, $^2J_{5ax,5eq}$ = $J_{5ax,4}$ = $J_{5ax,6}$ = 12.1 Hz, 1 H, 5-H^{ax}), 1.47 [s, 9 H, C(CH_3)$_3$], 1.48 [s, 9 H, C(CH_3)$_3$], 1.51 (ddd, $^2J_{5eq,5ax}$ = 13.3, $J_{5eq,4}$ = $J_{5eq,6}$ = 2.5 Hz, 1 H, 5-H^{eq}), 1.61 (q, $^3J_{CH3}$ = 7.4 Hz, 2 H, 2-CH_2-$CH_3^{\ddagger}$), AB signal (δ_A = 1.84, δ_B = 1.86, J_{AB} = 14.8 Hz, in addition split by $J_{A,CH3}$ = $J_{B,CH3}$ = 7.4 Hz, 2 H, 2-CH_2-$CH_3^{\dagger}$), AB signal (δ_A = 3.49, δ_B = 3.55, J_{AB} = 10.1 Hz, in addition split by $J_{A,6}$ = 4.6, $J_{B,6}$ = 5.7 Hz, 2 H, 1′′-H_2), AB signal (δ_A = 3.92, δ_B = 3.97, J_{AB} = 15.7 Hz, 2 H, 2′′′′-H_2), AB signal (δ_A = 4.00, δ_B = 4.06, J^{gem} = 16.5 Hz, 2 H, 1′′′-H_2), 4.12 (dddd, $J_{6,5ax}$ = 11.9, $J_{6,1''B}$ = 5.4, $J_{6,1''A}$ = 4.8, $J_{6,5äq}$

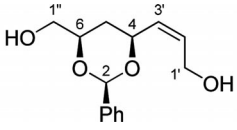
= 2.6 Hz, 1 H, 6-H), AB signal (δ_A = 4.18, δ_B = 4.21, J_{AB} = 12.6 Hz, in addition split by $J_{A,2'}$ = 6.4, $J_{A,3'}$ = 1.49, $J_{B,2'}$ = 6.2, $J_{B,3'}$ = 1.5 Hz, 2 H, 1′-H_2), 4.69 (ddd, $J_{4,5ax}$ = 11.4, $J_{4,3'}$ = 7.4, $J_{4,5eq}$ = 2.6 Hz, 1 H, 4-H), AB signal (δ_A = 5.56, δ_B = 5.65, J_{AB} = 11.3 Hz, in addition split by $J_{A,4}$ = 7.3, $^4J_{A,1'A}$ = $^4J_{A,1'B}$ = 1.1, $J_{B,1'A}$ = $J_{B,1'B}$ = 6.0 Hz, A: 3′-H, B: 2′-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 6.64 (2-CH_2-CH_3[‡]), 8.19 (2-CH_2-CH_3[†]), 22.40 (2-CH_2-CH_3[†]), 28.12 and 28.13 [2 × C(CH_3)$_3$], 31.14 (2-CH_2-CH_3[‡]), 33.31 (C-5), 64.77 (C-4), 67.01 (C-1′), 67.72 and 67.78 (C-6, C-2′′′′), 69.32 (C-1′′′), 74.75 (C-1′′), 81.54 and 81.58 [2 × C(CH_3)$_3$], 101.95 (C-2), 127.60 (C-2′), 133.95 (C-3′), 169.53 and 169.70 (C-2′′′, C-1′′′′) ppm. IR (film): $\tilde{\nu}$ = 2975, 2940, 2880, 1750, 1460, 1430, 1395, 1370, 1300, 1230, 1165, 1130, 1040, 965, 845, 700, 655 cm^{-1}. $C_{24}H_{42}O_8$ (458.59): calcd. C 62.86, H 9.23; found C 62.88, H 9.15.

(2*R*,4*R*,6*S*)-4-[(4-Methoxybenzyloxy)methyl]-6-[(*Z*)-3-(4-methoxybenzyloxy)prop-1-enyl]-2-phenyl-1,3-dioxane (12):[64]



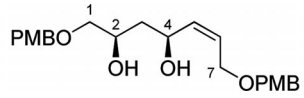
Camphorsulfonic acid (57 mg, 9.30 mmol, 2.5 mol-%) was added in one portion to a solution of diol *syn,cis*-**14** (3.95 g, 9.81 mmol, 1.0 equiv.) and benzaldehyde dimethyl acetal (2.9 mL, 20 mmol, 2.0 equiv.) in CH_2Cl_2 (60 mL). The mixture was stirred for 1 h at room temp., neutralized by the addition of half satd. aqueous $NaHCO_3$ (60 mL), and extracted with *t*BuOMe (2 × 60 mL). The combined organic layers were washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography[45] (cyclohexane/AcOEt, 5:1) to yield a colorless oil (4.57 g, 95%). ^{1}H NMR (300.1 MHz, $CDCl_3$/TMS): δ = 1.57–1.62 (m, 2 H, 5-H_2), AB signal (δ_A = 3.47, δ_B = 3.62, J_{AB} = 10.2 Hz, in addition split by $J_{A,4}$ = 4.8, $J_{B,4}$ = 5.9 Hz, 2 H, 1′′-H_2), 3.79 (s, 1 H, OCH_3), 3.80 (s, 1 H, OCH_3), 4.06 (m_c, 1 H, 4-H), 4.11 (m_c, 1 H, 3′-H), AB signal (δ_A = 4.43, δ_B = 4.46, J_{AB} = 11.4 Hz, 2 H, benzyl-H_2), AB signal (δ_A = 4.50, δ_B = 4.53, J_{AB} = 11.7 Hz, 2 H, benzyl-H_2), 4.61 (ddd, $J_{6,1''} \approx J_{6,5A} \approx J_{6,5B} \approx$ 7.0 Hz, 1 H, 6-H), 5.55 (s, 1 H, 2-H), 5.63–5.74 (m, 2 H, 1′-H, 2′-H), AA′BB′ signal centered at δ = 6.86 and 7.25 ppm, superimposed by another AA′BB′ signal centered at δ = 6.87 and 7.26 ppm, (8 H, 2 × C_6H_4), 7.46–7.51 (2 × m, 5 H, C_6H_5) ppm.

(*Z*)-3-[(2*R*,4*S*,6*R*)-6-(Hydroxymethyl)-2-phenyl-1,3-dioxan-4-yl]-prop-2-en-1-ol (13):



Aqueous phosphate buffer (pH = 7.1, 0.5 M, 10 mL) and DDQ (5.27 g, 23.3 mmol, 2.5 equiv.) were added to a solution of the PMB ether derivative **12** (4.57 g, 9.31 mmol, 1.0 equiv.) in CH_2Cl_2 (180 mL). The mixture quickly turned dark green and then yellow after 2 h. It was filtered and the filtrate was washed with half-satd. aqueous $NaHCO_3$ (2 × 50 mL). The aqueous phase was re-extracted with CH_2Cl_2 (5 × 20 mL) and the combined organic layers were washed with brine (50 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude was purified by flash chromatography[45] (8 cm; cyclohexane/AcOEt/NEt_3, 25:75:0.5) to yield a colorless oil (19.8 g, 85%). $[\alpha]_D^{20}$ = +42.1; $[\alpha]_{365}^{20}$ = +172.4 (in both instances *c* = 1.02 in $CDCl_3$, 10 cm); m.p. 80–83 °C. ^{1}H NMR (400.1 MHz, $CDCl_3$/TMS): δ = 1.54 [ddd, $^2J_{5eq,5ax}$ = 13.3, $J_{5eq,4}$ = $J_{5eq,6}$ = 2.7 Hz, 1 H, 5-H^{eq}], 1.71 [ddd, $^2J_{5ax,5eq}$ = 13.3, $J_{5ax,4}$ = $J_{5ax,6}$ = 11.4 Hz, 1 H, 5-H^{ax}], 2.00 and 2.23 (2 × br. s, 2 × 1 H, 1′-OH, 1′′-OH), AB signal (δ_A = 3.64, δ_B = 3.70, J_{AB} = 11.8 Hz, in addition split by $J_{A,6}$ = 6.3, $J_{B,6}$ = 3.4 Hz, 2 H, 1′′-H_2), 4.02 (dddd, $J_{6\text{-}5ax}$ = 11.4, $J_{6\text{-}1''A}$ = 6.1, $J_{6\text{-}1''B}$ = 3.3, $J_{6\text{-}5eq}$ = 2.7 Hz, 1 H, 6-H), AB signal (δ_A = 4.19, δ_B = 4.29, J_{AB} = 13.3 Hz, in addition split by $J_{A,4}$ = 6.2, $J_{B,4}$ = 6.7 Hz, 2 H, 1′-H_2), 4.70 (dddd, $J_{4,5ax}$ = 11.3, $J_{4,3'}$ = 7.2, $J_{4,5eq}$ = 2.8, $^4J_{4,2'}$ = 1.2 Hz, 1 H, 4-H), AB signal (δ_A = 5.61, δ_B = 5.77, J_{AB} = 11.2 Hz, in addition split by $J_{A,4}$ = 7.2, $^4J_{A,1'A}$ = $^4J_{A,1'B}$ = 1.4, $J_{B,1'B}$ = 6.7, $J_{B,1'A}$ = 6.2, $^4J_{B,4}$ = 1.2 Hz, A: 3′-H, B: 2′-H), superimposed by 5.60 (s, 1 H, 2-H), 7.31–7.40 and 7.48–7.56 (2 × m, 5 H, 2 × 2^{Ar}-H, 2 × 3^{Ar}-H, 4^{Ar}-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS): δ = 32.61 (C-5), 58.93 (C-1′), 65.48 (C-3′′), 73.14 (C-4), 77.13 (C-6), 100.93 (C-2), 126.31, 128.41, and 129.16 (2 × C-2_{Ar}, 2 × C-3_{Ar}, C-4_{Ar}), 131.31 (C-1′′), 131.82 (C-2′′), 138.08 (C-1^{Ar}) ppm. IR (film): $\tilde{\nu}$ = 3375, 3035, 2920, 2870, 1650, 1395, 1335, 1310, 1215, 1130, 1105, 1030, 1010, 840, 765, 720 cm^{-1}. $C_{14}H_{18}O_4$ (250.12): calcd. C 67.18, H 7.25; found C 66.91, H 7.31.

