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Novel Protoilludane Lead Structure for Veterinary Antibiotics: Total Synthesis of Pasteurestins A and B and Assignment of Their Configurations

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Dedicated to Professor Udo H. Brinker on the occasion of his 65th birthday

Keywords: Total synthesis / Cyclotrimerization / Antibiotics / Reformatsky reaction / Configurational assignment

Two novel protoilludane sesquiterpenoids, named pasteurestins A and B (**1** and **2**), were disclosed in a recent patent. These compounds were reported to exhibit strong and selective activity against some *Mannheimia haemolytica* strains, pathogen causatives for bovine respiratory disease. These properties qualified **1** and **2** as potential lead structures for new veterinary antibiotics; however, neither the absolute nor the relative configurations had been determined, nor were the compounds available any longer. We thus developed total syntheses of **1** and **2** and clarified their structures and their biological profiles. Key steps were two [2+2+2] $CpCo(CO)_2$-mediated Vollhardt cycloadditions in both syntheses, and a tin-mediated asymmetric Reformatsky-type condensation in the synthesis of **2** with a temperature-dependent product distribution.

Introduction

The total synthesis of a specific natural product may have different underlying motives: application of a specific methodology, procurement of biologically interesting material unavailable in sufficient quantities from the natural source, or the elucidation of structure and configuration. It is seldom that all these motivations should coincide in one target structure, and so we were particularly intrigued when we came across a recent Japanese patent in which two protoilludane sesquiterpenoid metabolites from the basidiomycete *Agrocybe cylindracea* Maire K-3793 (*Agrocybe aegeritta*) were described.[1] These two compounds, named pasteurestin A and B (**1** and **2**; Figure 1) were reported to show strong and selective activity against some *Mannheimia haemolytica* strains, pathogen causatives for bovine respiratory disease (BRD).[2] These properties made them interesting as potential antibiotics in veterinary applications, provided that the required biological tests could be performed. However, no material was available any longer; moreover, although the basic carbon skeleton common to **1** and **2** had been described, neither the relative nor the absolute configurations of these compounds had been determined. The structures of the two pasteurestins are each characterized by a highly strained hydrocyclobutaindane nucleus and an α,β-unsaturated γ-hydroxy moiety on the six-membered ring. Pasteurestin B (**2**) contains five contiguous stereocenters, pasteurestin A (**1**) four contiguous and one isolated quarternary stereogenic center. For both compounds, the relative configurations at C-4a, C-7a, and C-7b were assumed to be the same as in other protoilludanes,[3] of which illudol (**3**; Figure 1)[4] is representative. The stereocenters at C-4 and C-6 in **1** and C-4 and C-7 in **2**, together with the absolute configurations, had to be established by total synthesis, which appeared feasible as sufficient spectroscopic data (^1H and ^{13}C NMR, IR, and MS) and the optical rotations were given in the patent. Additionally, this was the only way to obtain **1** and **2**, and also their derivatives, for biological testing, as discussed in our previous communication.[5]

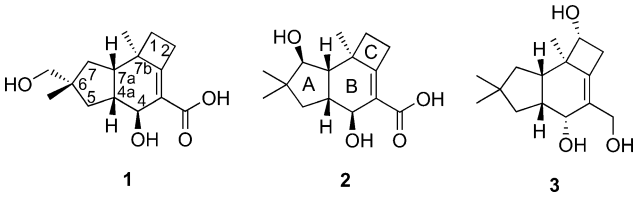

Figure 1. Pasteurestin A (**1**), pasteurestin B (**2**), and illudol (**3**).

Results and Discussion

From Vollhardt's synthesis of racemic **3**[4c] we concluded that cobalt-mediated [2+2+2] cycloadditions of enediynes **4**

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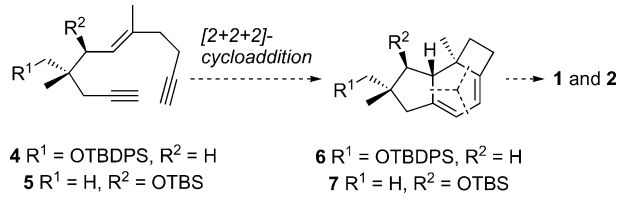
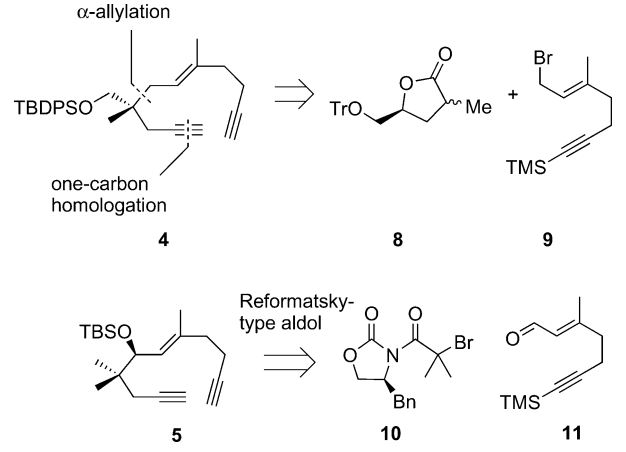
and **5** should lead to the tricyclic intermediates **6** and **7**, containing the characteristic carbon skeleton common to **1** and **2** (Scheme 1),[6] which might be convertible into the fully functionalized target molecules. From the methodology point of view, it was interesting to investigate how the pre-existing stereogenic centers in **4** and **5** would influence the stereochemical outcomes of the cycloadditions.



Scheme 1. Synthetic plan for pasteurestins A (**1**) and B (**2**). TBDPS = *tert*-butyldiphenylsilyl; TBS = *tert*-butyldimethylsilyl.

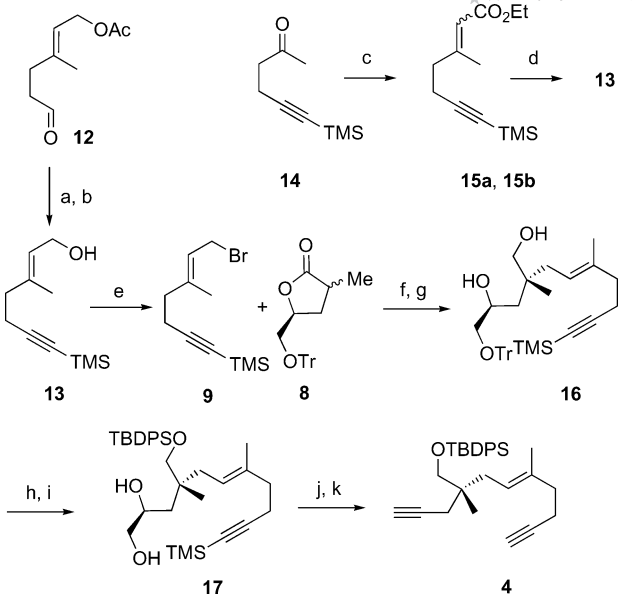
For the construction of enediyne **4**, a substrate-controlled α-alkylation of butyrolactone **8** with bromide **9** (Scheme 2) was envisaged, whereas for enediyne **5** a diastereoselective "Reformatsky-type" aldol addition of bromooxazolidinone **10** to aldehyde **11** was considered.



Scheme 2. Retrosynthetic analysis for enediynes **4** and **5**. Tr = triphenylmethyl; TMS = trimethylsilyl.

Allylic bromide **9** was obtained from geranyl acetate in five steps (Scheme 3). Specifically, selective epoxidation of geranyl acetate and oxidative cleavage of the resulting epoxide with $HIO_4 \cdot 2H_2O$ led to the known aldehyde **12**,[7] which was transformed into alkyne **13** by means of a Bestmann–Ohira ethynylation[8] and subsequent TMS protection of the resulting triple bond. Alternatively, Horner–Wadsworth–Emmons olefination with methyl ketone **14**, obtained in four straightforward steps from pent-4-yn-1-ol and triethyl phosphonoacetate, led to a mixture of (*E*) and (*Z*) isomers **15a** and **15b** in a 3.5:1 ratio and 72% yield. After DIBAl-H reduction, the corresponding alcohols could be separated.

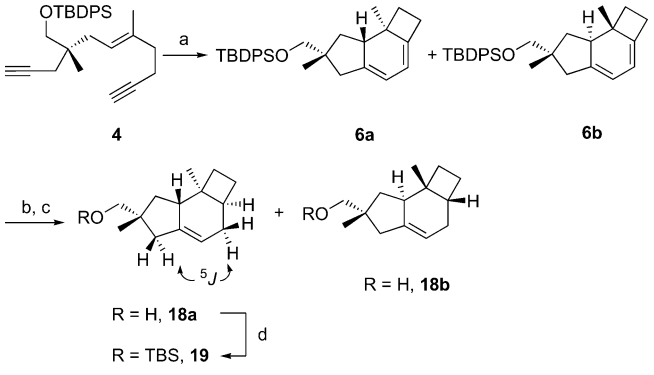
Bromination of **13** under Appel conditions led to bromide **9**. Separately, butyrolactone **8** was prepared in two steps from (*R*)-glycidol.[9] Alkylation of **8** with **9** proceeded in 71% yield and high diastereoselectivity (96% *de*). Reductive opening of the lactone with DIBAl-H furnished diol **16**, which was followed by selective TBDPS protection of the primary alcohol.[10]



Scheme 3. Synthesis of enediyne **4**. Reagents and conditions: (a) K_2CO_3, $(MeO)_2P(O)CN_2C(O)Me$, MeOH, 23 °C, 90%; (b) (i) *n*BuLi, TMSCl, THF, –78 °C, (ii) HCl 2 N, 23 °C, 95%; (c) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, 72%; (d) DIBAl-H, THF, –78 °C, 90%; (e) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 84%; (f) **8**, LDA, HMPA, THF, –78 °C, then **9**, 71%; (g) DIBAl-H, THF, –78 °C, 95%; (h) TBDPSCl, DMAP, NEt_3, CH_2Cl_2, 23 °C, 90%; (i) Et_2AlCl, CH_2Cl_2, –78 °C, 87%; (j) $Pb(OAc)_4$, CH_2Cl_2, 23 °C, 95%; (k) K_2CO_3, MeOH, $(MeO)_2P(O)CN_2C(O)Me$, 23 °C, 71%. HMPA = hexamethyl phosphoramide; LDA = lithium diisopropylamide; DIBAl-H = diisobutylaluminium hydride.

The bulky TBDPS group was chosen as a potentially stereocontrolling element in the [2+2+2] cycloaddition. The trityl group was selectively removed with Et_2AlCl, and the resulting diol **17** was cleaved with $Pb(OAc)_4$. Chain elongation of the resulting aldehyde to provide the desired alkyne **4** was again accomplished with dimethyl (1-diazo-2-oxopropyl)phosphonate.[8]

Cobalt-mediated [2+2+2] cycloaddition in toluene, followed by demetallation with the relatively mild $CuCl_2$, furnished a 4:3 mixture of the diastereomers **6a** and **6b** (Scheme 4). Not surprisingly, the stereogenic center in **4** was too remote from the olefin for significant stereoinduction. Dienes **6a** and **6b** were extremely apolar, were not separable by column chromatography, and proved to be highly air-sensitive. Following Vollhardt's precedent,[4c] this mixture of dienes was treated with lithium in liquid ammonia. We observed a regioselective reduction of the highly strained C-2a–C-3 double bond. Additionally, the phenyl groups of the TBDPS ether were also hydrogenated. Deprotection with TBAF delivered the primary alcohols **18a** and **18b**, which were separable by chromatography. It is interesting to note that an uncommon $^5J_{H,H}$ coupling of 2.5 Hz between protons attached to C-3 and C-5 can be observed (Scheme 4); this is caused by an almost planar system in the hydrindane

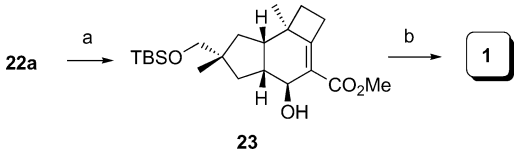


Scheme 4. [2+2+2] Cycloaddition and functionalization of dienes **6a** and **6b**. Reagents and conditions: (a) $CoCp(CO)_2$, toluene, reflux, then $CuCl_2 \cdot 2H_2O$, DME, 23 °C, 46%; (b) Li (excess), NH_3, *t*BuOH, THF, –78 °C, 85%; (c) TBAF, THF, 23 °C, 95%; HPLC separation; (d) TBSCl, imidazole, DMF, 23 °C, 90%. Cp = cyclopentadienyl; DME = 1,2-dimethoxyethane; TBAF = tetrabutylammonium fluoride.

nucleus of compound **18**. Diastereomer **18a** was then protected to give TBS ether **19**, which was subjected to further functionalization.

Next, an oxygen function at C-4 was introduced by hydroboration. All attempts to use bulky reagents for stereoselective hydroboration were unsuccessful, resulting in the total recovery of the starting material. With diborane, after oxidation with H_2O_2, we obtained two diastereomeric alcohols, which were treated with Dess–Martin periodinane to give a 2:1 mixture of ketones **20a** and **20b** in high yield (Scheme 5). The next steps required the introduction of the carboxy group to form the corresponding β-oxo ester. The use of methyl cyanoformate ("Mander's reagent"), delivered – probably because of the sterically demanding cyclobutane in the β-position – a 1:2 mixture of *O*- and *C*-carboxylated products.[11] However, carboxylation of the enolate anion with carbon dioxide[4b,4c] [followed by methylation with (trimethylsilyl)diazomethane] gave a mixture of β-oxo esters **21a** and **21b** in 55% yield. Unreacted starting material was recycled, so that the combined yield was increased to 75%. The configuration of bridgehead center C-4a was equilibrated by treatment with 2.5 equiv. of LDA, and the ratio of **21a**/**21b** was now increased to 4:1. Selenation at C-3 produced a mixture of diastereomers that was treated with H_2O_2 under weakly acidic conditions to furnish enoates **22a** and **22b**, which could be separated.

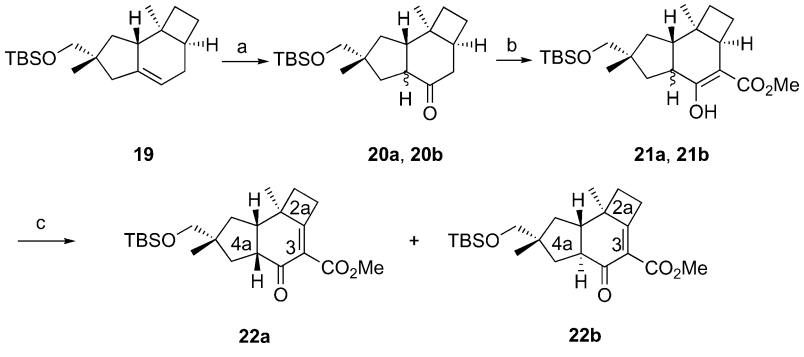
Diastereomer **22a** was reduced with $CeCl_3 \cdot 7H_2O$ and $NaBH_4$ in MeOH (Scheme 6) to give allylic alcohol **23** as a single isomer. This was desilylated with HF·pyridine and hydrolyzed with LiOH in THF/H_2O to give the target compound pasteurestin A (**1**). The high stereocontrol in the reduction step is amazing and must be due to prior complexation of **22a** with $CeCl_3 \cdot 7H_2O$, since C-4–OH mixtures were obtained with Red-Al in the synthesis of illudol.[4] We assume that the cerium complex is formed between the C-4 carbonyl and the C-3 ester groups on the less hindered *exo* face, so that the hydride attacks from the more hindered *endo* face.



Scheme 6. Endgame in the synthesis of pasteurestin A (**1**). Reagents and conditions: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 87%; (b) (i) HF·Py, THF, 23 °C; (ii) LiOH, H_2O/THF, 23 °C, 55%. Py = pyridine.

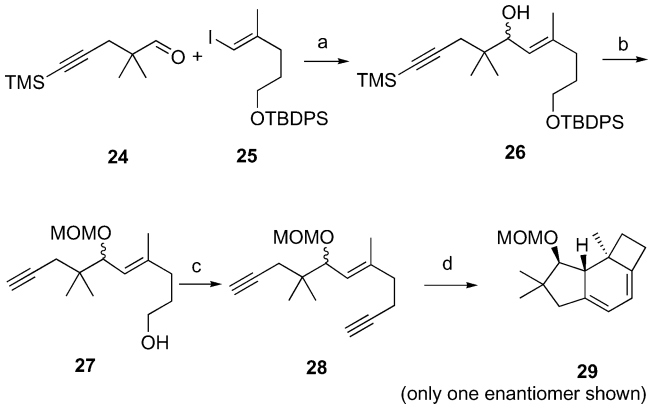
The determination of the relative configuration was accomplished by ^1H, ^{13}C, and 2D (COSY, NOESY, HMBC, HSQC) NMR spectroscopy, and showed that all data are in accord with those reported in the patent. The absolute configuration and the optical purity were confirmed by comparison of the optical rotation of our synthetic material with the literature value.