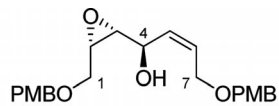
(*Z*)-(2*R*,4*S*)-1,7-Bis(4-methoxybenzyloxy)hept-5-ene-2,4-diol (*syn,cis*-14):[65]



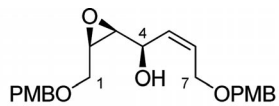
The 78:22 mixture of the epoxides *anti,cis*- and *syn,cis*-**16** (11.8 g, 29.4 mmol, containing 20.9 mmol of *anti,cis*-**16**) was dissolved in toluene (120 mL) and cooled to –40 °C. A Red-Al® solution (3.4 M in toluene, 62 mL, 210 mmol, 10-fold molar amount) was added dropwise under vigorous stirring. The solution was stirred for 18 h at the same temperature; the reaction was quenched by pouring it into aqueous Na/K tartrate solution (half-satd., 250 mL). After 2 h vigorous stirring, the mixture was extracted with *t*BuOMe (4 × 100 mL). The combined organic layers were washed with brine (200 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography[45] (8 cm; cyclohexane/AcOEt, 1:1) to yield *syn,cis*-**14** as a colorless oil (6.62 g, 46% from divinylcarbinol *cis,cis*-**17**; *ee* (HPLC): 95%).[66] ^{1}H NMR (300.1 MHz, $CDCl_3$/TMS): AB signal (δ_A = 1.55, δ_B = 1.70, J_{AB} = 14.1 Hz, in addition split by $J_{A,4}$ = 4.4, $J_{B,2}$ = 9.9, $J_{A,2}$ = 2.8, $J_{B,4}$ = 8.7 Hz, 2 H, 3-H_2), 3.09 and 3.12 (2 × br. s, 2 H, 2-OH, 4-OH), AB signal (δ_A = 3.34, δ_B = 3.40, J_{AB} = 9.4 Hz, in addition split by $J_{A,2}$ = 6.8, $J_{B,2}$ = 4.2 Hz, 2 H, 1-H_2), 3.79 and 3.80 (2 × s, 2 × 3 H, 2 × OCH_3), 3.95 (m_c, 1 H, 2-H), 4.00–4.14 (m, 1 H, 7-H_2), AB signal (δ_A = 4.43, δ_B = 4.46, J_{AB} = 11.4 Hz, 2 H, benzyl-H_2), 4.47 (s, 2 H, benzyl-H_2), 4.66 (ddd, $J_{4,5}$ = $J_{4,3B}$ = 8.1, $J_{4,3A}$ = 4.5 Hz, 1 H, 4-H), 5.55–5.72 (m, 2 H, 5-H, 6-H), AA′BB′ signal centered at δ = 6.87 and δ = 7.25 (8 H, 2 × C_6H_4) ppm,

***cis*-(2*S*,3*R*,4*R*)-2,3-Epoxy-1,7-bis(4-methoxybenzyloxy)hept-5-en-4-ol (*anti,cis*-16, Major Diastereomer) and**

***cis*-(2*R*,3*S*,4*R*)-2,3-Epoxy-1,7-bis(4-methoxybenzyloxy)hept-5-en-4-ol (*syn,cis*-16, Minor Diastereomer):**[69]



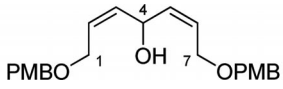
anti,cis-**16**



syn,cis-**16**

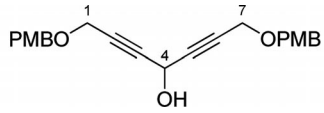
At –25 °C, Ti(O*i*Pr)$_4$ (11.2 mL, 37.9 mmol, 1.05 equiv.) was added to a suspension of D-(–)-DiPT (7.8 mL, 39.7 mmol, 1.1 equiv.) and 4 Å molecular sieves (16.6 g) in CH_2Cl_2 (35 mL). [We found the presence of 1.0 equiv. of Ti(O*i*Pr)$_4$[67] advantageous during the Sharpless epoxidation of divinylcarbinol *cis*,*cis*-**17**: the C=C bonds of this substrate reacted sluggishly, which is not unexpected in view of its *cis* configuration.[68,71]] After 1 h of stirring at room temp., a solution of diene *cis*,*cis*-**17** (13.88 g, 36.1 mmol, 1.0 equiv.) in CH_2Cl_2 (500 mL) was added dropwise at –25 °C. After 1 h agitation, a solution of *t*BuOOH (4.7 M in CH_2Cl_2, 15.4 mL, 72.2 mmol, 2.0 equiv.) was added and the suspension was stirred for 72 h at –25 °C. The reaction was quenched by cautious addition of a Fe^{II} solution (156 g of $FeSO_4$ and 57 g of citric acid in 500 mL of water) under vigorous agitation. After 30 min, the CH_2Cl_2 layer was separated and the aqueous suspension was extracted with *t*BuOMe (4 × 100 mL). The combined organic layers were concentrated to 200 mL and treated with aqueous NaOH/NaCl (15 g of NaOH, 2.5 g of NaCl in 45 mL of H_2O). After filtration through a 13 × 3 cm pad of Celite, the organic layer was separated, washed with brine (50 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude was purified by flash chromatography[45] (10 cm; cyclohexane/AcOEt, 2:1) to yield a colorless oil containing *anti*,*cis*- and *syn*,*cis*-**16** in a 78:22 ratio (11.79 g, 29.4 mmol, containing 20.9 mmol of *anti*,*cis*-**16**). The crude was submitted to reduction (→ *syn*,*cis*-**14**) without further purification.

(*Z*,*Z*)-1,7-Bis(4-methoxybenzyloxy)hepta-2,5-dien-4-ol (*cis*,*cis*-17):[69]



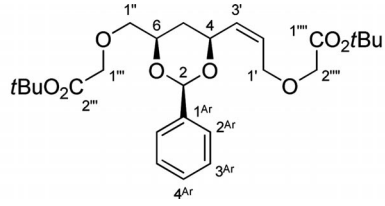
The first step consisted in the preparation of Cu^{II}- and Ag^{I}-activated zinc reactant.[70] Cu(OAc)$_2$·H$_2$O (16.1 g, 80.4 mmol, 1.0 equiv.) was added in one portion to a suspension of Zn dust (105 g, 1.61 mol, 20 equiv.) in water (700 mL) at room temp. After vigorous stirring at this temperature for 10 min, $AgNO_3$ (13.65 g, 80.4 mmol, 1.0 equiv.) was carefully added over 30 min (careful, very exothermic reaction occurring!). After stirring for 1 h at room temp., the suspension was filtered under an inert atmosphere maintained by placing over the apparatus an inverted funnel through which N_2 was passed. The zinc cake was successively washed with water (500 mL), methanol (500 mL), acetone (500 mL), and *t*BuOMe (500 mL). The metal powder was suspended in water/methanol (1:1, 700 mL) and a solution of dialkyne **18** (30.6 g, 80.4 mmol) in methanol (50 mL) was added at room temp. The resulting mixture was vigorously stirred at 40 °C for 15 h. The reaction mixture was cooled to room temp., filtered through a 13 × 3 cm pad of Celite, and the filter cake was washed with *t*BuOMe (200 mL). The filtrate and washings were washed with half-satd. aqueous $NaHCO_3$ (300 mL) and brine (300 mL), dried with $MgSO_4$, filtered, and the solvents evaporated. The residue was purified by flash chromatography[45] (10 cm; cyclohexane/AcOEt, 3:2) to yield a yellow oil (23.5 g, 76%). ^{1}H NMR (300.1 MHz, $CDCl_3$/TMS): δ = 2.38 (br. s, 1 H, 4-OH), 3.79 (s, 6 H, 2 × OCH_3), AB signal (δ_A = 4.01, δ_B = 4.08, J_{AB} = 12.4 Hz, in addition split by $J_{A,vic}$ = 4.9 Hz, $J_{B,vic}$ = 5.0 Hz, 4 H, 1-H$_2$, 7-H$_2$), 4.42 (s, 2 H, 2 × benzyl-H$_2$) 5.14 (t, $J_{4,3}$ = $J_{4,5}$ = 6.9 Hz, 1 H, 4-H), 5.59–5.73 (m, 4 H, 2-H, 3-H, 5-H, and 6-H), AA′BB′ signal centered at δ = 6.87 and δ = 7.25 (8 H, 2 × C_6H_4) ppm.

1,7-Bis(4-methoxybenzyloxy)hepta-2,5-diyn-4-ol (18):[69]



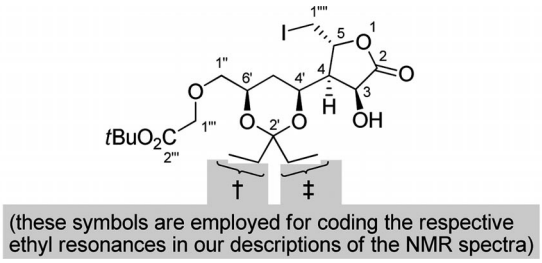
A solution of *n*Buli (2.5 M in hexanes, 39 mL, 97 mmol, 2.1 equiv.) was added dropwise to a solution of **15** (18.75 g, 106.4 mmol, 2.3 equiv.) in THF (400 mL) at –78 °C. After stirring for 1 h at this temperature, ethyl formate (3.73 mL, 46.3 mmol, 1.0 equiv.) was added and the solution was stirred at –35 °C for 17 h. The reaction was quenched by the addition of cold water (600 mL) and the mixture was extracted with *t*BuOMe (4 × 200 mL). The combined organic layers were washed with brine (300 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography[45] (10 cm; cyclohexane/AcOEt, 3:1) to afford **18** (15.60 g, 89%) as a colorless oil. ^{1}H NMR (300.1 MHz, $CDCl_3$/TMS): δ = 2.32 (d, $J_{OH,4}$ = 7.2, 4-OH), 3.80 (s, 2 × OCH_3), 4.19 (d, $^4J_{1,4}$. = $^4J_{7,4}$ = 1.8, 1-H$_2$, 7-H$_2$), 4.53 (s, 2 × benzyl-H$_2$), 5.23 (d, $J_{4,OH}$ = 7.3, 4-H), AA′BB′ signal centered at δ = 6.87 and δ = 7.27 (8 H, 2 × C_6H_4) ppm.

***tert*-Butyl 2-[(*Z*)-3-{(2*R*,4*S*,6*R*)-6-[(2-*tert*-Butoxy-2-oxoethoxy)-methyl]-2-phenyl-1,3-dioxan-4-yl}allyloxy]acetate (34):**



At room temp., 50% aqueous NaOH (200 mL) was added to a solution of diol **13** (2.69 g, 10.7 mmol, 1 equiv.) and *tert*-butyl bromoacetate (4.70 mL, 32.1 mmol, 3.0 equiv.) in CH_2Cl_2 (100 mL). The mixture was vigorously stirred. Bu_4N·HSO_4 (2.54 g, 7.49 mmol, 0.7 equiv.) was added. After 1 h the mixture was extracted with *t*BuOMe (3 × 70 mL). The combined organic layers were washed with half-satd. aqueous NH_4Cl (100 mL) and brine (100 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography[45] (4 cm; cyclohexane/AcOEt, 5:1) afforded the title compound as a colorless oil (4.09 g, 80%). $[\alpha]_D^{20}$ = +29.5 (*c* = 1.03, $CHCl_3$, 10 cm). ^{1}H NMR (499.9 MHz, $CDCl_3$/TMS): δ = 1.46 and 1.48 [2 × s, 2 × 9 H, 2 × C(CH$_3$)$_3$], 1.61–1.70 (m, 2 H, 5-H$_2$), AB signal (δ_A = 3.64, δ_B = 3.74, J_{AB} = 10.4 Hz, in addition split by $J_{A,4}$ = 4.5, $J_{B,4}$ = 5.9 Hz, 2 H, 1′′-H$_2$), AB signal (δ_A = 3.94, δ_B = 3.99, J_{AB} = 16.2 Hz, 2 H, 1′′′′-H$_2$), AB signal (δ_A = 4.03, δ_B = 4.08, J_{AB} = 16.4 Hz, 2 H, 1′′′-H$_2$), 4.17 (dddd, $J_{4,5ax}$ = 9.9, $J_{4,1''B}$ = 5.6, $J_{4,1''A}$ = $J_{4,5eq}$ = 4.3 Hz, 1 H, 4-H), AB signal (δ_A = 4.22, δ_B = 4.26, J_{AB} = 12.7 Hz, in addition split by $J_{A,2'}$ = 3.7, $J_{A,3'}$ = 1.2, $J_{B,2'}$ = 3.6, $J_{B,3'}$ = 1.1 Hz, 2 H, 1′-H$_2$), 4.71 (dddd, $J_{6,5ax}$ = 10.0, $J_{6,3'}$ = 5.0, $J_{6,5eq}$ = 3.8, $J_{6,2'}$ = 1.3 Hz, 1 H, 6-H), 5.60 (s, 1 H, 2-H), 5.64–5.76 (m, 2 H, 2′-H, 3′H), 7.28–7.36 and 7.45–7.51 (2 × m, 5 H, 2 × 2^{Ar}-H, 2 × 3^{Ar}-H, 4^{Ar}-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$/TMS): δ = 28.17 and 28.19 [2 × C(*C*H$_3$)$_3$], 33.47 (C-5), 67.09 (C-1′), 67.92 (C-2′′′′), 69.39 (C-1′′′), 73.24 (C-6), 74.06 (C-1′′), 75.96 (C-4), 81.70 [2 × *C*(CH$_3$)$_3$], 100.74 (C-2), 126.32 (2 × C-2^{Ar}),* 128.17 (C-2′), 128.24 (2 × C-3^{Ar}),* 128.83 (C-4^{Ar}),* 132.90 (C-3′), 138.32 (C-1^{Ar}),* 169.57 (C-2′′′),* 169.68 (C-1′′′′)* ppm; *: assignment corroborated by HMBC experiment. IR (film): $\tilde{\nu}$ = 2980, 1745, 1455, 1390, 1365, 1305, 1225, 1125, 1020, 955, 845, 755, 700, 570 cm^{-1}. $C_{26}H_{38}O_8$ (478.58): C 65.25, H 8.00; found C 64.95, H 8.00.

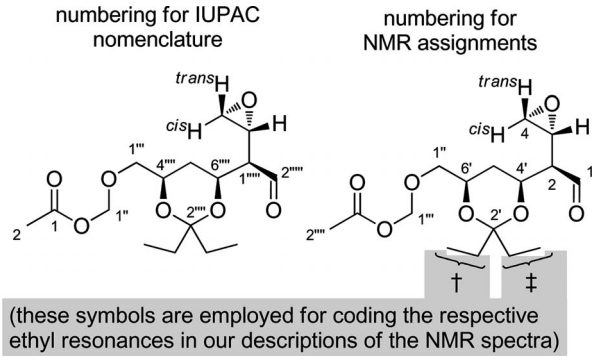
***tert*-Butyl 4-{(3*S*,4*S*,5*R*)-6-[(4*S*,6*R*)-(2-*tert*-Butoxy-2-oxoethoxy)-methyl]-2,2-diethyl-1,3-dioxan-4-yl}-3-hydroxy-5-(iodomethyl)-4,5-dihydrofuran-2(3*H*)-one (35):**



At –25 °C, I_2 (5.15 g, 20.3 mmol, 6.0 equiv.) was added in one portion to a suspension of homoallyl alcohol *syn*[3,*],*syn*[2,3]-**9** (1.55 g, 3.38 mmol, 1.0 equiv.), $NaHCO_3$ (1.42 g, 16.9 mmol, 5.0 equiv.), and LiI (565 mg, 4.22 mmol, 1.25 equiv.) in CH_3CN (85 mL). The temperature was allowed to rise to –15 °C. The mixture was stirred for 16 h. The reaction was quenched by adding satd. aqueous $Na_2S_2O_3$ until complete discoloration occurred. The mixture was extracted with *t*BuOMe (3 × 25 mL). The combined organic layers were washed with H_2O (50 mL) and with brine (50 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography[45] (5 cm; petroleum ether/Et_2O, 1:1) afforded **35** as a yellowish oil (1.26 g, 71%). $[\alpha]_D^{20}$ = +4.7 (*c* = 1.10, $CHCl_3$, 10 cm). ^{1}H NMR (400.1 MHz, $CDCl_3$/TMS): δ = 0.83 (dd, $^3J_{CH^AH^B}$ = $^3J_{CH^AH^B}$ = 7.5 Hz, 3 H, 2′-CH_2-$CH_3^{\dagger}$), 0.85 (t, $^3J_{CH2}$ = 7.4 Hz, 3 H, 2′-CH_2-$CH_3^{\ddagger}$), 1.45 (ddd, $^2J_{5'ax,5'eq}$ = $J_{5'ax,4'}$ = $J_{5'ax,6'}$ = 12.1 Hz, 1 H, 5′-H^{ax}), 1.48 [s, 9 H, $C(CH_3)_3$], 1.57 (q, $^3J_{CH3}$ = 7.5 Hz, 2 H, 2′-CH_2-$CH_3^{\ddagger}$), 1.58 (ddd, $^2J_{5'eq,5'ax}$ = 12.6, $J_{5'eq,4'}$ = $J_{5'eq,6'}$ = 2.7 Hz, 1 H, 5′-H^{eq}), AB signal (δ_A = 1.66, δ_B = 1.98, J_{AB} = 14.9 Hz, in addition split by $J_{A,CH3}$ = $J_{B,CH3}$ = 7.3 Hz, 2 H, 2′-CH_2-$CH_3^{\ddagger}$), 2.47 (ddd, $J_{4,3}$ = 8.7, $J_{4,4'}$ = 3.9, $J_{4,5}$ = 3.5 Hz, 1 H, 4-H), 2.58 (d, $J_{3OH,3}$ = 5.5 Hz, 1 H, 3-OH), AB signal (δ_A = 3.41, δ_B = 3.44, J_{AB} = 10.6 Hz, in addition split by $J_{A,5}$ = 4.5, $J_{B,5}$ = 5.9 Hz, 2 H, 1′′′′-H_2), AB signal (δ_A = 3.53, δ_B = 3.59, J_{AB} = 10.1 Hz, in addition split by $J_{A,6'}$ = 4.7, $J_{B,6'}$ = 5.4 Hz, 2 H, 1′′-H_2), AB signal (δ_A = 4.02, δ_B = 4.05, J_{AB} = 16.4 Hz, 2 H, 1′′′-H_2), 4.21 (dddd, $J_{6',5'ax}$ = 11.3, $J_{6',1''A}$ = $J_{6',1''B}$ = 5.1, $J_{6',5'eq}$ = 2.6 Hz, 1 H, 6′-H), 4.41 (ddd, $J_{4',5'ax}$ = 12.0, $J_{4',4}$ = 4.0, $J_{4',5'eq}$ = 3.0 Hz, 1 H, 4′-H), 4.62 (dd, $J_{3,4}$ = 8.8, $J_{3,3OH}$ = 5.5 Hz, 1 H, 3-H), 4.68 (ddd, $J_{5,1''''A}$ = $J_{5,1''''B}$ = 5.4, $J_{5,4}$ = 3.3 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 6.80 (2′-CH_2-$CH_3^{\ddagger}$), 7.62 (C-1′′′′), 8.11 (2′-CH_2-$CH_3^{\dagger}$), 22.48 (C-5′), 28.14 [$C(CH_3)_3$], 30.06 (2′-CH_2-$CH_3^{\dagger}$), 30.96 (2′-CH_2-$CH_3^{\ddagger}$), 47.69 (C-4), 64.45 (C-4′), 67.39 (C-3), 67.64 (C-6′), 69.29 (C-1′′′), 74.42 (C-1′′), 78.00 (C-5), 81.68 [$C(CH_3)_3$], 102.35 (C-2′), 169.64 and 175.73 (C-2′′′, C-2) ppm. IR (film): $\tilde{\nu}$ = 3445, 2975, 2935, 2880, 1785, 1745, 1460, 1365, 1225, 1135, 960, 845, 740 cm^{-1}. HRMS (EI, 70 eV): calcd. for $C_{18}H_{28}IO_8$ $[M - C_2H_5]^+$ 499.08290; found 499.08220 (Δ = –1.4 ppm).