We next turned to the total synthesis of the closely related pasteurestin B (**2**). In order to investigate the stereoselectivity of the cobalt-mediated cycloaddition, a racemic enediyne (**28**) was synthesized as test substrate (Scheme 7). For the construction of allylic alcohol **26**, we chose a vinyllithium addition to aldehyde **24**.[12] Vinyl iodide **25** was obtained from carboalumination of TBS-protected pent-4-yn-1-ol with $ZrCpCl_2/Me_3Al/I_2$.[13] Addition of **25** to aldehyde



Scheme 5. Functionalization of the six-membered ring. Reagents and conditions: (a) (i) BH_3, THF, 23 °C, then K_2CO_3, H_2O_2, reflux, (ii) DMP, CH_2Cl_2, 23 °C, 74%; (b) LDA, HMPA, THF, –78 °C, then CO_2 (excess), –58 °C, then 1 N HCl, 23 °C, then $TMSCHN_2$, 0 °C, 55%, 75% (based on recovered starting material); (c) (i) LDA, PhSeCl, THF, –78 °C, (ii) NH_4Cl, H_2O_2, H_2O/CH_2Cl_2, 0 °C, 50%. DMP = Dess–Martin periodinane.

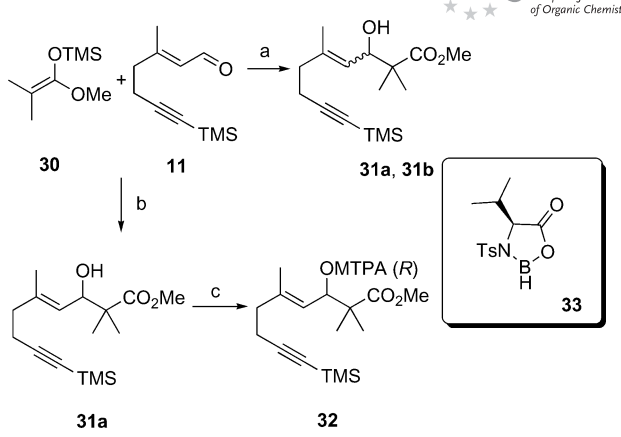
24 furnished the desired allylic alcohol **26** in 56% yield (Scheme 7). Further functionalization included MOM protection, TBS and TMS deprotection with TBAF, and Dess–Martin periodinane oxidation. Finally, C_1 homologation with dimethyl (1-diazo-2-oxopropyl)phosphonate[8] gave the racemic enediyne **28**, which was heated at reflux under irradiation with $CoCp(CO)_2$ in degassed toluene. The air-sensitive cycloadduct **29** was isolated in diastereomerically pure form. This result encouraged us to repeat the sequence with enantiomerically enriched enediyne **5**.



Scheme 7. Cyclotrimerization of test substrate **28**. Reagents and conditions: (a) **25**, *t*BuLi, –78 °C to 0 °C, then **24**, –78 °C to room temp., 56%; (b) (i) MOMCl, DIPEA, CH_2Cl_2, (ii) TBAF, THF, 80%; (c) (i) DMP, CH_2Cl_2, room temp., (ii) K_2CO_3, MeOH, $(MeO)_2P(O)CN_2C(O)Me$, 23 °C, 92%; (d) $CoCp(CO)_2$, toluene, reflux, then $CuCl_2{\cdot}2H_2O$, DME, 23 °C, 43%. MOM = methoxymethyl; DIPEA = diisopropylethylamine.

In our first approach to the optically active form of enediyne **5**, we applied the Kiyooka–Mukaiyama aldol reaction (Scheme 8).[14] Hence, ketene acetal **30** was added to a mixture of aldehyde **11** and oxazaborolidinone **33**, previously prepared in situ from diborane and *N*-tosyl-L-valine. Under these conditions, a ca. 4:1 mixture of (*E*) and (*Z*) isomers **31a** and **31b** was obtained. In order to avoid the isomerization of aldehyde **11**, reagent **33** was added to a mixture of **11** and **30**, and, indeed, the (*E*) isomer **31a** was formed exclusively. However, the conversion of alcohol **31a** into its Mosher ester **32** gave an unacceptably low *ee* of 41%.

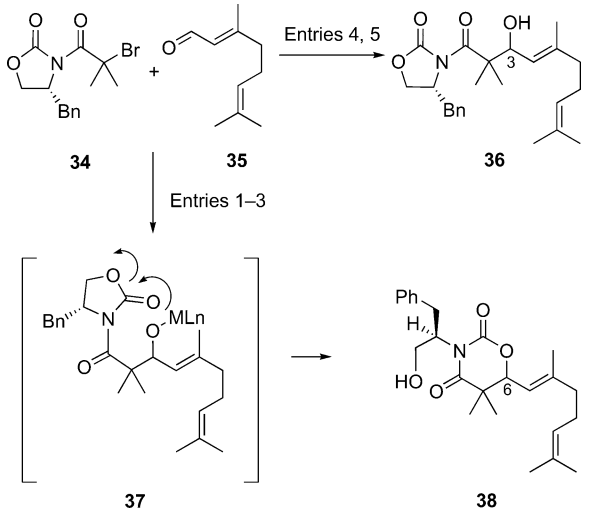
We thus switched to Reformatsky-type aldol reactions. Many versions of this reaction with different metals combined with chiral auxiliaries can be found in the literature.[15] The reaction was first tested with (bromoacyl)oxazolidinone **34**, easily available in one step from the (4*R*)-benzyloxazolidinone,[16] and geranial (**35**) (Table 1). By analogy with the literature precedent with Cr^{II} as the reducing metal at ambient temperature, an (*S*) configuration at C-3 was expected. However, we did not isolate the desired acyclic alcohol **36**, but only the unwanted 1,3-oxazine-2,6-dione **38**. The same product was also obtained under Sn^0 mediation at ambient temperature.[17] The formation of **38** might be explained by a rearrangement of the primary aldol



Scheme 8. Mukaiyama aldol reaction. Reagents and conditions: (a) (i) **33**, THF, DCM, room temp., (ii) **11**, DCM, –78 °C, (iii) **30**, DCM, –78 °C, 89%; (b) (i) **11**, **30**, DCM, –78 °C, (ii) **33**, DCM, room temp., 75%; (c) (*S*)-Mosher's acyl chloride, pyridine, DCM, 0 °C, 70%. Ts = *p*-toluenesulfonate.

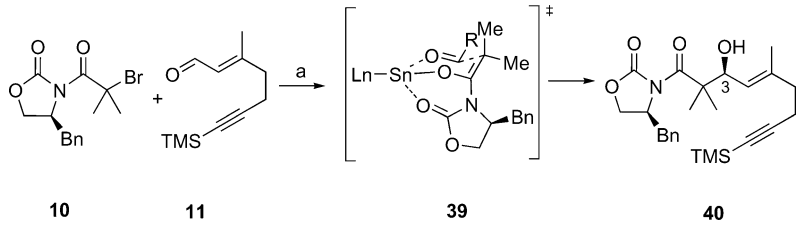
adduct, presumably driven by a Thorpe–Ingold effect. Interestingly, though, acyclic product **36** was obtained exclusively with SmI_2 at –78 °C. We were interested in finding out whether the rearrangement of **36** into **38** depends on the metal or can generally be suppressed at low temperatures. Under Sn^0 mediation at –78 °C, again only the desired acyclic product **36** was obtained in good yields. Because of the efficiency of the reaction and the low cost of the reagents, these reaction conditions were applied to substrates **10** and **11**.

Table 1. Reformatsky reaction with test substrates **34/35**. Bn = benzyl; M = metal; Ln = ligand.



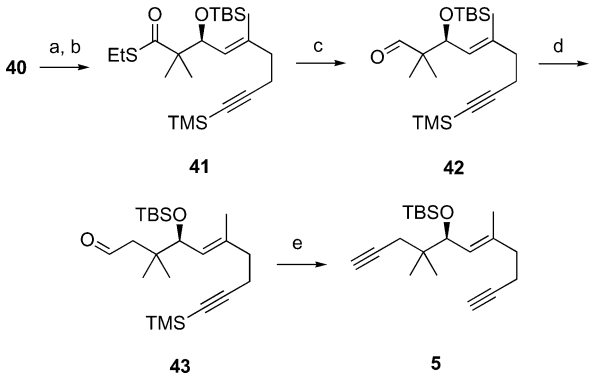
Entry	Metals and solvents	Temperature	Product[a]	Yield
1	$CrCl_2$, LiI, THF	23 °C	**38**	25%
2	$CrCl_2$, LiI, THF, DMF	23 °C	**38**	70%
3	$SnCl_2$, $LiAlH_4$, THF	23 °C	**38**	85%
4	$SnCl_2$, $LiAlH_4$, THF	–78 °C	**36**	75%
5	SmI_2, THF	–78 °C	**36**	30%

[a] The configurations at C-3 in **36** and C-6 in **38** were not determined. All compounds were formed in >99% *de*.



Scheme 9. Reformatsky reaction. Reagents and conditions: (a) (i) $SnCl_2$, $LiAlH_4$, THF, 23 °C; (ii) **10**, –78 °C; (iii) **11**, –78 °C, 78%.

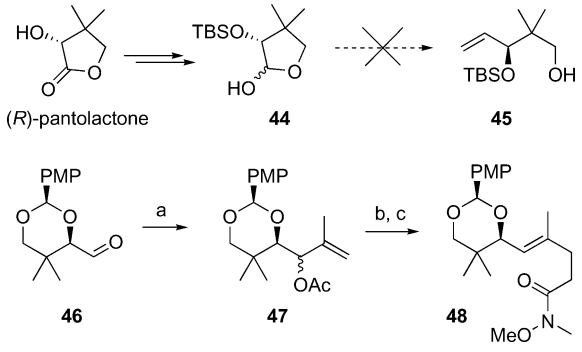
Aldehyde **11** was obtained by oxidation of the corresponding allylic alcohol **13** by the Swern protocol. Reduction of **10** with highly active Sn metal generated the Sn^{II} enolate, which was treated with aldehyde **11** at –78 °C (Scheme 9). The desired (3*S*) adduct **40** was obtained with >99% *de* and with complete retention of the (*E*)-alkene geometry in 78% yield. The stereochemical outcome is the opposite of that reported for additions at ambient reaction temperatures.[17] We think that this discrepancy might be interpreted by assuming that a fully complexed transition state **39** (Nerz–Stormes–Thornton model)[18] is adopted at low temperature (i.e., in our case), whereas the uncomplexed Pridgen-type transition state prevails at ambient temperature.[19] Anyway, alcohol **40** was protected as a TBS ether. Initial attempts to remove the auxiliary with $LiBH_4$ resulted in a mixture of products: the hydride attacked not only the amide, but also the oxazolidinone carbonyl group. This problem could be circumvented by preparing thioester **41** (Scheme 10),[20] which was reduced to aldehyde **42** with DIBAl-H in 75% yield.



Scheme 10. Synthesis of the enediyne **5**. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 95%; (b) *n*BuLi, EtSH, THF, 0 °C, 89%; (c) DIBAl-H, CH_2Cl_2, –78 °C, 75% (+15% alcohol); (d) $MeOCH_2PPh_3Cl$, *n*BuLi, 0 °C, then HCl 2 M, 23 °C, 60%; (e) K_2CO_3, $(MeO)_2P(O)CN_2C(O)Me$, MeOH, 23 °C, 94%. Tf = trifluoromethanesulfonate.

C_1 homologation with (methoxymethylidene)triphenylphosphane, followed by hydrolysis of the enol ether, gave aldehyde **43**. Finally, Bestmann–Ohira treatment of **43** furnished enediyne **5**, ready for [2+2+2] cyclotrimerization.

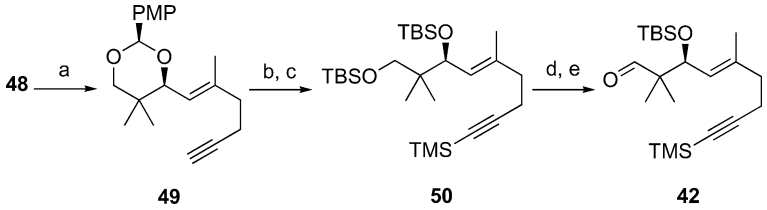
The absolute configuration of the stereogenic center in enediyne **5** was confirmed by an unambiguous formal synthesis from (*R*)-pantolactone. Initial attempts to prepare olefin **45** from the TBS-protected pantolactol **44** by means of a Wittig reaction failed (Scheme 11).[21] This might be due to a migration of the silyl moiety to the hydroxy group at C-1 under basic conditions.



Scheme 11. Pantolactone approach. Reagents and conditions: (a) (i) isopropenylMgBr, THF, 0 °C; (ii) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 23 °C, 80%; (b) LDA, TMSCl, –78 °C to 23 °C, 69%; (c) DIC, NEt_3, MeHNOMe·HCl, CH_2Cl_2, 23 °C, 98%. DMAP = 4-(dimethylamino)pyridine, LDA = lithium diisopropylamide; DIC = *N*,*N*′-diisopropylcarbodiimide; PMP = *p*-methoxyphenyl.

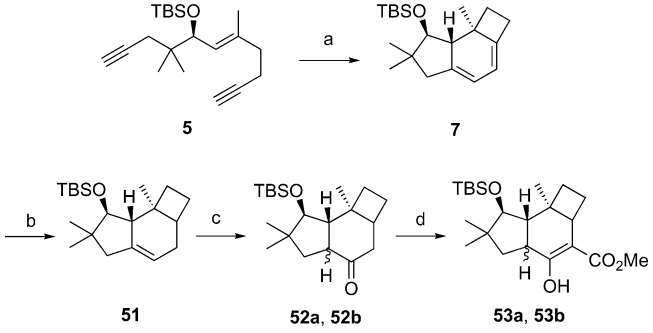
(*R*)-Pantolactone was therefore converted into the known aldehyde **46**,[22] which was treated with isopropenylmagnesium bromide to afford a 4:1 diastereomeric mixture of alcohols. These were subsequently converted into their acetates **47**. Claisen–Ireland rearrangement of this mixture, followed by conversion of the resulting carboxylic acid into the Weinreb amide **48** and final reduction, delivered the corresponding aldehyde (Scheme 12).[23] A Colvin reaction gave alkyne **49**. After TMS protection of the resulting triple bond, the acetal was removed under acidic conditions, and the resulting diol was protected as the bis(TBS) ether **50**. The primary TBS ether could be selectively cleaved under the conditions reported by Evans.[24] The alcohol was then oxidized to provide the aldehyde **42**, which was identical in all respects to the product obtained from the Reformatsky approach.

Enediyne **5** furnished diene **7** as the sole product by the previously described cobalt-mediated [2+2+2] cycloaddition in toluene. The proximity of the stereogenic center not surprisingly led to high asymmetric induction (Scheme 13). Functionalization of the six-membered ring was accomplished as described above. Regioselective Birch reduction delivered olefin **51**. Again, the β-face of the alkene is less hindered in the hydroboration with diborane; we thus obtained, after oxidation, an inseparable 2:1 mix-



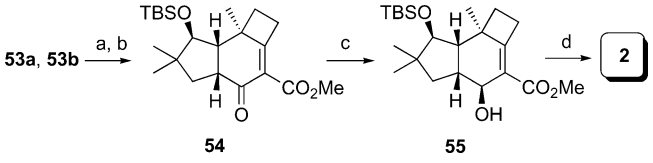
Scheme 12. Pantolactone approach II. Reagents and conditions: (a) (i) DIBAl-H, THF, –78 °C, 95%; (ii) $TMSCHN_2$, *n*BuLi, THF, –78 °C, 67%; (b) *n*BuLi, TMSCl, THF, –78 °C, 95%; (c) (i) 80% AcOH, THF, (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 91%; (d) HF·Py, THF, 23 °C, 65%; (e) DMP, CH_2Cl_2, 23 °C, 92%.

ture of diastereomeric alcohols favoring the *syn* configuration of the bridgehead protons. We carried on with the diastereomeric mixture, hoping for separation at a later stage of the synthesis. Oxidation of the alcohols with Dess–Martin periodinane gave an epimeric mixture of ketones **52a** and **52b**. Methoxycarbonylation of C-2 with carbon dioxide followed by methylation with (trimethylsilyl)diazomethane furnished esters **53a** and **53b**.



Scheme 13. [2+2+2] cycloaddition and functionalization of diene **7**. Reagents and conditions: (a) $CoCp(CO)_2$, toluene, reflux, then $CuCl_2·2H_2O$, DME, 23 °C, 40%; (b) Li (excess), NH_3, *t*BuOH, THF, –78 °C, 85%; (c) (i) BH_3, THF, 23 °C, then K_2CO_3, H_2O_2, THF/H_2O, reflux, (ii) DMP, CH_2Cl_2, 23 °C, 74%; (d) LDA, HMPA, THF, –78 °C, then CO_2 (excess), –58 °C, then 1 N HCl, 23 °C, then $TMSCHN_2$, 0 °C, 45%, 75% (based on recovered starting material); (e) (i) LDA, PhSeCl, THF, –78 °C, (ii) NH_4Cl, H_2O_2, H_2O/CH_2Cl_2, 0 °C, 45%.

Selenation with an excess of LDA/HMPA and addition of phenylselenyl chloride, followed by subjection to H_2O_2 under acidic conditions, was obviously accompanied by epimerization at C-4a, and the *syn* epimer **54** was formed exclusively. Ketone reduction with $CeCl_3·7H_2O$ and $NaBH_4$ in MeOH delivered alcohol **55** as a single isomer. Desilylation with HF·pyridine and subsequent hydrolysis provided pasteurestin B (**2**; Scheme 14).



Scheme 14. Endgame in the synthesis of pasteurestin B (**2**). Reagents and conditions: (a) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, 23 °C, 90%; (b) (i) HF·Py, THF, 23 °C, (ii) LiOH, H_2O/THF, 23 °C, 59%.

The relative configuration of **2** was assigned by ^1H and ^{13}C NMR and 2D NMR analysis (COSY, NOESY, HMBC, HSQC), and our spectroscopic data again match those reported for pasteurestin B (**2**). The absolute configuration was corroborated by comparison of the optical rotations.

Screening against a wide variety of bacteria showed that pasteurestin A (**1**) and pasteurestin B (**2**) exhibited millimolar activity and high selectivity for some versatile pathogenic *Pasteurella multocida* strains (for details see Supporting Information). *ent*-Pasteurestin B was also synthesized by the Reformatsky aldol route starting from (4*R*)-benzyloxazolidinone. This compound did not show any significant antibacterial activity under the test conditions.

Conclusions

We have completed the first total synthesis of pasteurestin A (**1**) in 22 steps over the longest linear sequence in 0.43% overall yield and of pasteurestin B (**2**) in 20 steps over the longest linear sequence in an overall yield of 0.78%. By doing so, we were able to elucidate the absolute and relative configurations of both compounds. Thanks to the functionalization of the six-membered ring at a very late stage, this versatile and flexible approach towards both target compounds should allow the preparation of suitable analogues for further biological testing. They should contribute to the assignment of the mode of action and help in determining the pharmacophore.

Experimental Section

General Remarks: ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 K with Bruker Avance DRX 400 or DRX 600 instruments at 400.13 MHz (100.61 MHz) or 600.13 MHz (150.90 MHz), respectively. Chemical shifts were referenced to residual $CHCl_3$ (δ_H = 7.26 ppm) and $CDCl_3$ (δ_C = 77.36 ppm). All chemical shifts are given in ppm, all coupling constants in Hz. Assignments of proton resonances were confirmed by two-dimensional homo- and heteronuclear spectroscopy. IR spectra were recorded as thin films on a silicon disc with a Perkin–Elmer 1600 FT-IR spectrometer. Mass spectra were measured with a Fisons Instruments Micro mass, trio 200. High-resolution mass spectra (HRMS) were performed with a Finnigan MAT 8230 with a resolution of 10000. Optical rotations were measured at 20 °C with a Perkin–Elmer 351 polarimeter in a 1 dm cell. Reaction progress was checked on precoated TLC plates (Merck Kieselgel 60 F_{254}). Spots were visualized under

254 nm UV light and/or by dipping the TLC plate into a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (20 g) and $CeSO_4\cdot 7H_2O$ (0.5 g) in H_2SO_4 (10%, 400 mL) followed by heating with a heat gun. Column chromatography was performed with Merck silica gel 60 (230–400 mesh). Analytical HPLC was performed with a Jasco System (PU-980 pump, UV 975 and RI 930) instrument with a Nucleosil 50 column (5 μm, ø 4 × 241 mm) at ambient temperature. Preparative HPLC was performed with a Dynamix Model SD-1 fitted with a Model UV-1 absorbance detector with Supersphere (60 Å pore size, 4 μm particle size, ø 25 × 250 mm) at ambient temperature. All solvents were distilled prior to use. THF and Et_2O were distilled from sodium/benzophenone, toluene from sodium. CH_2Cl_2 was dried with P_2O_5. DMF, NEt_3, *i*Pr_2NH, *i*Pr_2NEt, and 2,6-lutidine were distilled from CaH_2. All reactions were performed under argon with use of oven-dried glassware and standard syringe/septa techniques.

(2*E*)-3-Methyl-7-trimethylsilylhept-2-en-6-yn-1-ol (13): Dimethyl (1-diazo-2-oxopropyl)phosphonate (11.2 g, 58.6 mmol) was added at 0 °C to a solution of aldehyde **12** (10.0 g, 58.6 mmol) and K_2CO_3 (16.2 g, 117 mmol) in MeOH (500 mL). After the reaction mixture had been allowed to warm to room temp., stirring at the same temperature was continued for 8 h. At this point, aq. $NaHCO_3$ (5%, 150 mL) was added to the reaction mixture, and MeOH was removed under reduced pressure. After addition of Et_2O (300 mL), the phases were separated and the aqueous phase was extracted twice with Et_2O (50 mL). The combined organic phases were washed with brine and dried with $MgSO_4$, and after filtration and evaporation of the volatiles, a yellow oil was obtained. Purification by flash column chromatography, with elution with hexane/ethyl acetate (6:1), delivered the desired alcohol as a colorless oil (6.5 g, 52.7 mmol, 90%). R_f (hexane/ethyl acetate, 2:1) = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.46 (dt, J = 6.5, 1.2 Hz, 1 H), 4.15 (t, J = 6.5 Hz, 2 H), 2.29 (m, 4 H), 1.92 (t, J = 2.6 Hz, 1 H), 1.69 (d, J = 0.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3 (C), 124.9 (CH), 85.4 (C), 70.3 (CH), 59.6 (CH_2), 38.7 (CH_2), 19.2 (CH_2), 16.5 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 3350 (br.), 3290, 3030, 2920, 2110, 1665, 1440, 1000 cm^{-1}. *n*BuLi (2.5 M in hexanes, 58 mL, 145.1 mmol) was added dropwise to a solution of the alcohol obtained above (8.2 g, 66.1 mmol) in THF (100 mL), followed after stirring for 30 min by TMSCl (15.7 g, 145.0 mmol). After completion of the reaction, HCl (2 M, 50 mL) was added, and the reaction mixture was stirred for 30 min. Et_2O (50 mL) was then added, the phases were separated, and the aqueous phase was washed three times with Et_2O (20 mL). The combined organic phases were washed with satd. aq. $NaHCO_3$ and brine, dried with $MgSO_4$, and filtered. After removal of the solvents, the yellow liquid was purified by flash column chromatography (hexane/ethyl acetate, 6:1), and the desired alcohol **13** (12.2 g, 62.7 mmol, 95%) was obtained as a colorless liquid. R_f (hexane/ethyl acetate 2:1) = 0.24. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.46 (t, J = 6.5 Hz, 1 H), 4.15 (t, J = 6.5 Hz, 2 H), 2.36 (t, J = 6.8 Hz, 2 H), 2.24 (t, J = 6.8 Hz, 2 H), 1.69 (s, 3 H), 0.14 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3 (C), 124.9 (CH), 107.1 (C), 85.4 (C), 59.6 (CH_2), 38.7 (CH_2), 19.2 (CH_2), 16.5 (CH_3) 0.5 (3 × C) ppm. IR (thin film): $\tilde{\nu}$ = 3340 (br.), 2940, 2160, 1245, 1030, 1000 cm^{-1}.

(2*E*)-1-Bromo-3-methyl-7-(trimethylsilyl)hept-2-en-6-yne (9): A solution of CBr_4 (11.2 g, 34 mmol) in CH_2Cl_2 (30 mL) was added dropwise at 0 °C to a solution of triphenylphosphane (17.7 g, 67 mmol) in CH_2Cl_2 (100 mL). After the mixture had been stirred for 10 min, **13** (6.0 g, 31 mmol) in CH_2Cl_2 (30 mL) was added, and the solution was allowed to warm to room temp. After the mixture had been stirred for 1 h, the phosphonium salts were precipitated with pentane (150 mL) and filtered off through Celite. The solvents were removed in vacuo, and the residue with traces of Ph_3PO was adsorbed on silica gel and purified by flash column chromatography (hexane/ethyl acetate, 50:1) to give the desired allylic bromide **9** (6.7 g, 26 mmol, 84%). R_f (hexane) = 0.7. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.58 (dt, J = 1.2, 8.4 Hz, 1 H), 4.00 (d, J = 8.4 Hz, 2 H), 2.36 (t, J = 6.8 Hz, 2 H), 2.24 (t, J = 6.8 Hz, 2 H), 1.74 (s, 3 H), 0.14 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.8 (C), 122.1 (CH), 106.6 (C), 85.6 (C), 38.4 (CH_2), 29.3 (CH_2), 18.9 (CH_2), 16.5 (CH_3) 0.5 (3 × C) ppm.

(4*S*)-2-Methyl-4-[(trityloxy)methyl)]-4-butanolide (8a, 8b): *n*BuLi (2.5 M in hexanes, 108.4 mL, 271 mmol) was added at 0 °C to a solution of diisopropylamine (27.4 g, 37.9 mL, 271 mmol) in THF (400 mL). After the mixture had been stirred at 0 °C for 30 min, propionic acid (130 mmol, 9.7 mL) was slowly added. After the mixture had been stirred at 0 °C for 30 min and subsequently at room temp. for 1 h, a white precipitate had formed. The mixture was then cooled to –78 °C, and a solution of (*S*)-(trityloxymethyl) oxirane (24.0 g, 65 mmol) in THF (100 mL) was added. The reaction mixture was stirred at –78 °C for 3 h and was then allowed to warm to room temp. overnight. The reaction mixture was diluted with Et_2O and poured into satd. aq. $NaHCO_3$. The phases were separated, and the organic layer was washed extensively with four 70 mL portions of $NaHCO_3$. The combined aqueous layers were carefully acidified to pH ≈ 3 with HCl (2 M), and the cloudy aqueous phase was then washed with three portions of CH_2Cl_2 (50 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then dissolved in toluene and heated to reflux in a Dean–Stark trap for 2 h. After removal of the solvents, purification by flash column chromatography (hexane/ethyl acetate, 6:1) delivered a diastereomeric mixture of lactones **8a** and **8b** (*dr* = 1:1, 5.7 g, 50.7 mmol, 78%) as white crystals. M.p. 133–135 °C. IR (thin film): $\tilde{\nu}$ = 1772, 1490, 1449, 1172, 1034, 707 cm^{-1}. HRMS: calcd. for $[M]^+$ 372.1725; found 372.1710. **Diastereomer 8a:** R_f (hexane/ethyl acetate, 4:1) = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 15 H), 4.60 (m, 1 H), 3.28 (m, 2 H), 2.68 (m, 1 H), 2.38 (m, 1 H), 1.70 (m, 1 H), 1.29 (d, J = 7.36 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.8 (C), 143.9 (3 × C), 129.1 (3 × CH), 128.4 (6 × CH), 127.6 (6 × CH), 87.2 (C), 77.5 (CH), 65.7 (CH_2), 35.7 (CH), 33.5 (CH_2), 16.7 (CH_3) ppm. **Diastereomer 8b:** R_f (hexane/ethyl acetate, 4:1) = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 15 H), 4.52 (m, 1 H), 3.43, 3.13 (AB system, J = 10.4, 4.1 Hz, 2 H, dd), 2.90 (m, 1 H), 2.29 (m, 1 H), 1.93 (m, 1 H), 1.29 (d, J = 7.36 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.8 (C), 143.9 (3 × C), 129.0 (3 × CH), 128.3 (6 × CH), 127.6 (6 × CH), 87.2 (C), 77.0 (CH), 65.4 (CH_2), 34.5 (CH), 32.9 (CH_2), 15.7 (CH_3) ppm.

(2*R*,4*S*)-2-Methyl-2-[(2*E*)-3-methyl-7-(trimethylsilyl)hept-2-en-6-ynyl]-5-(trityloxy)pentane-1,4-diol (16): *n*BuLi (2.5 M, 10 , 25 mmol) was added at 0 °C to a solution of *i*Pr_2NH (3.5 mL, 25 mmol) in THF (60 mL). After the mixture had been stirred for 30 min, HMPA (4.4 mL, 25 mmol) was added, and the mixture was cooled to –78 °C. A solution of lactones **8a** and **8b** (9.5 g, 25 mmol) in THF (20 mL) was added dropwise over 30 min, and the mixture was stirred at –78 °C for 2 h. Allylic bromide **9** (5.0 g, 25 mmol) in THF (10 mL) was then added slowly at the same temperature, and the mixture was stirred at –78 °C for 4 h. The reaction was quenched with satd. aq. NH_4Cl, and the mixture was diluted with Et_2O (100 mL). The aqueous phase was extracted three times with Et_2O (50 mL). The combined organic phases were washed with satd. aq. NaCl, dried with $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (hexane/ethyl acetate, 10:1) gave the desired product (9.80 g, 17.8 mmol,

71%) as a colorless oil. R_f (hexane/ethyl acetate, 4:1) = 0.47. $[\alpha]_D^{20}$ = +2.1 (*c* = 2.8, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46 (m, 5 H), 7.28 (series of m, 10 H), 5.21 (dd~t, *J* = 6.3 Hz, 1 H), 4.51 (m, 1 H), 3.29 (dd, *J* = 10.4 Hz, 3.7 Hz, 1 H), 3.20 (dd, *J* = 10.4 Hz, 5.1 Hz, 1 H), 2.31 (m, 3 H), 2.23 (m, 3 H), 2.15 (dd, *J* = 13.0 Hz, 7.12 Hz, 1 H), 1.83 (dd, *J* = 13.0 Hz, 9.2 Hz, 1 H), 1.69 (s, 3 H), 1.26 (s, 3 H), 0.13 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.4 (C), 143.5 (3×C), 138.1 (C), 128.6 (6×CH), 127.9 (6×CH), 127.2 (3×CH), 119.3 (CH), 106.8 (C), 86.8 (C), 84.9 (C), 75.9 (CH), 65.1 (CH_2), 44.1 (C), 38.67 (CH_2), 36.1 (CH_2), 35.9 (CH_2), 23.6 (CH_3), 19.1 (CH_2), 16.2 (CH_3), 0.1 (3×CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 3058, 2961, 2872, 2172, 1773, 1490, 1449, 1249, 1185, 1157, 1103, 1053, 1002, 982, 912 cm^{-1}. HRMS: calcd for $[M]^+$ 550.2903; found 550.2912. DIBAl-H (1.5 M in toluene, 28.9 mL, 43 mmol) was added at –78 °C to a solution of the lactone obtained above (9.5 g, 17 mmol) in THF (100 mL), and the reaction mixture was warmed to 0 °C. After 4 h, TLC monitoring showed complete conversion to the diol, the reaction was quenched with satd. aq. sodium potassium tartrate solution (30 mL), and the mixture was vigorously stirred overnight. After dilution with Et_2O (50 mL), the layers were separated, and the aqueous phase was extracted four times with Et_2O (25 mL). The combined organic layers were washed with brine, dried with magnesium sulfate, and filtered. After concentration under reduced pressure, the crude product was purified by column chromatography (hexane/ethyl acetate, 4:1) to yield the desired diol **16** (8.9 g, 16.1 mmol, 95%). R_f (hexane/ethyl acetate, 4:1) = 0.58. $[\alpha]_D^{20}$ = +4.7 (*c* = 2.8, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46 (m, 5 H), 7.28 (series of m, 10 H), 5.18 (dd~t, *J* = 7.4 Hz, 1 H), 3.94 (m, 1 H), 3.46 (d, *J* = 11.4 Hz, 1 H), 3.30 (d, *J* = 11.4 Hz, 1 H), 3.05 (m, 2 H), 2.28 (m, 2 H), 2.19 (m, 2 H), 2.05 (dd, *J* = 14.3, 9.2 Hz, 1 H), 1.94 (dd, *J* = 14.3 Hz, 7.2 Hz, 1 H), 1.57 (s, 3 H), 1.25 (m, 2 H), 0.81 (s, 3 H), 0.13 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0 (3×C), 135.8 (C), 129.0 (6×CH), 128.3 (6×CH), 127.5 (3×CH), 121.5 (CH), 107.5 (C), 87.2 (C), 84.9 (C), 70.7 (CH_2), 68.6 (CH_2), 67.8 (CH), 41.2 (CH_2), 39.2 (CH_2), 39.0 (C), 33.7 (CH_2), 24.8 (CH_3), 19.5 (CH_2), 16.3 (CH_3), 0.5 (3×CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 3341 (br.), 2924, 2173, 1449, 1249, 1074, 1034, 900, 841, 761 cm^{-1}. HRMS (ESI): calcd. for [M + Na] 577.3114; found 577.3123.