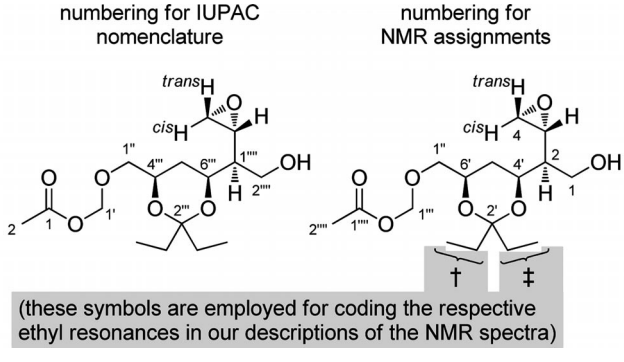
{[(4*R*,6*S*)-2,2-Diethyl-6-{(*S*)-1-[(*R*)-oxiran-2-yl]-2-oxoethyl}-1,3-dioxan-4-yl]methoxy}methyl Acetate (36):

At 0 °C, aqueous LiOH [prepared from LiOH·H_2O (48 mg, 1.1 mmol, 6.0 equiv.) and H_2O (0.6 mL)] and Ag_2O (31 mg, 130 μmol, 0.6 equiv.) were added to a solution of iodolactone **35** (98 mg, 190 μmol, 1.0 equiv.) in THF/methanol (2:1, 1.2 mL). The mixture was stirred at room temp for 1 h, cooled to 0 °C, and acidified (pH ≈ 3) by the cautious addition of ice-cold HCl (10% in H_2O). The aqueous layer was saturated with NaCl and extracted with Et_2O (6 × 1.5 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo to yield crude **37** as a colorless oil (63 mg, 95%, no further purification).



At 5 °C and exposed to a spot-light (visible, 150 W), a solution of the compound **37** (63 mg, 0.189 mmol, 1 equiv.) in THF (2 mL) was added dropwise during 5 min to a solution of $Pb(OAc)_4$ (80% in AcOH, 314 mg, 0.567 mmol, 3 equiv.) and $Cu(OAc)_2$ (2 mg, 9.5 μmol, 5 mol-%) in benzene (2 mL). After stirring/irradiating for another 15 min the reaction was quenched by adding ethylene glycol (0.1 mL) and phosphate buffer (pH = 7.1, 0.5 M, 4 mL). The resulting mixture was extracted with Et_2O (4 × 4 mL). The combined organic layers were washed with brine (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. We obtained **36** as a colorless oil (53 mg, 85% from **35** over the two steps) but could not purify it due to its incompatibility with silica gel. ^{1}H NMR (300.1 MHz, $CDCl_3$/TMS): δ = 0.83 (dd, $^3J_{CH^AH^B}$ = $^3J_{CH^AH^B}$ = 7.5 Hz, 3 H, 2′-CH_2-$CH_3^{\dagger}$), superimposed by 0.87 (dd, $^3J_{CH^AH^B}$ = $^3J_{CH^AH^B}$ = 7.4 Hz, 3 H, 2′-CH_2-$CH_3^{\ddagger}$), 1.35–1.55 (m, ^{2}H, 5′-H_2), superimposed by 1.51–1.67 (m, 2 H, 2′-CH_2-$CH_3^{\ddagger}$), 1.78–1.09 (m, 2 H, 2′-CH_2-$CH_3^{\dagger}$), 2.10 (s, 2′′′′-H_3), 2.37 (br. s, 1 H, 1-OH), 2.12 (ddd, $J_{2,3}$ = 7.5, $J_{2,4'}$ = 5.3, $J_{2,1}$ = 1.6 Hz, 1 H, 2-H), 2.59 (dd, $^2J_{4cis,4trans}$ = 4.8, $J_{4cis,3}$ = 2.7 Hz, 1 H, 4-H^{cis}), 2.92 (dd, $^2J_{4trans,4cis}$ = 4.8, $J_{4cis,3}$ = 4.0 Hz, 1 H, 4-H^{trans}), 3.36 (ddd, $J_{3,2}$ = 7.7, $J_{3,4trans}$ = 4.0, $J_{3,4cis}$ = 2.7 Hz, 1 H, 3-H), AB signal (δ_A = 3.57, δ_B = 3.66, J_{AB} = 10.5 Hz, in addition split by $J_{A,6'}$ = 4.7, $J_{B,6'}$ = 5.7 Hz, 2 H, 1′′-H_2), 4.01–4.12 (m, 1 H, 6′-H), 4.44 (ddd, $J_{4',5'ax}$ = 11.7, $J_{4',2}$ = 5.5, $J_{4',5'eq}$ = 2.8 Hz, 1 H, 4′-H), 5.29 (s, 2 H, 1′′′-H_2), 9.84 (d, $J_{1,2}$ = 1.7 Hz, 1 H, 1-H) ppm.

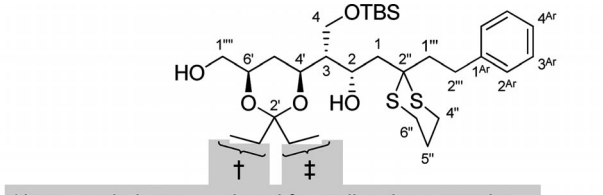
{[(4*R*,6*S*)-2,2-Diethyl-6-{(*S*)-2-hydroxy-1-[(*R*)-oxiran-2-yl]ethyl}-1,3-dioxan-4-yl]methoxy}methyl Acetate (38):



At 0 °C, $NaBH_4$ (47 mg, 820 μmol, 5.0 equiv.) was added in five portions to a solution of the crude aldehyde **36** (53 mg, 160 μmol, 1.0 equiv.) in dry methanol (45 mL). After stirring at room temp. for 2 h, aqueous phosphate buffer (pH = 7.1, 0.5 M, 2 mL) was added. The resulting mixture was extracted with AcOEt (4 × 2 mL). The combined organic layers were washed with brine (2 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography[45] (1.5 cm; cy-

clohexane/AcOEt, 3:2) to yield **38** as a colorless oil (fractions 11–20, 29 mg, 87 μmol, 46% over the three steps from iodolactone derivative **35**). ^{1}H NMR (400.1 MHz, $CDCl_3$/TMS): δ = 0.85 (dd, $^3J_{CH}{}^{A}{}_{H}{}^{B}$ = $^3J_{CH}{}^{A}{}_{H}{}^{B}$ = 7.5 Hz, 3 H, 2′-CH_2-C$H_3^{\dagger}$), superimposed by 0.88 (dd, $^3J_{CH}{}^{A}{}_{H}{}^{B}$ = $^3J_{CH}{}^{A}{}_{H}{}^{B}$ = 7.4 Hz, 3 H, 2′-CH_2-C$H_3^{\ddagger}$), 1.40 (ddt, $J_{2,3}$ = 7.4, $J_{2,4'}$ = 5.4, $J_{2,1A}$ = 4.6 Hz, 1 H, 2-H), 1.41 (ddd, $^2J_{5'ax,5'eq}$ = 12.8, $J_{5'ax,4'}$ = 12.0, $J_{5'ax,6'}$ = 11.0 Hz, 1 H, 5′-H^{ax}), 1.54 (ddd, $^2J_{5'eq,5'ax}$ = 12.6, $J_{5'eq,4'}$ = $J_{5'eq,6'}$ = 2.6 Hz, 1 H, 5′-H^{eq}), AB signal (δ_A = 1.58, δ_B = 1.63, J_{AB} = 14.6 Hz, in addition split by $J_{A,CH3}$ = $J_{B,CH3}$ = 7.4 Hz, 2 H, 2′-CH_2-C$H_3^{\ddagger}$), AB signal (δ_A = 1.82, δ_B = 1.88, J_{AB} = 14.8 Hz, in addition split by $J_{A,CH3}$ = $J_{B,CH3}$ = 7.4 Hz, 2 H, 2′-CH_2-C$H_3^{\dagger}$), 2.09 (s, 2′′′′-H_3), 2.37 (br. s, 1 H, 1-OH), 2.65 (dd, $^2J_{4cis,4trans}$ = 4.8, $J_{4cis,3}$ = 2.8, 1 H, 4-H^{cis}), 2.88 (dd, $^2J_{4trans,4cis}$ = 4.8, $J_{4cis,3}$ = 4.0 Hz, 1 H, 4-H^{trans}), 3.20 (ddd, $J_{3,2}$ = 7.3, $J_{3,4trans}$ = 4.1, $J_{3,4cis}$ = 2.8 Hz, 1 H, 3-H), AB signal (δ_A = 3.59, δ_B = 3.67, J_{AB} = 10.5 Hz, in addition split by $J_{A,6'}$ = 4.5, $J_{B,6'}$ = 5.8 Hz, 2 H, 1′′-H_2), 3.87 (m_c, 2 H, 1-H_2), 4.07 (dddd, $J_{6',5'ax}$ = 11.5, $J_{6',1''B}$ = 5.8, $J_{6',1''A}$ = 4.5, $J_{6',5'eq}$ = 2.6 Hz, 1 H, 6′-H), 4.20 (ddd, $J_{4',5'ax}$ = 11.7, $J_{4',2}$ = 5.6, $J_{4',5'eq}$ = 2.6 Hz, 1 H, 4′-H), AB signal (δ_A = 5.30, δ_B = 5.30, J_{AB} = 6.2 Hz, 2 H, 1′′′-H_2) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS): δ = 6.90 (2′-CH_2-$CH_3^{\ddagger}$), 8.05 (2′-CH_2-$CH_3^{\dagger}$), 21.05 (C-2′′′′), 22.24 (2′-CH_2-$CH_3^{\dagger}$), 30.79 (C-5′), 31.07 (2′-CH_2-$CH_3^{\ddagger}$), 47.24 (C-4), 48.17 (C-2), 51.17 (C-3), 61.58 (C-1′′), 67.65 (C-6′), 68.21 (C-4′), 73.44 (C-1), 89.54 (C-1′′′), 102.07 (C-2′), 170.57 (C-1′′′′) ppm. IR (film): $\tilde{\nu}$ = 3460, 2975, 2940, 2885, 1745, 1465, 1370, 1230, 1165, 1125, 1015, 925, 835 cm^{-1}.