(2*S*,4*R*,6*E*)-4-{[(2,2-Dimethyl-1,1-diphenylpropyl)silyloxy]methyl}-4,7-dimethyl-11-(trimethylsilyl)undec-6-en-10-yne-1,2-diol (17): The diol **16** (11 g, 19.8 mmol) was dissolved in CH_2Cl_2 (80 mL), and then TBDPSCl (7.64 g, 27.8 mmol), NEt_3 (3.9 mL, 27.8 mmol), and catalytic amounts of DMAP (0.1 g, 0.8 mmol) were added. After 18 h, the reaction was quenched by the addition of satd. aq. $NaHCO_3$. After phase separation, the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered, and then concentrated under reduced pressure. Purification by column chromatography (hexane/ethyl acetate, 10:1) delivered the monoprotected product (14.1 g, 17.8 mmol, 90%). R_f (hexane/ethyl acetate, 2:1) = 0.38. $[\alpha]_D^{20}$ = –4.1 (*c* = 3.7, CH_2Cl_2). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.60 (m, 4 H), 7.32 (series of m, 21 H), 5.10 (dd~t, *J* = 7.3 Hz, 1 H), 3.90 (m, 1 H), 3.39 (s, 2 H), 3.09 (dd, *J* = 9.0, 2.2 Hz, 1 H), 3.03 (s, 1 H), 3.0 (dd, *J* = 9.0, 4.7 Hz, 1 H), 2.2 (m, 2 H), 2.11 (m, 3 H), 1.94 (dd, *J* = 14.3, 7.2 Hz, 1 H, 1.51 (s, 3 H), 1.45 (m, 2 H), 1.03 (s, 9 H), 0.77 (s, 3 H), 0.10 (s, 9 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 144.1 (3×C), 135.8 (4×CH), 135.8 (C), 135.5 (2×C), 129.7 (2×CH), 129.0 (6×CH), 128.3 (6×CH), 127.7 (4×CH), 127.5 (3×CH), 121.5 (CH), 107.5 (C), 87.2 (C), 84.9 (C), 70.7 (CH_2), 68.6 (CH_2), 67.8 (CH), 41.2 (CH_2), 39.2 (CH_2), 39.0 (C), 33.7 (CH_2), 27.0 (3×CH_3) 24.8 (CH_3), 19.5 (CH_2), 19.6 (C), 16.3 (CH_3), 0.5 (3×CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 3422 (br.), 3070, 2958, 2930, 2857, 2172, 1491, 1472, 1450, 1428, 1249, 1113, 1077, 998, 908, 842, 760, 740 cm^{-1}. HRMS: calcd. for $[M]^+$ 793.2338; found 793.2328. Et_2AlCl (1.8 M in toluene, 13.4 mL, 24.2 mmol) was added dropwise at –78 °C to a solution of the alcohol obtained above (9.6 g, 12.1 mmol) in CH_2Cl_2 (300 mL). After 4 h at –78 °C, the reaction was quenched by the addition of satd. aq. $NaHCO_3$, warmed up, and stirred for 15 min. After addition of potassium sodium tartrate solution (100 mL), the mixture was vigorously stirred overnight. The layers were then separated, and the aqueous phase was extracted four times with CH_2Cl_2 (25 mL). The combined organic layers were washed with brine, dried with magnesium sulfate, and filtered. After concentration under reduced pressure, the crude product was purified by flash column chromatography (hexane/ethyl acetate, 10:1 → 1:1) to yield **17** (5.8 g, 10.5 mmol, 87%) as a colorless oil. R_f (hexane/ethyl acetate, 1:1) = 0.15. $[\alpha]_D^{20}$ = –6.1 (*c* = 2.4, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (m, 6 H), 7.43 (m, 4 H), 5.03 (dd~t, *J* = 7.0 Hz, 1 H), 3.87 (m, 1 H), 3.53 (dd, *J* = 10.8, 3.6 Hz, 1 H), 3.48 (s, 2 H), 3.43 (dd, *J* = 10.8, 7.6 Hz, 1 H), 2.20 (m, 2 H), 2.11 (m, 3 H), 1.84 (dd, *J* = 14.3, 7.2 Hz, 1 H), 1.55 (s, 3 H), 1.45 (m, 2 H), 1.09 (s, 9 H), 0.74 (s, 3 H), 0.10 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.3 (4×CH), 136.2 (C), 133.1 (C), 133.0 (C), 130.3 (2×CH), 128.2 (4×CH), 121.2 (CH), 107.6 (C), 84.9 (C), 71.8 (CH_2), 68.6 (CH), 68.1 (CH_2), 42.3 (CH_2), 39.2 (CH_2), 38.9 (C), 34.1 (CH_2), 27.4 (3×CH_3), 24.2 (CH_3), 19.6 (CH_2), 19.5 (C), 16.5 (CH_3), 0.5 (3×CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 3401 (br.), 3070, 2958, 2930, 2857, 1654, 1473, 1428, 1249, 1113, 842, 760, 740 cm^{-1}. HRMS: calcd. for $[M]^+$ 550.3299; found 550.3311.

***tert*-Butyl[(2*R*,4*E*)-2,5-dimethyl-2-(prop-2-ynyl)non-4-en-8-ynyloxy]-diphenylsilane (4):** $Pb(OAc)_4$ (5.8 g, 12.9 mmol) was added portionwise at 0 °C to a solution of the diol **17** (5.1 g, 9.3 mmol) obtained above in CH_2Cl_2 (100 mL). After TLC analysis showed complete consumption of the starting material, the reaction was quenched by addition of satd. aq. $NaHCO_3$. The organic phase was extracted four times with CH_2Cl_2 (30 mL), and the combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography (hexane/ethyl acetate, 20:1) delivered the desired aldehyde (4.6 g, 8.8 mmol, 95%) as a colorless oil. R_f (hexane/ethyl acetate, 20:1) = 0.38. $[\alpha]_D^{20}$ = –0.65 (*c* = 7.5, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.84 (t, *J* = 3.0 Hz, 1 H), 7.64 (m, 4 H), 7.41 (m, 6 H), 5.16 (dd~t, *J* = 7.0 Hz, 1 H), 3.47, 3.42 (AB system, *J* = 9.9 Hz, 2 H), 2.39 (dd, *J* = 15.0, 2.8 Hz, 1 H), 2.33 (dd, *J* = 15.0, 3.1 Hz, 1 H), 2.27 (m, 2 H), 2.19 (m, 3 H), 2.05 (dd, *J* = 14.2, 7.3 Hz, 1 H), 1.56 (s, 3 H), 1.09 (s, 9 H), 0.74 (s, 3 H), 0.10 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.4 (CH), 137.0 (C), 136.0 (4×CH), 133.6 (2×C), 130.1 (2×CH), 128.1 (4×CH), 120.8 (CH), 107.5 (C), 85.0 (C), 70.9 (CH_2), 51.2 (CH_2), 40.5 (C), 39.1 (CH_2), 35.7 (CH_2), 27.3 (3×CH_3), 22.3 (CH_3), 19.7 (C), 19.5 (CH_2), 16.5 (CH_3), 0.5 (3×CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 3070, 2958, 2930, 2857, 2174, 1719, 1473, 1428, 1390, 1362, 1249, 1113, 1007, 998, 842 cm^{-1}. HRMS: calcd. for $[M - Me]^+$ 503.2802; found 503.2796. Dimethyl (1-diazo-2-oxopropyl)phosphonate (0.48 g, 2.3 mmol) in MeOH (5 mL) was added at 0 °C to a solution of the aldehyde obtained above (0.96 g, 1.9 mmol) and K_2CO_3 in MeOH (30 mL). After warming to room temp., stirring was continued for 8 h. The reaction mixture was diluted with Et_2O (50 mL), washed with aq. $NaHCO_3$ (10%), and dried with $MgSO_4$. The solvents were evaporated under reduced pressure, and the remaining residue was purified by flash column chromatography (hexane/ethyl acetate, 20:1) to give **4** (1.35 mmol, 0.60 g, 71%) as a colorless liquid. R_f (hexane/ethyl acetate, 20:1) = 0.49. $[\alpha]_D^{20}$ = –5.5 (*c* = 1.5, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68 (m, 4 H), 7.41 (m,

6 H), 5.16 (dd~t, J = 7.0 Hz, 1 H), 3.44 (s, 2 H), 2.19 (series of m, 7 H), 2.06 (dd, J = 14.0, 7.6 Hz, 1 H), 1.93 (t, J = 2.6 Hz, 1 H), 1.86 (t, J = 2.6 Hz, 1 H), 1.59 (s, 3 H), 1.07 (s, 9 H), 0.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.1 (4 × CH), 135.8 (C), 134.0 (2 × C), 129.9 (2 × CH), 127.9 (4 × CH), 121.7 (CH), 84.6 (C), 82.8 (C), 70.3 (CH), 69.4 (CH_2), 68.9 (CH), 40.0 (C), 39.0 (CH_2), 34.6 (CH_2), 27.2 (3 × CH_3), 26.7 (CH_2), 21.5 (CH_3), 19.7 (C), 17.9 (CH_2), 16.3 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 3308, 2959, 2930, 2857, 1472, 1428, 1113, 1008, 826, 740, 702 cm^{-1}. HRMS: calcd. for [M – *t*Bu]$^+$ 385.1988; found 385.1995.

***tert*-Butyl[{(6*R*,7a*S*,7b*R*)-6,7b-dimethyl-2,5,6,7,7a,7b-hexahydro-1*H*-cyclobuta[*e*]inden-6-yl}methoxy]diphenylsilane and *tert*-Butyl[{(6*R*,7a*R*,7b*S*)-6,7b-dimethyl-2,5,6,7,7a,7b-hexahydro-1*H*-cyclobuta[*e*]inden-6-yl}methoxy]diphenylsilane (6a and 6b):** $CpCo(CO)_2$ (0.5 g, 2.9 mmol) in predried, degassed toluene (5 mL) and protected from light was added by syringe (syringe pump) over a period of 6 h to a solution of enediyne **4** (1.0 g, 2.2 mmol) in toluene at reflux and under irradiation with a halogen reflector lamp (visible light, max. 500 W). After completion of the addition, the solution was irradiated at reflux for another 2 h. When TLC analysis showed the complete disappearance of the enediyne, the crude reaction mixture was cooled to room temp., and the volatiles were removed by vacuum transfer. The brown residue was dissolved in dried, degassed DME (10 mL), and $CuCl_2 \cdot 2H_2O$ (1.0 g, 5.5 mmol) was added. The solution was stirred at room temp. for 3 h, the mixture was then partitioned between H_2O (30 mL) and hexane (50 mL), and the layers were separated. The aqueous layer was extracted four times with hexane (10 mL), and the combined organic phases were dried with $MgSO_4$ and concentrated in vacuo to furnish a very air-sensitive yellow oil. This material was eluted through a degassed silica gel column with degassed hexane to give an oily mixture of diastereomers **6a** and **6b** in a 4:3 ratio (0.45 g, 1.0 mmol, 46%). R_f (hexane) = 0.71. IR (thin film): $\tilde{\nu}$ = 3370 (br.), 2953, 2930, 2857, 1428, 1113, 822, 741, 701 cm^{-1}. HRMS: calcd. for [M]$^+$ 442.2692; found 442.2685. **Diastereomer 6a:** ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.81 (m, 4 H), 7.27 (m, 4 H), 7.26 (m, 2 H), 5.89 (br. s, 1 H), 5.76 (br. s, 1 H), 3.60 (AB system, J = 9.7 Hz, 2 H), 2.90 (m, 2 H), 2.47 (d, J = 16.3 Hz, 1 H), 2.12 (d, J = 16.3 Hz, 1 H), 1.76 (m, 3 H), 1.62 (ddd, J = 14.5, 8.0 Hz, 1 H), 1.36 (dd, J = 11.5, 7.7 Hz, 1 H), 1.24 (s, 3 H), 1.23 (s, 9 H), 0.97 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 144.7 (C), 144.4 (C), 136.1 (4 × CH), 134.3 (2 × C), 129.9 (4 × CH), 128.3 (2 × CH), 116.5 (CH), 113.6 (CH), 71.8 (CH_2), 48.3 (CH), 43.3 (C), 41.3 (C), 40.8 (CH_2), 34.8 (CH_2), 33.1 (CH_2), 28.5 (CH_2), 27.1 (3 × CH_3), 23.1 (CH_3), 19.6, (C), 15.4 (CH_3) ppm. **Diastereomer 6b:** ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.81 (m, 4 H), 7.27 (m, 4 H), 7.26 (m, 2 H), 5.78 (br. s, 1 H), 5.70 (br. s, 1 H), 3.49 (AB system, J = 9.7 Hz, 2 H), 2.90 (m, 1 H), 2.76 (m, 1 H), 2.43 (d, J = 18.0 Hz, 1 H), 2.00 (d, J = 18.0 Hz, 1 H), 1.84 (dd, J = 12.7, 8.5 Hz, 1 H), 1.70 (m, 2 H), 1.58 (ddd, J = 14.4, 8.0 Hz, 1 H), 1.29 (dd, J = 12.7, 12.4 Hz, 1 H), 1.23 (s, 9 H), 1.08 (s, 3 H), 1.03 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 144.8 (C), 144.7 (C), 136.1 (4 × CH), 134.3 (2 × C), 129.9 (4 × CH), 128.3 (2 × CH), 116.1 (CH), 113.5 (CH), 70.1 (CH_2), 48.7 (CH), 41.2 (CH_2), 43.6 (C), 41.1 (C), 34.9 (CH_2), 33.1 (CH_2), 28.5 (CH_2), 27.1 (3 × CH_3), 25.0 (CH_3), 19.6 (C), 15.3 (CH_3) ppm.

{(2a*S*,6*R*,7a*S*,7b*S*)-6,7b-Dimethyl-2,2a,3,5,6,7,7a,7b-octahydro-1*H*-cyclobuta[*e*]inden-6-yl}methanol (18a): Li (0.02 g, excess) was added at –78 °C to a stirred solution of liquid NH_3 (ca. 40 mL), dry THF (15 mL), and dry 2-methylpropan-2-ol (10 mL) contained in a 100 mL three-necked round-bottomed flask fitted with a dry ice/acetone condenser and septa. Upon formation of a persistent deep blue color, a solution of dienes **6a** and **6b** (0.86 g, 1.94 mmol) in dry THF (5 mL) was introduced by syringe over 1 min. The reaction was quenched after 1 h by treatment with portions of NH_4Cl (0.5 g, excess), and the NH_3 was allowed to evaporate overnight. Hexane was added, and the solids were removed by filtration. The filtrate was concentrated in vacuo to afford a solid-containing oil, which was purified by column chromatography (hexane/ethyl acetate, 50:1) to give a mixture of the regioselectively reduced olefins (0.73 g, 1.65 mmol, 85%) as a colorless oil. R_f (hexane) = 0.9. **Isomer a:** ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.52 (m, 8 H), 5.46 (m, 1 H), 3.54 (AB system, J = 9.8 Hz, 1 H), 3.48 (AB system, J = 9.8 Hz, 1 H), 2.75 (m, 2 H), 2.72 (m, 4 H), 2.52 (m, 1 H), 2.28 (m, 1 H), 2.27 (m, 1 H), 2.05 (m, 1 H), 2.04 (m, 1 H), 1.91 (m, 1 H), 1.80 (m, 1 H), 1.73 (m, 2 H), 1.67 (m, 1 H), 1.59 (m, 1 H), 1.19 (m, 1 H), 1.08 (s, 3 H), 1.03 (s, 9 H), 0.83 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 145.4 (C), 126.0 (2 × CH), 125.9 (2 × CH), 121.8 (2 × CH), 121.7 (2 × CH), 116.7 (CH), 70.2 (CH_2), 45.3 (CH), 44.1 (C), 41.6 (CH_2), 40.5 (C), 40.4 (CH), 35.5 (CH_2), 33.1 (CH_2), 29.9 (CH_2), 29.4 (CH_2), 29.1 (2 × CH), 27.7 (3 × CH_3), 26.1 (2 × CH_2), 24.7 (CH_3), 24.6 (CH_3), 22.0 (C) ppm. **Isomer b:** ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.80 (m, 4 H), 5.52 (m, 4 H), 5.50 (m, 1 H), 3.63 (s, 2 H), 2.75 (m, 2 H), 2.72 (m, 4 H), 2.62 (m, 1 H), 2.28 (m, 1 H), 2.27 (m, 1 H), 2.04 (m, 2 H), 1.98 (m, 1 H), 1.73 (m, 2 H), 1.67 (m, 1 H), 1.59 (m, 1 H), 1.55 (m, 1 H), 1.35 (m, 1 H), 1.04 (s, 9 H), 0.96 (s, 3 H), 0.84 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 145.2 (C), 126.2 (4 × CH), 121.7 (4 × CH), 117.0 (CH), 71.9 (CH_2), 44.8 (CH), 44.0 (C), 41.3 (CH_2), 40.6 (C), 40.5 (CH), 35.2 (CH_2), 33.2 (CH_2), 29.5 (CH_2), 29.2 (2 × CH), 27.7 (3 × CH_3), 26.1 (2 × CH_2), 24.9 (CH_2), 24.6 (CH_3), 23.1 (CH_3), 22.0 (C) ppm. TBAF (1 M in THF, 3.3 mmol, 3.3 mL) was added at room temp to a solution of the monoolefins obtained above (0.73 g, 1.7 mmol) in THF (10 mL). When TLC analysis showed full consumption of the starting material, the reaction was quenched with satd. aq. NH_4Cl, the mixture was diluted with Et_2O (10 mL), and the phases were separated. The aqueous phase was extracted four times with Et_2O (5 mL), and the combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography (hexane/ethyl acetate, 4:1) delivered a mixture of diastereomers **18a** and **18b** (0.32 g, 1.6 mmol, 95%), which could be separated by preparative HPLC [analytical HPLC data: hexane/ethyl acetate, 9:1; flow: 1 mL min^{-1}; t_r(**18a**) = 2.4 min, t_r(**18b**) = 3.0 min]. **Isomer 18a:** R_f (hexane/ethyl acetate, 4:1) = 0.60. $[\alpha]_D^{20}$ = +20.5 (c = 3.0, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.52 (m, 1 H), 3.48 (s, 2 H), 2.63 (ddd, J = 9.1, 7.6, 2.9 Hz, 1 H), 2.28 (m, 1 H), 2.08 (m, 4 H), 1.75 (m, 3 H), 1.61 (m, 1 H), 1.54 (br. s, OH), 1.47 (ddd, J = 11.6, 8.0, 2.4 Hz, 1 H), 1.40 (dd, J = 11.6, 11.6 Hz, 1 H), 1.0 (s, 3 H), 0.83 (s 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 144.4 (C), 117.4 (CH), 72.2 (CH_2), 44.7 (CH), 43.7 (C), 41.6 (CH_2), 40.5 (C), 40.4 (CH), 35.7 (CH_2), 33.1 (CH_2), 29.4 (CH_2), 24.9 (CH_2), 24.7 (CH_3), 22.8 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 3351 (br.), 2930, 2864, 2831, 1653, 1457, 1374, 1029, 872, 810 cm^{-1}. HRMS: calcd. for [M]$^+$ 206.1671; found 206.1668.

***tert*-Butyl[{(2a*S*,6*R*,7a*S*,7b*S*)-6,7b-dimethyl-2,2a,3,5,6,7,7a,7b-octahydro-1*H*-cyclobuta[*e*]inden-6-yl}methoxy]dimethylsilane (19):** TBSCl (176 mg, 1.5 mmol) was added in small portions to a solution of alcohol **18a** (150 mg, 0.73 mmol) and imidazole (124 mg, 1.8 mmol) in anhydrous DMF (5 mL), and the mixture was stirred for 10 h. Water (5 mL) and Et_2O (15 mL) were added, the phases were separated, and the aqueous phase was extracted five times with Et_2O (5 mL). The combined organic layers were washed four times with portions (5 mL) of water and then brine, and were dried with $MgSO_4$. After concentration in vacuo, the crude product was purified by flash column chromatography (hexane/ethyl acetate,

20:1) to give protected **19** (210 mg, 0.66 mmol, 90%) as a colorless oil. R_f (hexane) = 0.95. $[\alpha]_D^{20}$ = +15.0 (c = 2.8, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52 (m, 1 H), 3.41 (s, 2 H), 2.63 (ddd, J = 9.12, 7.6, 2.9 Hz, 1 H), 2.26 (m, 2 H), 2.08 (m, 2 H), 1.97 (d, J = 15.8 Hz, 1 H), 1.74 (m, 3 H), 1.65 (m, 1 H), 1.53 (dd, J = 11.7, 9.4 Hz, 1 H), 1.36 (ddd, J = 11.9, 7.8, 1.3 Hz, 1 H), 1.00 (s, 3 H), 0.89 (s, 9 H), 0.83 (s 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8 (C), 117.2 (CH), 71.2 (CH_2), 45.2 (CH), 44.3 (C), 41.7 (CH_2), 41.0 (C), 40.9 (CH), 35.5 (CH_2), 33.4 (CH_2), 29.8 (CH_2), 26.3 ($3\times CH_3$), 25.0 (CH_2), 23.5 (CH_3), 23.5 (CH_3), 18.6 (C), –2.6 (CH_3), –5.1 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 2955, 2942, 2929, 2856, 1256, 1091, 837, 774 cm^{-1}. HRMS: calcd. for $[M]^+$ 320.2535; found 320.2541.

(2a*S*,4a*R*,6*R*,7a*S*,7b*S*)-6-[(*tert*-Butyldimethylsilyloxy)methyl]-6,7b-dimethyldecahydro-cyclobuta[*e*]inden-4-one (20a, *syn*) and (2a*S*,4a*S*,6*R*,7a*S*,7b*S*)-6-[(*tert*-Butyldimethylsilyloxy)methyl]-6,7b-dimethyldecahydrocyclobuta[*e*]inden-4-one (20b, *anti*): B_2H_6·THF (1 M in THF, 1.9 mL, 1.9 mmol) was added at 0 °C to a solution of olefin **19** (200 mg, 0.6 mmol) in dry THF (8 mL). After 5 h at room temp., TLC analysis of the reaction mixture indicated no remaining olefin. Aq. K_2CO_3 (1 M, 2.5 mL, 2.5 mmol) and H_2O_2 (30% by wt., 1.1 mL, 10.0 mmol) were added sequentially at 0 °C to the vigorously stirred solution, the flask was then fitted with a reflux condenser, and the biphasic mixture was stirred for 3 h while heated to 60–65 °C in an oil bath. The cooled solution was then diluted with hexane (30 mL), the layers were separated, and the aqueous phase was extracted three times with hexane (10 mL); the combined organic phases were washed with satd. aq. $Na_2S_2O_3$ and then brine, dried with $MgSO_4$ and filtered, after which the volatiles were evaporated under reduced pressure to afford a colorless oil which was used without further purification. The crude mixture was dissolved in CH_2Cl_2 (5 mL), and Dess–Martin periodinane (419 mg, 1.00 mmol) was added. After the mixture had been stirred at room temp. for 2 h, TLC monitoring showed complete consumption of the starting material. A mixture (1:1) of satd. aq. $NaHCO_3$ and aq. $Na_2S_2O_3$ (1 M, 5 mL) was added, and the reaction mixture was stirred until the biphasic mixture became clear. The phases were then separated, and the aqueous phase was extracted three times with CH_2Cl_2 (3 mL). The combined organic phases were washed with brine, dried, and filtered. The solvent was removed in vacuo and purified by column chromatography (hexane/ethyl acetate, 10:1) to give an epimeric mixture of ketones **20a** and **20b** as a clear oil (155 mg, 0.46 mmol, 74% over two steps). R_f (hexane/ethyl acetate, 9:1) = 0.5. IR (thin film): $\tilde{\nu}$ = 2953, 1713, 1472, 1255, 1095, 837, 802, 776, 727 cm^{-1}. HRMS: calcd. for $[M]^+$ 336.2485; found 336.2485. **Epimer 20a:** ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.25, 3.21 (AB system, J = 9.5 Hz, 2 H), 2.87 (m, 1 H), 2.82 (dd, J = 14.6, 7.2 Hz, 1 H), 2.45 (m, 1 H), 2.21 (m, 1 H), 2.18 (m, 1 H), 2.09 (dm, J = 14.6 Hz, 1 H), 1.95 (dd, J = 14.8, 9.8 Hz, 1 H), 1.87 (ddd, J = 3×9.5 Hz, 1 H), 1.83 (m, 1 H), 1.61 (m, 1 H), 1.57 (dd, J = 14.8 Hz, 5.5 Hz, 1 H), 1.42 (m, 1 H), 1.32 (m, 1 H), 1.17 (s, 3 H), 0.98 (s, 3 H), 0.87 (s, 9 H), 0.006 (s, 6 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 216.8 (C), 70.0 (CH_2), 50.5 (CH), 50.2 (CH), 41.7 (CH_2), 40.1 (CH), 39.8 (CH_2), 39.4 (CH_2), 37.1 (C), 37.3 (C), 30.8 (CH_2), 27.1 (CH_3), 26.0 ($3\times CH_3$), 25.8 (CH_3), 21.3 (CH_2), 18.1 (C), –5.5 ($2\times CH_3$) ppm. **Epimer 20b:** (600 MHz, $CDCl_3$): δ = 3.28, 3.25 (AB system, J = 9.5 Hz, 2 H), 2.63 (m, 1 H), 2.51 (dddd, J = 8.5, 8.5, 8.5, 2.5 Hz, 1 H), 2.37 (m, 1 H), 2.35 (m, 1 H), 2.07 (m, 1 H), 1.95 (m, 1 H), 1.87 (m, 1 H), 1.81 (m, 1 H), 1.74 (m, 1 H), 1.67 (m, 1 H), 1.63 (m, 1 H), 1.36 (m, 1 H), 1.17 (m, 1 H), 1.11 (s, 3 H), 0.98 (s, 3 H), 0.87 (s, 9 H), 0.001 (s, 6 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 213.6 (C), 71.4 (CH_2), 49.5 (CH), 51.2 (CH), 44.0 (CH), 43.3 (CH_2), 42.1 (CH_2), 39.7 (C), 39.5 (C), 39.4 (CH_2), 30.9 (CH_2), 26.5 (CH_3), 26.0 ($3\times CH_3$), 22.8 (CH_2), 21.3 (CH_3), 18.1 (C), –5.5 ($2\times CH_3$) ppm.

Methyl (2a*S*,4a*R*,6*R*,7a*S*,7b*R*)-6-[(*tert*-Butyldimethylsilyloxy)-methyl]-6,7b-dimethyl-4-oxodecahydrocyclobuta[*e*]indene-3-carboxylate (21a, *syn*): *n*BuLi (2.5 M in THF, 0.42 mL, 1.05 mmol) was added at 0 °C to a solution of diisopropylamine (107 mg, 1.05 mmol) in THF (5 mL), and the mixture was stirred at this temperature for 30 min. After the system had been cooled to –78 °C, HMPA (194 mg, 0.18 mL, 1.05 mmol) and a solution of epimeric ketones **20a** and **20b** (140 mg, 0.42 mmol) were slowly added, and the mixture was stirred at –78 °C for 2 h. Dry carbon dioxide (generated from dry ice and passed through concentrated sulfuric acid) was then bubbled into the mixture at –58 °C for 1 h. After addition of aq. HCl (1 M, 0.5 mL), the mixture was quickly warmed to 0 °C with an ice bath. (Trimethylsilyl)diazomethane (2 M in diethyl ether, 0.35 mL, 0.70 mmol) was added slowly to the reaction mixture. When TLC showed the acid no longer to be present, the excess of (trimethylsilyl)diazomethane was quenched with additional HCl (1 M), Et_2O was added, and the phases were separated. The aqueous phase was extracted several times with Et_2O, the combined organic phases were washed with satd. aq. $NaHCO_3$ and dried, and the volatiles were evaporated under reduced pressure. Purification by column chromatography delivered a mixture of diastereomers **21a** and **21b** in a 4:1 ratio (0.23 mmol, 91 mg, 55%). R_f (hexane/ethyl acetate, 9:1) = 0.8. IR (thin film): $\tilde{\nu}$ = 2953, 2857, 1653, 1611, 1440, 1361, 1292, 1255, 1236, 1094, 837, 775, 668 cm^{-1}. HRMS: calcd. for $[M]^+$ 394.2539; found 394.2547. **Diastereomer 21a:** ^{1}H NMR (600 MHz, $CDCl_3$): δ = 12.40 (s, 1 H), 3.72 (s, 3 H), 3.19, 3.17 (AB system, J = 9.4 Hz, 2 H), 2.91 (t, J = 7.8 Hz, 1 H), 2.58 (m, 1 H), 2.43 (m, 1 H), 2.30 (dd, J = 13.9, 1.9 Hz, 1 H), 2.03 (m, 1 H), 1.93 (dd, J = 20.0, 10.1 Hz, 1 H), 1.53 (dd, J = 13.9, 8.8 Hz, 1 H), 1.43 (m, 1 H), 1.36 (m, 1 H), 1.25 (m, 4 H), 1.14 (t, J = 12.7 Hz, 1 H), 0.98 (s, 3 H), 0.85 (s, 9 H), –0.02, (s, 3 H), –0.03 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.6 (C), 172.8 (C), 100.9 (C), 71.9 (CH_2), 51.7 (CH_3), 46.2 (CH), 43.5 (C), 42.0 (CH), 38.3 (CH_2), 37.4 (CH_2), 37.3 (C), 36.2 (CH), 30.0 (CH_2), 26.8 (CH_3), 26.7 (CH_2), 26.2 ($3\times CH_3$), 21.0 (CH_3), 18.6 (C), –5.2 ($2\times CH_3$) ppm.

Methyl (4a*R*,6*R*,7a*S*,7b*R*)-6-[(*tert*-Butyldimethylsilyloxy)methyl]-6,7b-dimethyl-4-oxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-cyclobuta[*e*]-indene-3-carboxylate (22a): A solution of β-oxo esters **21a** and **21b** (90 mg, 0.23 mmol) in THF (2 mL) was added slowly at –78 °C to a stirred solution of lithium diisopropylamide (0.25 M in THF, 0.27 mmol, 1.09 mL), and the mixture was allowed to warm to 0 °C. After the solution had been stirred for 45 min, a solution of phenylselenyl chloride (52 mg, 0.27 mmol) in THF (0.5 mL) was added, and the mixture was stirred for another 20 min. It was then quenched by addition of satd. aq. NH_4Cl and diluted with Et_2O, and the aqueous phase was extracted three times with Et_2O. The combined organic phases were washed with brine and dried with $MgSO_4$. After concentration of the crude product in vacuo, the product was filtered through a pad of silica gel to deliver the desired epimeric mixture (0.13 mmol, 79 mg, 55%) as a yellow oil. The two undesired diastereomers with opposite configuration at C-3 were also obtained (26 mg, 0.042 mmol, 18%) but could be removed chromatographically. The epimers with the phenylselenide *anti* to the cyclobutane (60 mg, 0.11 mmol) were dissolved in CH_2Cl_2 (5 mL), and satd. aq. NH_4Cl (0.5 mL) and aq. H_2O_2 (30% by wt., 2.5 mL) were added at 0 °C. The biphasic mixture was stirred vigorously at the same temperature for 2 h. After dilution with H_2O (1 mL) and CH_2Cl_2 (5 mL), the phases were separated, the aqueous phase was extracted twice with CH_2Cl_2, and the combined organic phases were washed with aq. $Na_2S_2O_3$ (10%) and

brine, dried with $MgSO_4$, and concentrated in vacuo. The semisolid product was purified by column chromatography (hexane/ethyl acetate, 10:1) to provide a 72% yield (31 mg, 0.08 mmol) of the desired α,β-unsaturated β-oxo ester **22a**, which could be separated from **22b**. R_f (hexane/ethyl acetate, 4:1) = 0.35. $[\alpha]_D^{20}$ = –43.5 (*c* = 0.55, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.75 (s, 3 H), 3.39 (s, 2 H), 3.30 (ddd, *J* = 18.9, 8.8, 1.3 Hz, 1 H), 3.18 (dd, *J* = 8.8, 4.1 Hz, 1 H), 3.13 (m, 1 H), 2.83 (ddd, *J* = 11.5, 8.8, 7.8 Hz, 1 H), 2.01 (m, 2 H), 1.79 (dd, *J* = 13.4, 7.8 Hz, 1 H), 1.65 (m, 2 H), 1.36 (ddd, *J* = 13.4, 9.1, 1.1 Hz, 1 H), 1.20 (s, 3 H), 0.92 (s, 3 H), 0.87 (s, 9 H), 0.02 (s, 6 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 197.9 (C), 185.5 (C), 163.7 (C), 125.7 (C), 70.6 (CH_2), 52.8 (CH), 51.9 (CH_3), 47.3 (C), 45.5 (C), 44.7 (CH), 37.3 (CH_2), 34.7 (CH_2), 34.5 (CH_2), 31.0 (CH_2), 26.4 (3 × CH_3), 24.0 (CH_3), 23.1 (CH_3), 18.8 (C), –5.2 (2 × CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 2955, 2368, 2345, 1735, 1718, 1700, 1696, 1685, 1437, 1319, 1257, 1093, 856, 836 cm^{-1}. HRMS: calcd. for $[M]^+$ 392.2383; found 392.2391.