(2*S*,3*R*)-4-(*tert*-Butyldimethylsiloxy)-3-[(4*S*,6*R*)-2,2-diethyl-6-(hydroxymethyl)-1,3-dioxan-4-yl]-1-[2-(2-phenylethyl)-1,3-dithian-2-yl]butan-2-ol (45):



At 0 °C, *n*BuLi (2.4 M in hexanes, 135 μL, 326 μmol, 3.5 equiv.) was added dropwise to a solution of dithiane **44** (84 mg, 370 μmol, 4.0 equiv.) in THF (1.5 mL). The resulting mixture was stirred for 30 min. At –78 °C, a solution of epoxide **7b** (35 mg, 93 μmol, 1.0 equiv.) in THF (1.5 mL)/HMPA (67 μL, 370 μmol, 4.0 equiv.) was added. After stirring for 16 h at –40 °C, the reaction mixture was quenched by the addition of aqueous satd. NH_4Cl. After extraction with Et_2O (3 × 2 mL), the combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography[45] (1.5 cm; petroleum ether/Et_2O, 7:3) of the residue afforded the title compound as a colorless oil (fractions 30–45, 39 mg, 70%). Excess dithiane **44** was also isolated (fractions 2–6, 49 mg, 78% of initial excess of this reagent). $[a]_D^{20}$ = +11.0 (*c* = 1.20, $CDCl_3$, 10 cm). ^{1}H NMR (499.6 MHz, C_6D_6): δ = 0.07 and 0.08 (2 × s, 2 × 3 H, 2 × $SiCH_3$), 0.77 (dd, $^3J_{CH}{}^{A}{}_{H}{}^{B}$ = $^3J_{CH}{}^{A}{}_{H}{}^{B}$ = 7.5 Hz, 3 H, 2′-CH_2-C$H_3^{\dagger}$), 0.93 (t, $^3J_{CH2}$ = 7.4 Hz, 3 H, 2′-CH_2-C$H_3^{\ddagger}$), 0.97 [s, 9 H, $SiC(CH_3)_3$], 1.17 (ddd, $^2J_{5'eq,5'ax}$ = 12.7, $J_{5'eq,4'}$ = $J_{5'eq,6'}$ = 2.4 Hz, 1 H, 5′-H^{eq}), 1.42–1.59 (m, 2 H, 5′′-H_2), superimposed by 1.51–1.62 (m, 1 H, 5′-H^{ax}), superimposed by 1.56–1.64 (m, 1 H, 1′′′′-OH), superimposed by 1.57 (q, $^3J_{CH3}$ = 7.7 Hz, 2 H, 2′-CH_2-$CH_3^{\ddagger}$), 1.67 (dddd, $J_{3,4A}$ = 6.8, $J_{3,4B}$ = 4.8, $J_{3,4'}$ = 4.5, $J_{3,2}$ = 1.9 Hz, 1 H, 3-H), AB signal (δ_A = 1.68, δ_B = 1.73, J_{AB} = 14.6 Hz, in addition split by $J_{A,CH3}$ = $J_{B,CH3}$ = 7.4 Hz, 2 H, 2′-CH_2-$CH_3^{\dagger}$), 2.35 (dd, $^2J_{1A,1B}$ = 15.0, $J_{1A,2}$ = 1.3 Hz, 1 H, 1-H^A), 2.31–2.50 (m, 4 H, 4′′-H_2, 6′′-H_2), superimposed by 2.47 (ddd, $^2J_{1'''A,1'''B}$ = 14.1, $J_{1'''A,2'''B}$ = 12.3, $J_{1'''A,2'''A}$ = 4.5 Hz, 1 H, 1′′′-H^A), 2.64 (dd, $^2J_{1B,1A}$ = 14.9, $J_{1B,2}$ = 8.2 Hz, 1 H, 1-H^B), 2.68 (ddd, $^2J_{1'''B,1'''A}$ = 14.1, $J_{1'''B,2'''A}$ = 12.3, $J_{1'''B,2'''B}$ = 4.7 Hz, 1 H, 1′′′-H^B), 3.00 (ddd, $^2J_{2'''A,2'''B}$ = $J_{2'''A,1'''B}$ = 12.7, $J_{2'''A,1'''A}$ = 4.4 Hz, 1 H, 2′′′-H^A), 3.23 (ddd, $^2J_{2'''B,2'''A}$ = $J_{2'''B,1'''A}$ = 12.8, $J_{2'''B,1'''B}$ = 4.6 Hz, 1 H, 2′′′-H^B), 3.42–3.52 (m, 2 H, 1′′′′-H_2), 3.62 (d, $J_{2\text{-}OH,2'}$ = 3.9 Hz, 1 H, 2-OH), 3.63 (dddd, $J_{6',5'ax}$ = 11.7, $J_{6',1''''A}$ = $J_{6',1''''B}$ = $J_{6',5'eq}$ = 2.5 Hz, 1 H, 6′-H), AB signal (δ_A = 3.94, δ_B = 3.99, J_{AB} = 10.5 Hz, in addition split by $J_{A,3}$ = 6.3, $J_{B,3}$ = 4.9 Hz, 2 H, 4-H_2), 4.29 (ddd, $J_{4',5'ax}$ = 11.9, $J_{4',3}$ = 4.9, $J_{4',5'eq}$ = 2.40, 1 H, 4′-H), 4.87 (dddd, $J_{2,1B}$ = 8.2, $J_{2,2\text{–}OH}$ = 4.0, $J_{2,3}$ = $J_{2,1A}$ = 2.0 Hz, 1 H, 2-H), 7.06 (m_c, 1 H, 4^{Ar}-H), 7.17 (m_c, 2 H, 2 × 3^{Ar}-H), 7.29 (m_c, 2 H, 2 × 2^{Ar}-H) ppm. ^{13}C NMR (125.6 MHz, C_6D_6): δ = –5.36 (2 × SiCH_3), 7.21 (2′-CH_2-$CH_3^{\ddagger}$), 8.22 (2′-CH_2-$CH_3^{\dagger}$), 18.33 [Si$C(CH_3)_3$], 22.59 (2′-CH_2-$CH_3^{\dagger}$), 25.58 (C-5′′), 26.02 and 26.11 (C-4′′, C-6′′), 26.08 [$SiC(CH_3)$], 30.73 (C-5′), 31.44 (2′-CH_2-$CH_3^{\ddagger}$), 31.86 (C-2′′′), 41.17 (C-1′′′), 44.88 (C-1), 52.40 (C-3), 53.61 (C-2′′), 60.27 (C-4), 66.18 (C-1′′′′), 67.39 (C-2), 68.28 (C-4′), 69.53 (C-6′), 102.25 (C-2′), 126.09 (C-4^{Ar}), 128.71 (2 × C-3^{Ar}), 129.00 (2 × C-2^{Ar}), 142.76 (C-1^{Ar}) ppm. IR (film): $\tilde{\nu}$ = 3455, 2955, 2930, 2880, 2860, 1465, 1380, 1360, 1255, 1165, 1105, 980, 940, 835, 775, 665 cm^{-1}. $C_{19}H_{38}O_5Si$ (374.59): C 60.92, H 10.22; found C 60.71, H 10.47.

Supporting Information (see footnote on the first page of this article): Experimental details of the Wittig rearrangement model study, NMR comparison of the rearrangement products, NMR spectra, X-ray data.

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[1] For reviews, see: a) J. M. T. Hamilton-Miller, *Bacteriol. Rev.* **1973**, *37*, 166–196; b) J.-M. Beau, G. Lukacs, in: *Recent Progress in the Chemical Syntheses of Antibiotics* (Ed.: M. Ohno), Springer, Berlin, **1990**, p. 137–179; c) S. Omura, H. Tanaka, *Macrolide Antibiotics: Chemistry, Biochemistry* and *Practice* (Ed.: S. Omura), Academic Press, New York, **1984**, p. 351–404; d) S. D. Rychnovsky, *Chem. Rev.* **1995**, *95*, 2021–2040; e) S. B. Zotchev, *Curr. Med. Chem.* **2003**, *10*, 211–223.

[2] a) For the isolation from *Streptomyces nodosus*, see: J. Vanderputte, J. L. Wachtel, E. T. Stiller, *Antibiot. Ann.* **1956**, 587–591; for connectivity and configuration, see: b) W. Mechlinski, C. P. Schaffner, P. Ganis, G. Avitabile, *Tetrahedron Lett.* **1970**, *11*, 3873–3876; c) P. Ganis, G. Avitabile, W. Mechlinski, C. P. Schaffner, *J. Am. Chem. Soc.* **1971**, *93*, 4560–4564.

[3] For the isolation from *Streptomyces noursei*, see: a) E. L. Hazen, R. Brown, *Science* **1950**, *112*, 423–430; b) E. L. Hazen, R. Brown, *Proc. Soc. Exp. Biol. Med.* **1951**, *76*, 93–98; for connectivity, see: c) C. N. Chong, R. W. Rickards, *Tetrahedron Lett.* **1970**, *11*, 5145–5149; d) E. Borowski, J. Zieliński, L. Falkowski, T. Zimiński, J. Golik, P. Kołodziejczyk, E. Jereczek, M. Gdulewicz, Yu. Shenin, T. Kotienko, *Tetrahedron Lett.* **1971**, *12*, 685–690; e) for the relative configuration, see: J.-M. Lancelin, F. Paquet, J.-M. Beau, *Tetrahedron Lett.* **1988**, *23*, 2827–2830; for the absolute configuration, see: f) K. C. Nicolaou, K. H. Ahn, *Tetrahedron Lett.* **1989**, *30*, 1217–1220; g) J.-M. Lancelin, J.-M. Beau, *Tetrahedron Lett.* **1989**, *30*, 4521–4524.

[4] a) For the isolation from *Streptomyces natalensis*, see: A. P. Struyk, I. Hoette, G. Drost, J. M. Waisvisz, T. van Eek, J. C. Hoogerheide, *Antibiot. Ann.* **1957**–**1958**, *5*, 878–885; b) for cconnectivity, see: B. T. Golding, R. W. Richards, W. E. Meyer, J. B. Patrick, M. Barber, *Tetrahedron Lett.* **1966**, *7*, 3551–3557; c) for the absolute configuration, see: J.-M. Lancelin, J.-M. Beau, *J. Am. Chem. Soc.* **1990**, *112*, 4060–4061.