Methyl (4*S*,4a*R*,6*R*,7a*S*,7b*R*)-6-[(*tert*-Butyldimethylsilyloxy)-methyl]-4-hydroxy-6,7b-dimethyl-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-cyclobuta[*e*]indene-3-carboxylate (23): A solution of the β-oxo ester **22a** (15 mg, 0.04 mmol) in MeOH (2 mL), together with $CeCl_3 \cdot 7H_2O$ (134 mg, 0.38 mmol), was stirred at 0 °C for 30 min. Sodium borohydride (3 mg, 0.077 mmol) was then added, and the reaction mixture was stirred at 0 °C for another 15 min. At this point, the reaction was quenched with water, MeOH was evaporated, and the remaining aqueous phase was diluted with CH_2Cl_2 (5 mL). The phases were separated, and the aqueous phase was extracted three times with CH_2Cl_2 (3 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane/ethyl acetate, 10:1) to yield the alcohol **23** (13 mg, 0.03 mmol, 87%). R_f (hexane/ethyl acetate, 4:1) = 0.64. $[\alpha]_D^{20}$ = –35.7 (*c* = 0.65, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.26 (d, *J* = 1.4 Hz, 1 H), 4.23 (m, 1 H), 3.75 (s, 3 H), 3.39 (s, 2 H), 3.04 (ddd, *J* = 19.0, 8.0, 3.9 Hz, 1 H), 2.98 (m, 1 H), 2.36 (m, 2 H), 1.90 (m, 2 H), 1.70 (m, 1 H), 1.56 (dd, *J* = 13.2, 9.5 Hz, 1 H), 1.37 (dd, *J* = 12.4, 10.0 Hz, 1 H), 1.25 (m, 1 H), 1.08 (s, 3 H), 0.91 (s, 9 H), 0.87 (s, 3 H), 0.01 (s, 6 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.5 (C), 168.3 (C), 121.5 (C), 71.5 (CH), 70.7 (CH_2), 51.3 (CH_3), 48.7 (CH), 47.3 (C), 45.1 (C), 44.1 (CH), 41.1 (CH_2), 35.4 (CH_2), 35.1 (CH_2), 29.3 (CH_2), 25.9 (3 × CH_3), 22.9 (CH_3), 20.2 (CH_3), 18.3 (C), –5.5 (2 × CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 2927, 2787, 1694, 1560, 1113, 887, 876, 612 cm^{-1}. HRMS: calcd. for $[M]^+$ 337.1835; found 337.1840.

Pasteurestin A (1): The α,β-unsaturated ester **23** (8.0 mg, 0.020 mmol) was dissolved in THF (2 mL) in a polyethylene vessel, and the solution was cooled to 0 °C. HF·pyridine (70%, 0.14 mL, 1.0 mmol) was added, and the reaction mixture was stirred at room temp. overnight. It was quenched by addition of satd. aq. $NaHCO_3$ (2 mL) and diluted with CH_2Cl_2 (5 mL). The aqueous phase was extracted three times with CH_2Cl_2 (2 mL), and the combined organic extracts were washed with HCl (2 M, 2 mL) and subsequently with satd. aq. $NaHCO_3$. The organic phase was then dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was dissolved in THF (1.4 mL), and H_2O (0.6 mL) was added. After the addition of $LiOH \cdot H_2O$ (1.6 mg, 0.038 mmol), the reaction mixture was stirred overnight. When TLC analysis showed the hydrolysis to be complete, HCl (2 M, 0.5 mL) was added. The reaction mixture was again diluted with CH_2Cl_2 (5 mL), and after phase separation the aqueous phase was extracted three times with CH_2Cl_2 (2 mL). The organic phases were washed with satd. aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated in vacuo. Purification by flash column chromatography (hexane/ethyl acetate, 1:1 → ethyl acetate) delivered **1** (3.0 mg, 0.011 mmol, 55%) as a colorless oil. R_f (ethyl acetate) = 0.13. $[\alpha]_D^{20}$ = –60 (*c* = 0.13, MeOH). ^{1}H NMR (600 MHz, CD_3OD): δ = 4.24 (ddd, *J* = 8.3, 3.0, 2.5 Hz, 1 H, C*H*OH), 3.43 (AB system, *J* = 11 Hz, 2 H, HOCH_2C), 3.15 (dddd, *J* = 18.0, 9.2, 9.2, 3.5 Hz, 1 H, CCC*H*H), 3.06 (dddd, *J* = 18.0, 8.4, 4.4, 2.5 Hz, 1 H, CCCH*H*), 2.46 (ddd, *J* = 11.9, 10.5, 8.0 Hz, 1 H, CH_2CHCCH_3), 2.41 (dddd, *J* = 11.9, 10.4, 8.3, 8.0 Hz, 1 H, $CH_2CHCHOH$), 1.97 (m, 2 H, $CCCH_2CH_2$), 1.74 (ddd, *J* = 12.5, 8.0, 1.8 Hz, 1 H, C*H*HCHCHOH), 1.56 (dd, *J* = 12.9, 10.5 Hz, 1 H, C*H*HCHCCH$_3$), 1.39 (ddd, *J* = 12.9, 8.0, 1.8 Hz, 1 H, CH*H*CHCCH$_3$), 1.33 (dd, *J* = 12.5, 10.4 Hz, 1 H, CH*H*CHCHOH), 1.18 (s, 3 H, CHCCH_3), 1.03 (s, 3 H, HOCH$_2$CCH_3) ppm. ^{13}C NMR (150 MHz, CD_3OD): δ = 175.4 (C), 165.1 (C), 126.2 (C), 73.9 (CH), 72.9 (CH_2), 51.5 (CH), 49.2 (C), 47.1 (C), 46.9 (CH), 43.2 (CH_2), 37.7 (CH_2), 37.6 (CH_2), 30.8 (CH_2), 23.9 (CH_3), 21.3 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 3369 (br.), 2930, 2854, 1687, 1651, 1463, 1248, 1036, 895, 862 cm^{-1}. HRMS: calcd. for $[M]^+$ 280.1675; found 280.1672 (methyl ester).

(4*R*)-4-Benzyl-3-[(3*S*,4*E*)-3-hydroxy-2,2,5-trimethyl-9-(trimethylsilyl)non-4-en-8-ynoyl]oxazolidin-2-one (40): Lithium aluminium hydride (1 M in THF, 23 mL, 23 mmol) was added portionwise at 0 °C to a THF solution (80 mL) of anhydrous stannous chloride (8.78 g, 46 mmol), which was previously dried by heating in vacuo at 120 °C for 1 h. Spontaneous exothermic reaction occurred, and a dark gray material deposited. The mixture was stirred at room temp. for 20 min. Subsequently, bromide **10** (7.50 g, 23 mmol) in THF (20 mL) was added to this mixture, which was stirred for another 2 h. The reaction mixture was then cooled to –78 °C, and aldehyde **11** (4.5 g, 23 mmol), dissolved in THF (20 mL), was added over a period of 30 min. The reaction mixture was stirred at –78 °C for 8 h. The reaction was quenched with water (50 mL), and the mixture was diluted with Et_2O (50 mL). After phase separation, the aqueous phase was extracted four times with portions of Et_2O (50 mL), and the combined organic extracts were stirred with satd. aq. KF (50 mL) and water (50 mL) for 30 min. The phases were again separated, and the organic extracts were dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give a yellow oil, which was purified by flash column chromatography (hexane/ethyl acetate, 9:1) to yield alcohol **40** (7.92 g, 18 mmol, 78%). R_f (hexane/ethyl acetate, 4:1) = 0.2. $[\alpha]_D^{20}$ = +2.4 (*c* = 2.8, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (m, 5 H), 5.33 (d, *J* = 9.1 Hz, 1 H), 5.21 (d, *J* = 9.1 Hz, 1 H), 4.74 (m, 1 H), 4.16 (m, 2 H), 3.30 (dd, *J* = 13.4, 2.4 Hz, 1 H), 2.78 (dd, *J* = 13.4, 9.8 Hz, 1 H), 2.39 (m, 2 H), 2.26 (m, 3 H), 1.79 (s, 3 H), 1.38 (s, 6 H), 0.14 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.1 (C), 152.8 (C), 139.8 (C), 136.0 (C), 129.8 (2 × CH), 129.2 (2 × CH), 127.8 (CH), 124.4 (CH), 107.0 (C), 85.3 (C), 71.9 (CH), 66.8 (CH_2), 58.1 (CH), 51.0 (C), 38.9 (CH_2), 38.1 (CH_2), 20.5 (CH_3), 19.1 (CH_3), 18.9 (CH_2), 17.3 (CH_3), 0.47 (3 × CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 3530 (br.), 2958, 2173, 1781, 1685, 1477, 1471, 1453, 1417, 1388, 1371, 1348, 1316, 1251, 1229, 1193, 1153, 1140, 1125, 1104, 1066, 1031, 991 cm^{-1}. HRMS: calcd. for $[M]^+$ 441.2335; found 441.2327.

***S*-Ethyl (3*S*,4*E*)-3-(*tert*-Butyldimethylsilyloxy)-2,2,5-trimethyl-9-(trimethylsilyl)non-4-en-8-ynethioate (41):** TBSOTf (8.1 g, 7.1 mL, 31 mmol) was added dropwise at 0 °C to a solution of alcohol **40** (9.0 g, 20 mmol) and 2,6-lutidine (8.7 g, 9.5 mL, 82 mmol) in CH_2Cl_2 (50 mL), and the reaction mixture was stirred at 0 °C for 30 min. After TLC analysis showed full consumption of the starting material, the reaction was quenched by the addition of satd. aq. $NaHCO_3$. The phases were separated, the organic phase was washed twice with CH_2Cl_2 (10 mL), and the combined organic phases were washed with HCl (2 M) and then with satd. aq. $NaHCO_3$ and dried with $MgSO_4$. Filtration and concentration in

vacuo, together with purification by column chromatography, delivered the TBS-protected alcohol (10.6 g, 19 mmol, 95%) as a clear oil. R_f (hexane/ethyl acetate, 4:1) = 0.6. $[\alpha]_D^{20}$ = –19.9 (*c* = 1.8, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31 (m, 5 H), 5.73 (d, *J* = 9.2 Hz, 1 H), 5.21 (d, *J* = 9.2 Hz, 1 H), 4.60 (m, 1 H), 4.13 (m, 2 H), 3.45 (dd, *J* = 13.0, 2.3 Hz, 1 H), 2.64 (dd, *J* = 13.0, 10.9 Hz, 1 H), 2.37 (t, *J* = 7.3 Hz, 2 H), 2.24 (t, *J* = 7.3 Hz, 2 H), 1.79 (s, 3 H), 1.35 (s, 3 H), 1.25, (s, 3 H), 0.85 (s, 9 H), 0.14 (s, 9 H), 0.03 (s, 3 H), –0.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.13 (C), 153.2 (C), 137.5 (C), 136.4 (C), 129.7 (2 × CH), 129.6 (2 × CH), 127.5 (CH), 126.2 (CH), 107.2 (C), 85.1 (C), 70.1 (CH), 66.7 (CH_2), 58.9 (CH), 52.6 (C), 38.9 (CH_2), 38.6 (CH_2), 26.1 (3 × CH_3), 20.7 (CH_3), 20.0 (CH_3), 19.3 (CH_2), 18.9 (C), 17.3 (CH_3), 0.45 (3 × CH_3), –3.4 (CH_3), –4.2 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 2955, 2942, 2929, 2856, 1781, 1692, 1473, 1387, 1346, 1250, 1190, 1144, 1102, 834, 733, 701 cm^{-1}. HRMS: calcd. for [M^+ – *t*Bu] 498.2496; found 489.2505. *n*BuLi (2.5 M, 17 mL, 42.5 mmol) was added dropwise at 0 °C to a solution of EtSH (2.7 g, 3.2 mL, 43 mmol) in THF (50 mL), and the mixture was stirred for 1 h. The mixture was then cooled to –78 °C, and the TBS ether obtained above (6.0 g, 10.8 mmol) was added. The solution was gradually warmed to 0 °C and stirred for 2 h, and was then was quenched with satd. aq. NH_4Cl and extracted with ethyl acetate. The combined organic phases were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/ethyl acetate (10:1) delivered thioester **41** (4.2 g, 9.6 mmol, 89%) as a yellow oil. R_f (hexane/ethyl acetate, 10:1) = 0.9. $[\alpha]_D^{20}$ = –12.8 (*c* = 2.8, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.15 (dd, *J* = 9.5, 1 Hz, 1 H), 4.61 (d, *J* = 9.2 Hz, 1 H), 2.80 (dq, *J* = 7.4, 1.7 Hz, 2 H), 2.33 (t, *J* = 7.2 Hz, 2 H), 2.21 (t, *J* = 7.2 Hz, 2 H), 1.73 (s, 3 H), 1.22 (m, 6 H), 1.04 (s, 3 H), 0.82 (s, 9 H), 0.13 (s, 9 H), 0.024 (s, 3 H), –0.069 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.4 (C), 136.8 (C), 125.9 (CH), 107.2 (C), 85.1 (C), 73.7 (CH), 56.0 (C), 38.9 (CH_2), 26.1 (3 × CH_3), 23.4 (CH_2), 22.6 (CH_3), 19.3 (CH_2), 19.0 (CH_3), 18.4 (C), 17.4 (CH_3), 14.8 (CH_3), 0.45 (3 × CH_3), –3.4 (CH_3), –4.9 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 2958, 2175 2176, 1672, 1472, 1249, 1069, 945, 839, 776 cm^{-1}. HRMS: calcd. for [M – Me]$^+$ 425.2366; found 425.2363.

(3*S*,4*E*)-3-(*tert*-Butyldiphenylsilyloxy)-2,2,5-trimethyl-9-(trimethylsilyl)non-4-en-8-ynal (42): A solution of the thioester **41** (5.0 g, 11.4 mmol) in CH_2Cl_2 (100 mL) was cooled to –78 °C, and DIBAl-H (13.7 mL) in hexane (1 M, 13.7 mmol) was slowly added. After 3 h, the reaction was quenched with satd. aq. NH_4Cl, and the mixture was extracted three times with CH_2Cl_2. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated in vacuo to give a yellow oil, which was purified by flash column chromatography (hexane/ethyl acetate, 20:1) to yield aldehyde **42** (3.3 g, 8.5 mmol, 75%) and its corresponding alcohol (0.7 g, 1.7 mmol, 15%). R_f (hexane/ethyl acetate, 10:1) = 0.81. $[\alpha]_D^{20}$ = –12.8 (*c* = 2.8, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.64 (s, 1 H), 5.26 (dd, *J* = 9.5, 1 Hz, 1 H), 4.53 (d, *J* = 9.2 Hz, 1 H), 2.43 (m, 2 H), 2.30 (t, *J* = 7.1 Hz, 2 H), 1.76 (s, 3 H), 1.12 (s, 3 H), 1.02 (s, 3 H), 0.90 (s, 9 H), 0.20 (s, 9 H), 0.079 (s, 3 H), 0.033 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8 (CH), 137.2 (C), 125.9 (CH), 106.2 (C), 85.1 (C), 73.7 (CH), 51.5 (C), 39.5 (CH_2), 26.6 (3 × CH_3), 18.9 (CH_3), 18.8 (CH_2), 17.9 (C), 16.8 (CH_3), 15.9 (CH_3), –0.28 (3 × CH_3), –3.9 (CH_3), –5.1 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 2958, 2871, 2858, 2176, 1733, 1472, 1362, 1250, 1067, 840, 776 cm^{-1}. HRMS: calcd. for [M – Me]$^+$ 365.2328; found 365.2332.

(4*S*,5*E*)-4-(*tert*-Butyldimethylsilyloxy)-3,3,6-trimethyl-10-(trimethylsilyl)dec-5-en-9-ynal (43): (Methoxymethyl)triphenylphosphonium chloride (4.9 g, 14.2 mmol) was suspended in THF (30 mL) and cooled with an ice/salt bath to –10 °C. *n*BuLi (2.5 M in hexane, 5.7 mL, 14.2 mmol) was added slowly, and the bright red mixture was then stirred at room temp. for 1 h. Aldehyde **42** (2.7 g, 7.1 mmol) was dissolved in THF (15 mL) and added dropwise to the resulting solution by syringe at 0 °C. After stirring at room temp. for 30 min, the reaction mixture was quenched by the addition of H_2O (10 mL), followed by ethyl acetate (80 mL). After phase separation, the aqueous phase was extracted three times with ethyl acetate (50 mL), and the combined organic phases were washed with brine and dried with $MgSO_4$. After removal of the solvents in vacuo, a crude (*E*)/(*Z*) mixture of enol ethers was obtained. The crude product was stirred in HCl (1 M, 9 mL) and THF (6 mL) for 8 h and was then diluted with Et_2O (50 mL) and brine (10 mL). The phases were separated, the aqueous phase was washed three times with Et_2O (15 mL), and the combined organic phases were washed with satd. aq. $NaHCO_3$ and brine and dried with $MgSO_4$. Removal of the volatiles in vacuo and purification of the C_1-homologated aldehyde delivered compound **43** (1.7 g, 4.3 mmol, 60%). R_f (hexane/ethyl acetate, 10:1) = 0.6. $[\alpha]_D^{20}$ = –6.7 (*c* = 0.55, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.85 (t, *J* = 1.6 Hz, 1 H), 5.20 (d, *J* = 9.4 Hz, 1 H), 4.07 (d, *J* = 9.4 Hz, 1 H), 2.38 (m, 3 H), 2.22 (m, 2 H), 2.16 (dd, *J* = 14.6, 2.8 Hz, 1 H), 1.65 (s, 3 H), 1.08 (s, 3 H), 0.97 (s, 3 H), 0.87 (s, 9 H), 0.13 (s, 9 H), 0.00 (s, 3 H), –0.05 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.7 (CH), 136.3 (C), 126.7 (CH), 107.1 (C), 85.2 (C), 76.4 (CH), 52.4 (CH_2), 40.6 (C), 38.9 (CH_2), 26.2 (3 × CH_3), 24.7 (CH_3), 24.4 (CH_3), 19.2 (CH_2), 18.4 (C), 17.3 (CH_3), 0.47 (3 × CH_3), –3.6 (CH_3), –4.7 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 2957, 2367, 2174, 1844, 1720, 1560, 1472, 1307, 1250, 1202, 1063, 963, 839, 804, 776 cm^{-1}. HRMS: calcd. for [M – Me]$^+$ 379.2488; found 379.2484.

***tert*-Butyl[(1*S*,2*E*)-1-(1,1-dimethylbut-3-ynyl)-3-methylhept-2-en-6-ynyloxy]dimethylsilane (5):** Dimethyl (1-diazo-2-oxopropyl)phosphonate (0.48 g, 2.3 mmol) in MeOH (5 mL) was added at 0 °C to a solution of the aldehyde **43** (0.75 g, 1.9 mmol) and K_2CO_3 in MeOH (30 mL). After warming to room temp., stirring was continued for 8 h. The reaction mixture was diluted with Et_2O (50 mL), washed with aq. $NaHCO_3$ (10%), and dried with $MgSO_4$. After filtration, the solvents were evaporated under reduced pressure and the residue purified by flash column chromatography (hexane/ethyl acetate, 20:1) to give **5** (0.70 g, 1.8 mmol, 94%) as a colorless oil. R_f (hexane/ethyl acetate, 20:1) = 0.79. $[\alpha]_D^{20}$ = –21.4 (*c* = 2.5, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.17 (d, *J* = 9.4 Hz, 1 H), 4.19 (dd, *J* = 9.4, 2.0 Hz, 1 H), 2.27 (m, 5 H), 2.08 (dt, *J* = 16.5, 2.5 Hz, 1 H), 1.95 (m, 2 H), 1.67 (s, 3 H), 0.92 (s, 3 H), 0.90 (s, 3 H), 0.87, (s, 9 H), 0.024 (s, 3 H), –0.04 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.1 (C), 127.4 (CH), 85.5 (CH), 83.4 (C), 74.6 (CH), 70.1 (C), 69.1 (CH), 39.7 (C), 38.9 (CH_2), 28.8 (CH_2), 26.2 (3 × CH_3), 23.1 (CH_3), 22.3 (CH_3), 18.5 (C), 17.7 (CH_2), 17.1 (CH_3), –3.6 (CH_3), –4.7 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 3312, 2957, 2943, 2929, 2871, 1472, 1384, 1362, 1255, 1113, 1064, 1006, 939, 856, 847, 836 cm^{-1}. HRMS: calcd. for [M – *t*Bu]$^+$ 261.1675; found 261.1679.

1-[(2*R*,4*R*)-2-(4-Methoxyphenyl)-5,5-dimethyl-1,3-dioxan-4-yl]-2-methylallyl Acetate (47): Isopropenylmagnesium bromide (0.5 M in THF, 48.2 mL, 24.1 mmol) was added at 0 °C to a solution of aldehyde **46** (5.5 g, 21.9 mmol) in Et_2O (70 mL). The reaction mixture was allowed to warm to room temp. and stirred at this temperature for 1 h. TLC analysis showed full consumption of the starting material, and the reaction was quenched by the addition of satd. aq. NH_4Cl. The aqueous phase was extracted four times with Et_2O (30 mL), and the combined organic phases were washed with brine and dried with $MgSO_4$. After filtration and concentration, the

crude reaction mixture was purified by column chromatography to give a mixture of diastereomers in a ratio of 4:1. The crude reaction mixture was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C. NEt_3 (12.2 mL, 8.8 mmol) and acetic anhydride (6.1 mL, 6.6 mmol) were added, and the mixture was stirred for 1 h. It was quenched with satd. aq. $NaHCO_3$, and the aqueous phase was extracted four times with CH_2Cl_2 (20 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. After filtration, the volatiles were evaporated under reduced pressure to give a diastereomeric mixture of acetates **47a** and **47b** (5.9 g, 17.5 mmol, 80%). IR (thin film): $\tilde{\nu}$ = 3674 (br.), 2956, 2838, 1734, 1651, 1394, 1369, 1302, 1240, 1171, 1125, 1101, 1081, 1032, 981, 910 cm^{-1}. HRMS: calcd. for $[M]^+$ 334.1780; found 334.1772. **Major Isomer 47a:** R_f (hexane/ethyl acetate, 4:1) = 0.36. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, J = 8.8 Hz, 2 H), 6.89 (d, J = 8.8 Hz, 2 H), 5.48 (d, J = 4.7 Hz, 1 H), 5.42 (s, 1 H), 5.10 (m, 1 H), 4.98 (t, J = 4.6 Hz, 1 H), 3.80 (s, 3 H), 3.69 (d, J = 4.8 Hz, 1 H), 3.63, 3.57 (AB system, J = 10.9 Hz, 2 H), 2.06 (s, 3 H), 1.81 (dd, J = 1.2, 0.8 Hz, 3 H), 1.20 (s, 3 H), 0.87 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (C), 160.2 (C), 142.4 (C), 128.0 (2×CH), 115.7 (C), 115.5 (CH_2), 114.2 (2×CH), 102.1 (CH), 84.4 (CH), 80.2 (CH_2), 75.2 (CH) 55.6 (CH_3), 33.4 (C), 21.9 (CH_3), 21.7 (CH_3), 19.6 (CH_3), 19.2 (CH_3) ppm. **Minor Isomer 47b:** R_f (hexane/ethyl acetate, 4:1) = 0.36. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, J = 8.8 Hz, 2 H), 6.89 (d, J = 8.8 Hz, 2 H), 5.39 (s, 1 H), 5.32 (d, J = 8.6 Hz, 1 H), 5.07 (m, 1 H), 4.97 (t, J = 4.6 Hz, 1 H), 3.79 (s, 3 H), 3.74 (d, J = 4.8 Hz, 1 H), 3.60 (m, 2 H), 2.06 (s, 3 H), 1.79 (m, 3 H), 1.19 (s, 3 H), 0.86 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (C), 160.2 (C), 142.7 (C), 127.6 (2×CH), 115.9 (C), 115.7 (CH_2), 114.2 (2×CH), 101.8 (CH), 84.1 (CH), 79.3 (CH_2), 76.1 (CH), 55.6 (CH_3), 33.0 (C), 21.6 (CH_3), 19.4 (CH_3), 19.3 (CH_3), 19.0 (CH_3) ppm.

(4*E*)-*N*-Methoxy-*N*-methyl-5-[(2*R*,4*S*)-2-(4-Methoxyphenyl)-5,5-dimethyl-1,3-dioxan-4-yl]-4-methylpent-4-enamide (48): A solution of acetates **47a** and **47b** (1.0 g, 3.0 mmol) in THF (15 mL) was added slowly at –78 °C to a solution of lithium diisopropylamide (0.25 M, 35.6 mL, 8.9 mmol). After the mixture had been stirred for 2 h, TMSCl (1.15 mL, 8.9 mmol) was added, and the reaction mixture was allowed to warm slowly to room temp. The reaction was quenched by the addition of satd. aq. NH_4Cl. After phase separation, the aqueous phase was extracted four times with ethyl acetate, and the combined organic phases were washed with brine, dried with $MgSO_4$, and concentrated in vacuo to give a colorless semisolid product, which was purified by flash column chromatography (hexane/ethyl acetate, 4:1→1:1) to yield the desired acid (2.10 g, 6.1 mmol, 69%). R_f (hexane/ethyl acetate, 2:1) = 0.20. $[\alpha]_D^{20}$ = –30.0 (c = 0.20, CH_2Cl_2). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.43 (d, J = 9.5 Hz, 2 H), 6.87 (d, J = 9.5 Hz, 2 H), 5.49 (s, 1 H), 5.29 (dd, J = 8.8, 1.2 Hz, 1 H), 4.27 (d, J = 8.8 Hz, 1 H), 3.79 (s, 3 H), 3.77, 3.65 (AB system, J = 11.2 Hz, 2 H), 2.51 (m, 2 H), 2.39 (m, 2 H), 1.75 (d, J = 1.2 Hz, 3 H), 1.17 (s, 3 H), 0.69 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 178.0 (C), 160.1 (C), 138.9 (C), 131.5 (C), 128.0 (2×CH), 122.4 (CH), 114.0 (2×CH), 102.3 (CH), 81.9 (CH), 79.3 (CH_2), 55.7 (CH_3), 34.9 (CH_2), 34.2 (C), 32.7 (CH_2), 21.8 (CH_3), 19.3 (CH_3), 17.6 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 2924, 2853, 1717, 1699, 1695, 1683, 1652, 1615, 1517, 1456, 1248, 1092, 1035 cm^{-1}. HRMS: calcd. for $[M]^+$ 334.1780; found 334.1175. Diisopropyl carbodiimide (0.87 mL, 56.0 mmol) was added at 0 °C to a solution of the acid obtained above (1.7 g, 5.1 mmol), NEt_3 (0.85 mL, 61.0 mmol), MeHNOMe·HCl (0.59 g, 61.0 mmol), and DMAP (cat.) in CH_2Cl_2 (30 mL). The reaction mixture was allowed to warm to room temp. and stirred overnight. It was quenched by the addition of satd. aq. NH_4Cl and diluted with CH_2Cl_2 (30 mL), and the phases were separated. The aqueous phase was extracted three times with CH_2Cl_2, and the combined organic phases were washed with brine and dried with $MgSO_4$. After filtration and concentration in vacuo, purification by column chromatography delivered Weinreb amide **48** (1.9 g, 5.0 mmol, 98%). $[\alpha]_D^{20}$ = –44.8 (c = 0.25, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, J = 8.7 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 5.49 (s, 1 H), 5.27 (dd, J = 8.8, 1.2 Hz, 1 H), 4.28 (d, J = 8.8 Hz, 1 H), 3.79 (s, 3 H), 3.76, 3.65 (AB system, J = 11.2 Hz, 2 H), 3.69 (s, 3 H), 3.17 (s, 3 H), 2.58 (m, 2 H), 2.38 (t, J = 7.7 Hz, 2 H), 1.76 (d, J = 1.2 Hz, 3 H), 1.17 (s, 3 H), 0.71 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5 (C), 160.3 (C), 139.9 (C), 131.6 (C), 127.9 (2×CH), 121.6 (CH), 114.0 (2×CH), 102.3 (CH), 82.0 (CH), 79.3 (CH_2), 61.6 (CH_3), 55.6 (CH_3), 34.7 (CH_2), 34.3 (C), 32.7 (CH_3), 30.7 (CH_2), 21.8 (CH_3), 19.2 (CH_3), 17.9 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 2928, 2854, 1653, 1616, 1517, 1465, 1387, 1248, 1171, 1091, 1032, 985 cm^{-1}. HRMS: calcd. for $[M]^+$ 377.2202; found 377.2192.

(2*R*,4*S*)-2-(4-Methoxyphenyl)-5,5-dimethyl-4-[(1*E*)-2-methylhex-1-en-5-ynyl]-1,3-dioxane (49): DIBAl-H (1.5 M in toluene, 4.7 mL, 7.1 mmol) was added dropwise at –78 °C to a solution of Weinreb amide **48** (1.3 g, 3.5 mmol) in THF (30 mL). The reaction mixture was stirred for 20 min. When TLC analysis indicated full consumption of the starting material, the reaction was quenched by addition of satd. aq. $NaHCO_3$ and potassium sodium tartrate, and the mixture was stirred at room temp. for 3 h. It was then diluted with Et_2O (30 mL), and the phases were separated. The aqueous phase was extracted four times with Et_2O (20 mL), and the combined organic phases were washed with brine and dried with $MgSO_4$. The solvents were removed from the reaction mixture in vacuo. $TMSCHN_2$ (2 M in Et_2O, 2.0 mL, 4.0 mmol) in THF (20 mL) was cooled to –78 °C, and *n*BuLi (2.5 M, 2.0 mL, 4.9 mmol) was added. After the reaction mixture had been stirred for 1 h, the crude aldehyde obtained above, dissolved in THF (5 mL), was added, and the mixture was stirred at –78 °C for 4 h and allowed to warm to room temp. overnight. After the addition of satd. aq. NH_4Cl (30 mL), the reaction mixture was diluted with Et_2O (30 mL), and the phases were separated. The aqueous phase was extracted with three portions of Et_2O (20 mL) and the combined organic solvents were washed with brine. After drying with $MgSO_4$, filtration, and removal of the volatiles in vacuo, the crude product was purified by column chromatography (hexane/ethyl acetate, 20:1) to give **49** as a clear oil (2.3 mmol, 0.72 g, 67%). R_f (hexane/ethyl acetate, 20:1) = 0.6. $[\alpha]_D^{20}$ = –49.4 (c = 0.30, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 5.50 (s, 1 H), 5.32 (dd, J = 8.9, 1.1 Hz, 1 H), 4.29 (d, J = 8.8 Hz, 1 H), 3.79 (s, 3 H), 3.78, 3.66 (AB system, J = 11.1 Hz, 2 H), 2.35 (m, 2 H), 2.37 (m, 2 H), 1.95 (t, J = 2.6 Hz, 1 H), 1.74 (d, J = 1.28 Hz, 3 H), 1.20 (s, 3 H), 0.73 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3 (C), 138.7 (C), 131.6 (C), 128.0 (2×CH), 125.9 (CH), 122.9 (2×CH), 102.3 (CH), 84.3 (C), 82.0 (CH), 79.3 (CH_2), 69.2 (CH), 55.7 (CH_3), 38.9 (CH_2), 34.3 (C), 21.8 (CH_3), 19.3 (CH_3), 17.6 (CH_3), 17.4 (CH_2) ppm. IR (thin film): $\tilde{\nu}$ = 2924, 1614, 1517, 1388, 1245, 1091, 1029, 868, 828 cm^{-1}. HRMS: calcd. for $[M]^+$ 314.1882; found 314.1875.