[5] The compound known as "pimaricin" has also been called natamycin (H. Brik, *Analytical Profiles of Drug Substances* **1981**, *10*, 513–561) and tennecetin (P. V. Divekar, J. L. Bloomer, J. F. Eastham, D. F. Holtman, D. A. Shirley, *Antibiot. Chemother.* **1961**, *11*, 377–380).

[6] a) For a web site on pimaricin, see: http://www.codexalimentarius.net/gsfaonline/additives/details.html?id=208&lang=en; b) for pimaricin as a food additive, see: F. Aguilar, U. R. Charrondiere, B. Dusemund, P. Galtier, J. Gilbert, D. M. Gott, S. Grilli, R. Guertler, J. Koenig, C. Lambré, J.-C. Larsen, J.-C. Leblanc, A. Mortensen, D. Parent-Massin, I. Pratt, I. M. C. M. Rietjens, I. Stankovic, P. Tobback, T. Verguieva, R. A. Woutersen, *EFSA J.* **2009**, *7*, 1412–1427; (http://www.efsa.europa.eu/en/efsajournal/pub/1412.htm).

[7] a) For the isolation from *Streptomyces viridoflavus*, see: W. A. Taber, L. C. Vining, S. A. Waksman, *Antibiot. Chemother.* **1954**, *4*, 455–461; b) for connectivity, see: E. Borowski, L. Falkowski, J. Golik, J. Zieliński, T. Zimiński, W. Mechliński, E. Jereczek, P. Kołodziejczyk, H. Adlercreutz, C. P. Schaffner, S. Neelakantan, *Tetrahedron Lett.* **1971**, *12*, 1987–1992; c) for the absolute configuration, see: J. Pawlak, P. Sowinski, E. Borowski, P. Gariboldi, *J. Antibiot.* **1993**, *46*, 1598–1603.

[8] a) For the isolation from *Streptomyces rimosus*, see: J. W. Davisson, F. W. Tanner, A. C. Finlay, I. A. Solomons, *Antibiot. Chemother.* **1951**, *1*, 289–290; b) for connectivity, see: A. C. Cope, R. K. Bly, E. P. Burrows, O. J. Ceder, E. Ciganek, B. T. Gillis, R. F. Porter, H. E. Johnson, *J. Am. Chem. Soc.* **1962**, *84*, 2170–2181; c) for the absolute configuration, see: P. Sowiński, J. Pawlak, E. Borowski, P. Gariboldi, *J. Antibiot.* **1995**, *48*, 1288–1291.

[9] T. Brautaset, H. Sletta, A. Nedal, S. E. F. Borgos, K. F. Degnes, I. Bakke, O. Volokhan, O. N. Sekurova, I. D. Treshalin, E. P. Mirchink, A. Dikiy, T. E. Ellingsen, S. B. Zotchev, *Chem. Biol.* **2008**, *15*, 1198–1206.

[10] For example, the following polyol,polyene macrolides, amphotericin A: a) for isolation from *Streptomyces nodosus*, see: J. Vandeputte, J. L. Wachtel, E. T. Stiller, *Antibiot. Ann.* **1955**–**1956**, 587–591; for connectivity, see: b) P. Sowiński, J. K. Pawlak, E. Borowski, T. Iwashita, *J. Antibiot.* **1985**, *38*, 175–180; c) A. Aszalos, A. Bax, N. Burlinson, P. Roller, C. McNeal, *J. Antibiot.* **1985**, *38*, 1699–1713; lucensomicin: d) for the isolation from *Streptomyces lucensis*, see: F. Arcamone, C. Bertazzoli, G. Canevazzi, A. Dimarco, M. Ghione, A. Grein, *Giorn. Microbiol.* **1957**, *4*, 119–128; e) for connectivity, see: G. Gaudiano, P. Bravo, A. Quilico, *Tetrahedron Lett.* **1966**, *7*, 3559–3565; G. Gaudiano, P. Bravo, A. Quilico, *Tetrahedron Lett.* **1966**, *7*, 3567–3571; tetrin A and B: f) for the isolation from *Streptomyces Illinois*, see: D. Gottlieb, H. L. Pote, *Phytopathology* **1960**, *50*, 817–822; g) for the connectivity of tetrin A, see: R. C. Pandey, V. F. German, Y. Nishikawa, K. L. Rinehart Jr, *J. Am. Chem. Soc.* **1971**, *93*, 3738–3747; h) for the connectivity of tetrin B, see: K. L. Rinehart Jr., W. P. Tucker, R. C. Pandey, *J. Am. Chem. Soc.* **1971**, *93*, 3747–3751; tetrin C: i) for the isolation from *Streptomyces* sp. GK9244 and connectivity, see:G. Ryu, W.-C. Choi, S. Hwang, W.-H. Yeo, C.-S. Lee, S.-K. Kim, *J. Nat. Prod.* **1999**, *62*, 917–919; HA-2–91: j) for the isolation from *Streptomyces* sp. UK10, see: T. E. Gupte, S. R. Naik, *Hind. Antibiot. Bull.* **1991**, *33*, 1–6; k) for connectivity, see: T. E. Gupte, R. K. Nanda, N. R. Chatterjee, S. R. Naik, *Indian J. Chem. Sect. B* **2000**, *39*, 936–940; 3874 H1, 3874 H2, and 3874 H3: l) for the isolation from *Streptomyces* sp. HAG 003874 and connectivities, see: L. Vértesy, W. Aretz, E. Ehlers, S. Hawser, D. Isert, M. Knauf, M. Kurz, M. Schiell, M. Vogel, J. Wink, *J. Antibiot.* **1998**, *51*, 921–928.

[11] For reviews, see: a) J. Bolard, *Biochim. Biophys. Acta - Reviews on Biomembranes* **1986**, *864*, 257–304; b) S. C. Hartsel, C. Hatch, W. Ayenew, *J. Liposome Res.* **1993**, *3*, 377–408; c) ref.[1e]

[12] S. Hartsel, J. Bolard, *Trends Pharmacol. Sci.* **1996**, *17*, 445–449.

[13] Amphotericin B (**1**) has a higher affinity to ergosterol than to cholesterol in lipid bilayers: a) T. Teerlink, B. de Kruijff, R. A. Demel, *Biochim. Biophys. Acta - Biomembranes* **1980**, *599*, 484–492; b) I. Fournier, J. Barwicz, P. Tancrède, *Biochim. Biophys. Acta - Biomembranes* **1998**, *1373*, 76–86; c) M. J. Paquet, I. Fournier, J. Barwicz, P. Tancrède, M. Auger, *Chem. Phys. Lipids* **2002**, *11*, 1–11.

[14] a) M. Szpilman, D. M. Cereghetti, J. M. Manthorpe, N. R. Wurtz, E. M. Carreira, *Chem. Eur. J.* **2009**, *15*, 7117–7128; b) D. S. Palacios, T. M. Anderson, M. D. Burke, *J. Am. Chem. Soc.* **2007**, *129*, 13804–13805; c) A. A. Volmer, A. M. Szpilman, E. M. Carreira, *Nat. Prod. Rep.* **2010**, *27*, 1329–1349; d) M. P. Croatt, E. M. Carreira, *Org. Lett.* **2011**, *13*, 1390–1393; e) D. S. Palacios, I. Dailey, D. M. Siebert, B. C. Wilcock, M. D. Burke, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 6733–6738.

[15] For pimaricin (**4**), see: a) B. De Kruijff, W. J. Gerritsen, A. Oerlemans, R. A. Demel, L. L. M. van Deenen, *Biochim. Biophys. Acta - Biomembranes* **1974**, *339*, 30–43; for Rimocidin (**5**), see: b) V. W. Dennis, N. W. Stead, T. E. Andreoli, *J. Gen. Physiol.* **1970**, *55*, 375–400; c) W. A. Zygmunt, *Appl. Microbiol.* **1966**, *14*, 953–956.

[16] M. R. Van Leeuwen, E. A. Golovina, J. Dijksterhuis, *J. Appl. Microbiol.* **2009**, *106*, 1908–1918.

[17] Y. M. te Welscher, L. Jones, M. R. van Leeuwen, J. Dijksterhuis, B. de Kruijff, G. Eitzen, E. Breukink, *Antimicrob. Agents Chemother.* **2010**, *54*, 2618–2625.

[18] For reviews, see: a) T. Oishi, T. Nakata, *Synthesis* **1990**, 635–645; b) C. Schneider, *Angew. Chem.* **1998**, *110*, 1445–1448; *Angew. Chem. Int. Ed.* **1998**, *37*, 1375–1378; c) J. Dougherty, M. Zhou, G. A. O'Doherty, *Chemtracts: Org. Chem.* **2005**, *18*, 349–363; d) S. E. Bode, M. Wolberg, M. Müller, *Synthesis* **2006**, *4*, 557–588; e) D. M. Cereghetti, E. M. Carreira, *Synthesis* **2006**, 914–942; f) A. M. Szpilman, E. M. Carreira, *Angew. Chem.* **2010**, *122*, 9786–9823; *Angew. Chem. Int. Ed.* **2010**, *49*, 9592–9628.

[19] For the total synthesis of amphotericin B (**1**), see: a) K. C. Nicolaou, T. K. Chakraborty, Y. Ogawa, R. A. Daines, N. S. Simpkins, G. T. Furst, *J. Am. Chem. Soc.* **1988**, *110*, 4660–4672; b) K. C. Nicolaou, R. A. Daines, J. Uenishi, W. S. Li, D. P. Papahatjis, T. K. Chakraborty, *J. Am. Chem. Soc.* **1988**, *110*, 4672–4685; c) K. C. Nicolaou, R. A. Daines, T. K. Chakraborty, *J. Am. Chem. Soc.* **1988**, *110*, 4685–4696; d) K. C. Nicolaou, R. A. Daines, Y. Ogawa, T. K. Chakraborty, *J. Am. Chem. Soc.* **1988**, *110*, 4696–4705; for the total synthesis of the methyl ester of 35-deoxyamphotericin B, see: e) A. M. Szpilman, D. M. Cereghetti, N. R. Wurtz, J. M. Manthorpe, E. M. Carreira, *Angew. Chem.* **2008**, *120*, 4407–4410; *Angew. Chem. Int. Ed.* **2008**, *47*, 4335–4338; for the total synthesis of the methyl ester of 35-deoxyamphotericin B, see: f) A. M. Szpilman, J. M. Manthorpe, E. M. Carreira, *Angew. Chem.* **2008**, *120*, 4411–4414; *Angew. Chem. Int. Ed.* **2008**, *47*, 4339–4342; for the formal total synthesis of amphotericinolide B, see: g) D. Boschelli, T. Takemasa, Y. Nishitani, S. Masamune, *Tetrahedron Lett.* **1985**, *26*, 5239–5242; h) R. M. Kennedy, A. Abiko, S. Masamune, *Tetrahedron Lett.* **1988**, *29*, 447–450; i) R. M. Kennedy, A. Abiko, T. Takemasa, H. Okumoto, S. Masamune, *Tetrahedron Lett.* **1988**, *29*, 451–454; g) for the relay synthesis of unnatural glycosides of amphoteronolide B, see ref.[14c]

[20] For the total synthesis of the aglycon of rimocidin (**5**), see: a) G. K. Packard, Y. Hu, A. Vescovi, S. D. Rychnovsky, *Angew. Chem.* **2004**, *116*, 2882–2886; *Angew. Chem. Int. Ed.* **2004**, *43*, 2822–2826; b) A. B. Smith III, M. A. Foley, S. Dong, A. Orbin, *J. Org. Chem.* **2009**, *74*, 5987–6001; c) for the preparation of the C^1-C^{18} fragment of rimocidin, see: A. B. Smith III, S. M. Pitram, M. J. Fuertes, *Org. Lett.* **2003**, *5*, 2751–2754.

[21] a) For the synthesis of the C^1–C^{19} polyol fragment of nystatin A_1 (**2**), see: I. Kadota, Y. Hu, G. K. Packard, S. D. Rychnovsky, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11992–11995; b) for the synthesis of the C^1-C^{13} fragment of nystatin A_1 (**2**), see: G. Solladié, N. Wilb, C. Bauder, *J. Org. Chem.* **1999**, *64*, 5447–5452.

[22] For the synthesis of the C^1–C^{19} polyol fragment of candidin (**3**), see ref.[21a]

[23] For the total synthesis of pimaricin (**4**), see: A. J. Duplantier, S. Masamune, *J. Am. Chem. Soc.* **1990**, *112*, 7079–7081.

[24] For the total synthesis of RK-397, see: a) S. A. Burova, F. E. McDonald, *J. Am. Chem. Soc.* **2004**, *128*, 2495–2500; b) S. E. Denmark, S. Fujimori, *J. Am. Chem. Soc.* **2005**, *127*, 8971–8973; c) M. J. Mitton-Fry, A. J. Cullen, T. Sammakia, *Angew. Chem.* **2007**, *119*, 1084–1088; *Angew. Chem. Int. Ed.* **2007**, *46*, 1066–1070; for the synthesis of the $C^{11–28}$ fragment of RK-397, see: d) S. A. Burova, F. E. McDonald, *J. Am. Chem. Soc.* **2002**, *124*, 8188–8189; e) C. Schneider, F. Tolksdorf, M. Rehfeuter, *Synlett* **2002**, 2098–2100; f) S. Gerber-Lemaire, A. T. Carmona, K. T. Meilert, P. Vogel, *Eur. J. Org. Chem.* **2006**, 891–900; for the formal total synthesis of RK-397, see: g) H. Guo, M. S. Mortensen, G. A. O'Doherty, *Org. Lett.* **2008**, *10*, 3149–3152.

[25] For the total synthesis of mycotycin A, see: a) C. S. Poss, S. D. Rychnovsky, S. L. Schreiber, *J. Am. Chem. Soc.* **1993**, *115*, 3360–3361; for the formal total synthesis of mycotycin A, see: b) A. B. Smith III, S. M. Pitram, *Org. Lett.* **1999**, *1*, 2001–2004; c) S. D. Dreher, J. L. Leighton, *J. Am. Chem. Soc.* **2001**, *123*, 341–342.

[26] For the total synthesis of roxaticin, see: a) S. D. Rychnovsky, R. C. Hoye, *J. Am. Chem. Soc.* **1994**, *116*, 1753–1765; b) D. A. Evans, B. T. Connell, *J. Am. Chem. Soc.* **2003**, *125*, 10899–10905; c) S. B. Han, A. Hassan, I. S. Kim, M. J. Krische, *J. Am. Chem. Soc.* **2010**, *132*, 15559–15561; for the synthesis of the C^{12}-C^{30} fragment of roxaticin, see: d) S. D. Rychnovsky, C. Rodriguez, *J. Org. Chem.* **1992**, *57*, 4793–4795; for the synthesis of the C^{11}-C^{26} fragment of roxaticin, see: Y. Mori, M. Asai, A. Okumura, H. Furukawa, *Tetrahedron* **1995**, *51*, 5299–5314.

[27] For the total synthesis of roflamycoin, see: a) S. D. Rychnovsky, U. R. Khire, G. Yang, *J. Am. Chem. Soc.* **1997**, *119*, 2058–2059; for the total synthesis of the spiroketal derivative of roflamycoin, see: b) S. D. Rychnovsky, G. Griegraber, R. Schlegel, *J. Am. Chem. Soc.* **1994**, *116*, 2621–2622; for the synthesis of the $C^{12–35}$ fragment of roflamycoin, see: c) B. H. Lipshutz, R. Moretti, R. Crow, *Tetrahedron Lett.* **1989**, *30*, 15–18.

[28] For the total synthesis of dermostatin A, see: a) C. J. Sinz, S. D. Rychnovsky, *Angew. Chem.* **2001**, *113*, 3324–3327; *Angew. Chem. Int. Ed.* **2001**, *40*, 3224–3227; b) C. J. Sinz, S. D. Rychnovsky, *Tetrahedron* **2002**, *58*, 6561–6576.

[29] R. Brückner, *Tetrahedron Lett.* **1988**, *29*, 5747–5750.

[30] a) R. Kramer, R. Brückner, *Eur. J. Org. Chem.* **2013**, DOI: 10.1002/ejoc.201300182 (following contribution in this journal); the article describes the synthesis of the mirror image of the C^{12}-C^{18} building block **7a**; b) the mirror image of the dioxane **12** of Scheme 2 was first described by R. Kramer, *Ph.D. Dissertation*, University of Freiburg, Germany, **2007**, p. 151–152, 447–449.

[31] T. Berkenbusch, R. Brückner, *Synlett* **2003**, 1813–1816.

[32] R. Kramer, T. Berkenbusch, R. Brückner, *Adv. Synth. Catal.* **2008**, *350*, 1131–1148.

[33] Our preparation of diol *syn*,*cis*-**14** from divinylcarbinol *cis*,*cis*-**17** via epoxy alcohol *anti*,*cis*-**16** meant a modification of earlier protocols[31,32] and an adoption of the protocol optimized in the enantiomeric series.[30a] However, the yield here (46% *syn*,*cis*-**14** over the two steps from *cis*,*cis*-**17**) was less than the yield in ref.[30a] (59% *ent*-*syn*,*cis*-**10** over the two steps from *cis*,*cis*-**17**). In essence, *cis*-divinylcarbinol *cis*,*cis*-**17** was submitted to asymmetric epoxidation under Sharpless' stoichiometric conditions[68,71] (plus molecular sieves). After 70 h at –25 °C, a 78:22 mixture of the desired epoxy alcohol *anti*,*cis*-**16** and its undesired diastereomer *syn*,*cis*-**16** was obtained. The reaction was also feasible by using Sharpless' catalytic conditions, but distinctly slower. Separation by flash chromatography on silica gel[45] was tedious, particularly on a large scale. We circumvented this problem by treating the 78:22 *anti*,*cis*-**16**/*syn*,*cis*-**16** mixture with a 10-fold molar amount of Red-Al® (toluene, –40 °C). Under these conditions, diastereomer *syn*,*cis*-**16** remained unchanged, whereas diastereomer *anti*,*cis*-**16** gave the diol *syn*,*cis*-**14**. The resulting mixture was easily separated by flash chromatography on silica gel.[45] The yield of *syn*,*cis*-**14** was 46% over the two steps from *cis*,*cis*-**17** and its *ee* was >95% according to chiral HPLC.

[34] For vanadium(V)-catalyzed epoxidation reactions of β-substituted γ,δ-unsaturated alcohols in which C^α and C^β possess the same relative configurations as in **7b**, see: a) E. D. Mihelich, K. Daniels, D. J. Eickhoff, *J. Am. Chem. Soc.* **1981**, *103*, 7690–7692; b) C. Kouklovsky, S. V. Ley, S. S. P. Marsden, *Tetrahedron Lett.* **1994**, *35*, 2091–2094; c) M. Oikawa, T. Ueno, H. Oikawa, A. Ichihara, *J. Org. Chem.* **1995**, *60*, 5048–5068; d) H. Oikawa, Y. Yoneta, T. Ueno, M. Oikawa, T. Wakayama, A. Ichihara, *Tetrahedron Lett.* **1997**, *38*, 7897–7900; e) E. Menager, E. Merifield, M. Smallridge, E. J. Thomas, *Tetrahedron* **1997**, *53*, 9377–9392; f) J. D. White, G. Wang, L. Quaranta, *Org. Lett.* **2003**, *5*, 4109–4112; g) K. Prantz, J. Mulzer, *Chem. Eur. J.* **2010**, *16*, 485–506.

[35] For reviews, see: a) T. Nakai, K. Mikami, *Chem. Rev.* **1986**, *86*, 885–902; b) R. Brückner, *Kontakte (Darmstadt)* **1991**, *2*, 3–14; c) R. Brückner, *Kontakte (Darmstadt)* **1991**, *3*, 3–15; also see: d) R. Brückner, *Heteroatom Manipulation* (Ed.: E. Winterfeldt), in: *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, UK, **1991**, vol. 6, p. 873–908; e) K. Mikami, T. Nakai, *Synthesis* **1991**, 594–604; f) T. Nakai, K. Mikami, *Org. React.* **1994**, *46*, 105–210.

[36] a) R. Brückner, H. Priepke, *Angew. Chem.* **1988**, *100*, 285–286; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 278–280; b) R. Brückner, *Chem. Ber.* **1989**, *122*, 703–710.

[37] B. Herradón, *Tetrahedron: Asymmetry* **1991**, *2*, 191–194.

[38] P. J. Kocieński, C. Yeates, S. D. A. Street, S. F. Campbell, *J. Chem. Soc. Perkin Trans. 1* **1987**, 2183–2187.

[39] R. C. Corcoran, *Tetrahedron Lett.* **1990**, *31*, 2101–2104.

[40] J. P. Parikh, W. von E. Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

[41] A. J. Mancuso, S.-L. Huang, D. Swern, *J. Org. Chem.* **1978**, *43*, 2480–2482.

[42] For the formation of ethers using phase-transfer catalysis, see: H. H. Freedman, R. A. Dubois, *Tetrahedron Lett.* **1975**, *16*, 3251–3254.

[43] CCDC-849003 (for $syn^{3,*}$,$syn^{2,3}$–**26a**), -849005 (for $anti^{3,*}$, $syn^{2,3}$–**26d**), and -849004 (for **30a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[44] These data are available in the Supporting Information.

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

[46] For V^V-catalyzed epoxidations of achiral homoallyl alcohols with CumylOOH, see: W. Zhang, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 286–287.

[47] $VO(OEt)_3$ was a better catalyst than $VO(acac)_2$ for the epoxidation of homoallylic alcohols, see: ref.[29] The same holds true for the epoxidation of allylic alcohols, see footnote 21 in: T. Katsuki, A. W. M. Lee, P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless, D. Tuddenham, F. J. Walker, *J. Org. Chem.* **1982**, *47*, 1373–1378.

[48] For selected iodocarbonate formations from homoallyl alcohols by in-situ formed lithium homoallylic carbonates, see: a) A. Bongini, G. Cardillo, M. Orena, G. Porzi, S. Sandri, *J. Org. Chem.* **1982**, *47*, 4626–4633; b) M. Majewski, D. L. J. Clive, P. C. Anderson, *Tetrahedron Lett.* **1984**, *25*, 2101–2104; c) R. Tirado, J. Prieto, *J. Org. Chem.* **1993**, *58*, 5666–5673.

[49] The alcohol **22d** was deprotonated by *n*BuLi (1.05 equiv.) in THF at –78 °C while stirring for 30 min. After warming to –40 °C, dry CO_2 was bubbled through the solution. After 15 min iodine (4 equiv.) was added. The resulting mixture was kept at 0 °C for 16 h.

[50] The intramolecular opening of an iodonium ion by a CO_2H group, that is, the formation of an (iodomethyl)-γ-lactone in the absence of a base, occurs reversibly, that is, under thermodynamic control: P. A. Bartlett, J. Myerson, *J. Am. Chem. Soc.* **1978**, *100*, 3950–3952.

[51] The presence of $NaHCO_3$ was necessary to avoid cleavage of the ketal group through HI; the latter is the stoichiometric side-product of iodolactonization reactions. Fortunately, $NaHCO_3$ was unlikely to shift the diastereocontrol from thermodynamic (desired) to kinetic (undesired) (as would be the case if the substrate was an unsaturated acid[50]).

[52] We could not determine the ring size or elucidate the configuration at the starred stereocenter of iodo ether **31** because it was inseparable from the iodolactone **30**.

[53] B. O. Lindgren, T. Nilsson, *Acta Chem. Scand.* **1973**, *27*, 888–890.

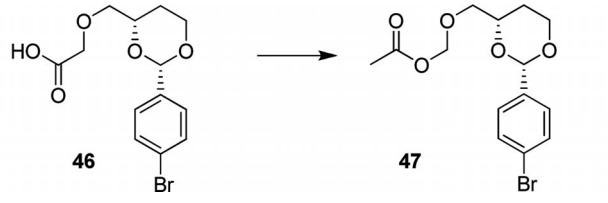
[54] For the synthetic procedure, see: N. Hashimoto, T. Aoyama, T. Shioiri, *Chem. Pharm. Bull.* **1981**, *29*, 1475–1478.

[55] a) Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Lett.* **1982**, *23*, 885–888; b) for a precedent for the deprotection of a PMB ether in the presence of a benzaldehyde acetal, see: M. Nilsonn, T. Norberg, *Carbohydr. Res.* **1988**, *183*, 71–82.

[56] This selectivity (*ds* = 85:15) did not reach the level (*ds* = 91:9) of the model rearrangement **23d**→ *syn*^{3,*},*syn*^{2,3}–**26**. Similarly, we effected [2,3]-Wittig rearrangements with the phenyl and dimethyl ketal analogues of diethyl ketal **37**. These proceeded with *ds* = 67:33 and 89:11, respectively.

[57] THF was added because the dicarboxylic acid **37** is insoluble in pure benzene. Nonetheless, we do not consider THF an essential ingredient of the reaction mixture because the model α-alkoxycarboxylic acid **46** was defunctionalized in pure benzene under the best conditions of a model study, which is summarized in ref.[58]

[58] The decarboxylative degradation of compound **37** was performed under the best conditions, which we established for the decarboxylative degradation of the model α-alkoxyacetic ester **46** (except that we needed to modify the solvent[57]). That reaction proceeded in 84% yield with $Pb(OAc)_4$ (1.2 equiv.), $Cu(OAc)_2$ (0.1 equiv.), and visible-light irradiation (tungsten lamp, 150 W) in pure benzene at room temp. during 15 min. The concomitant use of catalytic Cu^{II} and light prevented the formation of byproducts.



[59] Aliphatic carboxylic acids without a heteroatom α to the CO_2H group are also decarboxylated by $Pb(OAc)_4$ and $Cu(OAc)_2$ in benzene solutions: either at 30 °C if 350 ± 50 nm light is shone into the reactant solution or at 80 °C in the dark (J. D. Bacha, J. K. Kochi, *Tetrahedron* **1968**, *24*, 2215–2226). Such decarboxylation reactions take a different course than the oxidation **37**→**36**. This is because hydrocarbon carboxylic acids react to give a carbenium ion (i.e., no carboxonium ion as when starting from **37**, **40**, **41** or **46** and no iminium ion as when starting from **42** or **43**). The carbenium ion is usually deprotonated by the acetate ion (and not nucleophilically attacked like the mentioned carboxonium or iminium ions). This renders 1-olefins. However, significant amounts of carbenium ion (with or without an intervening Wagner–Meerwein rearrangement)/acetate recombination products resulted from analogous decarboxylations of cyclobutanecarboxylic acid: J. K. Kochi, J. D. Bacha, *J. Org. Chem.* **1968**, *33*, 2746–2754. This indicates a strain-induced deceleration of cyclobutene formation.

[60] Light-supported $Pb(OAc)_4$ decarboxylation reactions of aliphatic carboxylic acids without a heteroatom α to the CO_2H group have been performed by using in CCl_4 and I_2. This furnished C_1-shortened aliphatic iodides: D. H. R. Barton, H. P. Faro, E. P. Serebryakov, N. F. Woolsey, *J. Chem. Soc.* **1965**, 2438–2444.

[61] a) Y. Ohishi, T. Nakanishi, *Chem. Pharm. Bull.* **1983**, *31*, 3418–3423; b) J. E. H. Buston, A. Coop, R. Keady, M. G. Moloney, R. M. Thompson, *J. Chem. Res. (M)* **1994**, 1101–1116.

[62] For an example of a $Pb(OAc)_4$-mediated degradation of an *N*-arylglycinamide, see: O. Süs, *Justus Liebigs Ann. Chem.* **1949**, *564*, 137–140.

[63] For an example of a $Pb(OAc)_4$-mediated degradation of an *N*-alkylglycinamide, see: J. Kalvoda, M. Kessler, R. Lattmann, G. Ramos, U.S. Pat. 5317100, **2011**.

[64] For the synthesis and full characterization of the mirror image of **12** (^{1}H and ^{13}C NMR, IR, elemental analysis), see ref.[30a]

[65] For the reaction conditions for the preparation of the mirror image of diol *syn*,*cis*-**14** and full characterization (^{1}H and ^{13}C NMR, IR, elemental analysis), see ref.[31]

[66] The *ee* of the epoxide *syn*,*cis*-**14** was determined by chiral HPLC [Chiralpak AD-H column; *n*-heptane/EtOH, 70:30 (v/v), flow-rate 1.0 mL min^{-1}; 15 °C isothermal; $\lambda_{UV\ detector}$ = 227 nm; *syn*,*cis*-**14**: t_R = 21.0 min; *ent*-*syn*,*cis*-**14**: t_R = 17.6 min].

[67] a) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976; b) R. M. Hanson, K. B. Sharpless, *J. Org. Chem.* **1986**, *51*, 1922–1925; c) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.

[68] For reviews, see: a) A. Pfenniger, *Synthesis* **1986**, 89–116; b) T. Katsuki, V. S. Martin, *Org. React.* **1996**, *48*, 1–299; c) T. Katsuki, in: *Comprehensive Asymmetric Catalysis* (Eds: A. Pfaltz, E. N. Jacobsen, H. Yamamoto), Springer, Berlin, **1999**, p. 621–648; d) J. A. Johnson, K. B. Sharpless, in: *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed., Wiley-VCH, Weinheim, Germany, **2000**, p. 231–286.

[69] For the synthesis, ^{1}H and ^{13}C NMR spectra, IR spectrum, and elemental analysis, see ref.[32]

[70] This reductant was introduced by: W. Boland, N. Schroer, C. Sieler, *Helv. Chim. Acta* **1987**, *70*, 1025–1040.

[71] Note added in proof (August 23, 2013): Having learnt to proceed from divinylcarbinol *cis*,*cis*-**17** to the diol *syn*,*cis*-**14** on the multi-gram scale reproducibly, we did not study whether the catalytic asymmetric desymmetrization conditions for other divinylcarbinols (Z. Li, W. Zhang, H. Yamamoto, *Angew. Chem.* **2008**, *120*, 7630–7632; *Angew. Chem. Int. Ed.* **2008**, *47*, 7520–7522) apply to the *anti*-selective desymmetrization *cis*,*cis*-**17**→*anti*,*cis*-**16**, too.

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