(5*E*,7*S*)-7,9-Bis(*tert*-butyldimethylsilyloxy)-5,8,8-trimethyl-1-(trimethylsilyl)non-5-en-1-yne (50): Acetal **49** (200 mg, 0.64 mmol) in THF (2 mL) was added slowly at –78 °C to a solution of lithium diisopropylamide (1 M, 1.91 mL, 1.91 mmol). After the mixture had been stirred for 1 h, TMSCl (0.24 mL, 1.91 mmol) was added, and the mixture was allowed to warm to room temp. over 16 h. It was quenched by the addition of satd. aq. NH_4Cl and diluted with EtOAc (10 mL), and the phases were subsequently separated. The

aqueous phase was extracted five times with EtOAc (5 mL), and the combined organic phases were washed with brine and dried with $MgSO_4$. After filtration and removal of the organic solvents in vacuo, the product was purified by column chromatography (hexane/ethyl acetate, 20:1) to give the TMS-protected acetylene (0.53 g, 1.65 mmol, 95%) as a colorless oil. R_f (hexane/ethyl acetate, 20:1) = 0.7. $[\alpha]_D^{20}$ = –27.8 (*c* = 0.65, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 5.50 (s, 1 H), 5.32 (dd, *J* = 8.9, 1.1 Hz, 1 H), 4.29 (d, *J* = 8.8 Hz, 1 H), 3.79 (s, 3 H), 3.78, 3.66 (AB system, *J* = 11.1 Hz, 2 H), 2.35 (m, 2 H), 2.37 (m, 2 H), 1.74 (d, *J* = 1.3 Hz, 3 H), 1.20 (s, 3 H), 0.73 (s, 3 H), 0.13 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3 (C), 138.7 (C), 131.6 (C), 128.0 (2 × CH), 125.9 (CH), 122.9 (2 × CH), 107.0 (C), 102.3 (CH), 84.3 (C), 82.0 (CH), 79.3 (CH_2), 55.7 (CH_3), 38.9 (CH_2), 34.3 (C), 21.8 (CH_3), 19.3 (CH_3), 17.6 (CH_3), 17.4 (CH_2), 0.5 (3 × CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 2957, 1682, 1615, 1519, 1249, 1091, 1040, 841 cm^{-1}. HRMS: calcd. for $[M]^+$ 386.2277; found 386.2285. The product obtained above (0.53 g, 1.7 mmol) was dissolved in THF/CH_3CN (1:1, 6 mL) and cooled to 0 °C. Acetic acid (80%, 9 mL) was then added, and the ice bath was removed. After the mixture had been stirred at room temp. for 24 h, TLC analysis showed full consumption of the starting material. The reaction was quenched by the addition of satd. aq. $NaHCO_3$, and THF was removed in vacuo. After addition of CH_2Cl_2 (20 mL) and H_2O (5 mL), the reaction mixture was filtered through a pad of Celite, the phases were separated, and the aqueous phase was extracted four times with CH_2Cl_2 (6 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, and filtered. The removal of the organic solvents from the reaction mixture in vacuo delivered a yellow oil, which was used without further purification. TBSOTf (0.66 g, 0.57 mL, 2.5 mmol) was added dropwise at 0 °C to the crude product obtained above and 2,6-lutidine (0.54 g, 0.59 mL, 5.0 mmol) in CH_2Cl_2 (50 mL), and the reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched by the addition of satd. aq. $NaHCO_3$. The phases were separated, the organic phase was washed twice with CH_2Cl_2 (10 mL), and the combined organic phases were washed with HCl (2 M) and then with $NaHCO_3$ and dried with $MgSO_4$. Filtration and concentration in vacuo, together with purification by column chromatography, delivered bis(TBS)-protected alcohol **50** (0.74 g, 1.6 mmol, 91%) as a clear oil. R_f (hexane/ethyl acetate, 50:1) = 0.8. $[\alpha]_D^{20}$ = –13.6 (*c* = 0.85, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.19 (d, *J* = 9.6 Hz, 1 H), 4.30 (d, *J* = 9.6 Hz, 1 H), 3.43, 3.21 (AB system, *J* = 9.3 Hz, 2 H), 2.38 (m, 2 H), 2.16 (t, *J* = 7.4 Hz, 2 H), 1.64 (d, *J* = 0.9 Hz, 3 H), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.80 (s, 3 H), 0.74 (s, 3 H), 0.14 (s, 9 H), 0.02 (s, 6 H), 0.00 (s, 3 H), –0.06 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.6 (C), 127.5 (CH), 107.5 (C), 84.9 (C), 72.1 (CH), 69.4 (CH_2), 41.5 (C), 39.0 (CH_2), 26.3 (6 × CH_3), 21.1 (CH_3), 19.6 (CH_3), 19.3 (CH_2), 18.6 (C), 17.2 (CH_3), 17.4 (CH_2), 0.5 (3 × CH_3), –3.5 (CH_3), –4.7 (CH_3), –5.0 (CH_3), –5.1 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 2957, 2930, 2857, 1652, 1471, 1464, 1456, 1360, 1250, 1060, 840 cm^{-1}. HRMS: calcd. for $[M^+ - t\text{Bu}]$ 439.2884; found 439.2880.

(3*S*,4*E*)-3-(*tert*-Butyldimethylsilyloxy)-2,2,5-trimethyl-9-(trimethylsilyl)non-4-en-8-ynal (42): HF·pyridine (70% HF in pyridine, 0.92 mL, 6.50 mmol) was added to a solution of bis(TBS) ether **50** (65 mg, 0.13 mmol) in THF (3 mL), and the solution was stirred at room temp. for 48 h. When TLC analysis showed consumption of the starting material, satd. aq. $NaHCO_3$ was added, the mixture was diluted with Et_2O (10 mL), and the aqueous phase was further extracted four times with Et_2O (5 mL). The combined organic extracts were washed with HCl (2 M, 5 mL), then with $NaHCO_3$ (10 mL), and were finally dried with $MgSO_4$. After filtration, the volatiles were removed from the reaction mixture, and the crude product was purified by column chromatography (hexane/ethyl acetate, 10:1) to give the mono(TBS)-protected alcohol (32 mg, 0.08 mmol, 65%). R_f = 0.4 (hexane/ethyl acetate, 10:1). $[\alpha]_D^{20}$ = –2.0 (*c* = 0.25, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.30 (dd, *J* = 9.5, 1.2 Hz, 1 H), 4.22 (d, *J* = 9.5 Hz, 1 H), 3.67 (dd, *J* = 10.7, 3.8 Hz, 1 H), 3.28 (dd, *J* = 10.7, 6.8 Hz, 1 H), 3.06 (dd, *J* = 6.8, 3.8 Hz, 1 H), 2.36 (m, 2 H), 2.24 (m, 2 H), 1.50 (d, *J* = 1.3 Hz, 3 H), 0.98 (s, 3 H), 0.87 (s, 9 H), 0.77 (s, 3 H), 0.13 (s, 9 H), 0.05 (s, 3 H), 0.00 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0 (C), 126.8 (CH), 107.0 (C), 85.2 (C), 71.3 (CH_2), 72.1 (CH), 40.3 (C), 38.9 (CH_2), 26.1 (3 × CH_3), 22.9 (CH_3), 20.9 (CH_3), 19.2 (CH_2), 18.6 (C), 17.3 (CH_3), 0.47 (3 × CH_3), –3.62 (CH_3), –4.80 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 3465 (br.), 2957, 2857, 2175, 1472, 1249, 1056, 840, 775, 760 cm^{-1}. HRMS: calcd. for $[M^+ - t\text{Bu}]$ 325.2019; found 325.2012. Dess–Martin periodinane (220 mg, 0.52 mmol) was added in one portion to a solution of the alcohol obtained above (100 mg, 0.26 mmol) in CH_2Cl_2 (5 mL). The solution was stirred for 2 h, a mixture of satd. aq. $Na_2S_2O_3$ and $NaHCO_3$ (1:1, 3 mL) was added, and the mixture was stirred until the the organic phase became clear. After phase separation, the aqueous phase was washed three times with CH_2Cl_2. The combined organic phases were washed with brine, dried with $MgSO_4$, and concentrated in vacuo to give a yellow oil, which was purified by flash column chromatography (hexane/ethyl acetate, 10:1), to yield aldehyde **42** (88 mg, 0.24 mmol, 92%). The analytical data obtained for this compound are identical in all respects to those for **42** from the Reformatsky approach described above.

***tert*-Butyldimethyl{(7*S*,7a*S*,7b*R*)-6,6,7b-trimethyl-2,5,6,7,7a,7b-hexahydro-1*H*-cyclobuta[*e*]inden-7-yloxy}silane (7):** $CpCo(CO)_2$ (0.48 g, 2.7 mmol) in predried, degassed toluene (5 mL) and protected from light was added by syringe (syringe pump) over a period of 6 h to a solution of enediyne **5** (0.80 g, 2.1 mmol) in toluene at reflux under irradiation with a halogen reflector lamp (visible light, max. 500 W). After completion of the addition, the solution was irradiated at reflux for another 2 h. When TLC analysis showed the complete disappearance of the enediyne, the crude reaction mixture was cooled to room temp., and the volatiles were removed by vacuum transfer. The brown residue was dissolved in dried, degassed DME (10 mL), and $CuCl_2 \cdot 2H_2O$ (1.00 g, 5.5 mmol) was added. The black solution was stirred at room temp. for 3 h, the mixture was then partitioned between H_2O (30 mL) and hexane (50 mL), and the layers were separated. The aqueous layer was extracted four times with hexane (10 mL), and the combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo to furnish a very air-sensitive yellow oil. This material was eluted through a degassed silica gel column with degassed hexane to give **7** (0.40 g, 0.9 mmol, 40%). R_f (hexane) = 0.7. $[\alpha]_D^{20}$ = –47.3 (*c* = 2.3, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.68 (s, 1 H), 5.54 (s, 1 H), 3.66 (d, *J* = 9.6 Hz, 1 H), 2.90 (ddd, *J* = 19.3, 10.0, 2.0 Hz, 1 H), 2.68 (dm, *J* = 9.6 Hz, 1 H), 2.61 (ddd, *J* = 19.3, 8.3, 3.2 Hz, 1 H), 2.16 (d, *J* = 17.4 Hz, 1 H), 1.95 (d, *J* = 17.4 Hz, 1 H), 1.89 (m, 1 H), 1.86 (m, 1 H), 1.01 (s, 3 H), 1.00 (s, 3 H), 0.83 (s, 3 H), 0.88 (s, 9 H), 0.02 (s, 3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 145.4 (C), 139.5 (C), 116.4 (CH), 112.6 (CH), 80.1 (CH), 54.9 (CH), 43.5 (CH_2), 40.0 (C), 39.6 (C), 33.0 (CH_3), 28.4 (CH_2), 27.2 (CH_2), 26.0 (3 × CH_3), 20.7 (CH_3), 17.9 (C), 15.1 (CH_3), –3.9 (CH_3), –3.8 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 2956, 2942, 2929, 2876, 2858, 1468, 1462, 1366, 1257, 1254, 1129, 1113, 1098, 863, 836 cm^{-1}. HRMS: calcd. for $[M]^+$ 318.2379; found 318.2374.

***tert*-Butyldimethyl{(2a*S*,7*S*,7a*S*,7b*S*)-6,6,7b-trimethyl-2,2a,3,5,6,7,7a,7b-octahydro-1*H*-cyclobuta[*e*]inden-7-yloxy}silane**

(51): Li (0.02 g, excess) was added at –78 °C to a stirred solution of liquid ammonia (ca. 40 mL), dry THF (15 mL), and dry 2-methylpropan-2-ol (10 mL) contained in a 100 mL three-necked round-bottomed flask fitted with a dry ice/acetone condenser and septa. Upon formation of a persistent deep blue color, a solution of diene **7** (0.62 g, 1.94 mmol) in dry THF (5 mL) was introduced by syringe over 1 min. The reaction was quenched after 1 h by treatment with portions of NH_4Cl (0.5 g, excess), the NH_3 was allowed to evaporate overnight, hexane was added, and the solids were removed by filtration. The filtrate was concentrated in vacuo to afford a solid-containing oil, which was purified by column chromatography (hexane/ethyl acetate, 50:1) to give olefin **51** (0.53 g, 1.65 mmol, 85%) as a colorless oil. R_f (hexane) = 0.9. $[\alpha]_D^{20}$ = +10.5 (*c* = 2.2, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.46 (m, 1 H), 3.69 (d, *J* = 9.1 Hz, 1 H), 2.48 (m, 1 H), 2.25 (m, 1 H), 2.02 (m, 5 H), 1.82 (m, 1 H), 1.66 (m, 2 H), 1.01 (s, 3 H), 0.96 (s, 3 H), 0.91 (s, 9 H), 0.90, (s, 3 H), 0.09 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.7 (C), 118.3 (CH), 81.8 (CH), 52.1 (CH), 44.3 (C), 44.4 (CH_2), 41.6 (CH), 41.7 (CH_2), 41.0 (C), 33.9 (CH_2), 29.6 (CH_2), 27.5 (CH_3), 26.3 ($3\times CH_3$), 25.2 (CH_3), 21.1 (C), 23.5 (CH_3), –2.6 (CH_3), –5.1 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 2958, 2871, 2857, 1472, 1463, 1257, 1254, 1250, 1121, 875, 835, 773 cm^{-1}. HRMS: calcd. for $[M]^+$ 320.2535; found 320.2529.

(2a*S*,4a*R*,7*S*,7a*S*,7b*S*)-7-(*tert*-Butyldimethylsilyloxy)-6,6,7b-trimethyldecahydro-cyclobuta[*e*]inden-4-one (52a, *syn*): B_2H_6·THF (1 M in THF, 1.9 mL, 1.9 mmol) was added at 0 °C to a solution of olefin **51** (202 mg, 0.6 mmol) in dry THF (8 mL). After 5 h at room temp., TLC analysis of the reaction mixture indicated no remaining olefin. Aq. K_2CO_3 (1 M, 2.5 mL, 2.5 mmol) and H_2O_2 (30% by wt., 1.1 mL, 10.0 mmol) were added sequentially at 0 °C to the vigorously stirred solution, the flask was then fitted with a reflux condenser, and the biphasic mixture was stirred with heating to 60–65 °C in an oil bath for 3 h. The cooled solution was then diluted with hexane (30 mL), the layers were separated, the aqueous phase was extracted three times with hexane (10 mL), and the combined organic phases were washed with satd. aq. $Na_2S_2O_3$ and then with brine, dried with $MgSO_4$, and filtered, after which the volatiles were evaporated under reduced pressure. The crude product was filtered through a short pad of silica gel, to afford a mixture of inseparable diastereomers as a colorless oil. The product obtained above (166 mg, 0.49 mmol) was dissolved in CH_2Cl_2 (5 mL), and Dess–Martin periodinane (510 mg, 1.20 mmol) was added. After the mixture had been stirred at room temp. for 2 h, TLC reaction monitoring showed complete consumption of the starting material. A mixture of satd. aq. $NaHCO_3$ and $Na_2S_2O_3$ (1:1, 5 mL) was added to the reaction mixture, which was stirred until the biphasic mixture became clear. The phases were then separated, and the aqueous phase was extracted three times with CH_2Cl_2 (3 mL). The combined organic phases were washed with brine, dried, and filtered. The solvent was removed in vacuo, and the product was purified by column chromatography (hexane/ethyl acetate, 10:1) to give an epimeric mixture of ketones **52a** and **52b** (2:1) as a clear oil (156 mg, 0.47 mmol, 74%). R_f (hexane/ethyl acetate, 9:1) = 0.7. IR (thin film): $\tilde{\nu}$ = 2953, 1713, 1472, 1255, 1095, 837, 802, 776, 727 cm^{-1}. HRMS: calcd. for $[M]^+$ 336.2485; found 336.2475. **Epimer 52a:** ^1H NMR (400 MHz, $CDCl_3$): δ = 3.83 (d, *J* = 7.6 Hz, 1 H), 2.99 (m, 1 H), 2.67 (dd, *J* = 11.6, 7.6 Hz, 1 H), 2.65 (dd, *J* = 12.8, 8.8 Hz, 1 H), 2.46 (m, 1 H), 2.26 (m, 1 H), 2.18 (ddd, *J* = 12.8, 4.8, 1.3 Hz, 1 H), 1.94 (m, 1 H), 1.71 (m, 2 H), 1.62 (m, 1 H), 1.40 (m, 1 H), 1.15 (s, 3 H), 1.05 (s, 3 H), 0.92 (s, 3 H), 0.90 (s, 9 H), –0.11 (s, 3 H), –0.072 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.9 (C), 83.5 (CH), 55.7 (CH), 47.7 (CH), 44.4 (CH), 43.44 (C), 42.6 (CH_2), 42.5 (C), 41.1 (CH_2), 32.8 (CH_2), 27.9 (CH_3), 27.3 (CH_3), 26.7 ($3\times CH_3$), 26.4 (CH_3), 24.3 (CH_2), 23.3 (C), –2.0 (CH_3), –3.5 (CH_3) ppm.

Methyl (2a*R*,4a*R*,7*S*,7a*S*,7b*S*)-7-(*tert*-Butyldimethylsilyloxy)-4-hydroxy-6,6,7b-trimethyl-2,2a,4a,5,6,7,7a,7b-octahydro-1*H*-cyclobuta-[*e*]indene-3-carboxylate (53a, *syn*): *n*BuLi (2.5 M in THF, 0.18 mL, 0.46 mmol) was added at 0 °C to a solution of diisopropylamine (47 mg, 0.46 mmol) in THF (5 mL), and the mixture was stirred at this temperature for 30 min. After it had then been cooled to –78 °C, HMPA (82 mg, 0.46 mmol) and a solution of epimeric ketones **52a** and **52b** (140 mg, 0.42 mmol) in THF (2 mL) were slowly added, and the mixture was stirred at –78 °C for 2 h. Dry carbon dioxide (generated from dry ice and passed through concentrated sulfuric acid) was then bubbled into the mixture at –58 °C for 1 h. After addition of aq. HCl (1 M, 0.5 mL), the mixture was quickly warmed to 0 °C with an ice bath. (Trimethylsilyl)diazomethane (2 M in Et_2O, 0.35 mL, 0.7 mmol) was slowly added to the reaction mixture. When TLC showed the acid no longer to be present, the excess of (trimethylsilyl)diazomethane was quenched with additional HCl (1 M), Et_2O was added, and the phases were separated. The aqueous phase was extracted several times with Et_2O, the combined organic phases were washed with satd. aq. $NaHCO_3$ and dried, and the volatiles were evaporated under reduced pressure. Purification by column chromatography delivered an inseparable mixture of β-oxo esters **53a** and **53b** (0.19 mmol, 75 mg, 45%). IR (thin film): $\tilde{\nu}$ = 2953, 2930, 2858, 1653, 1648, 1617, 1457, 1437, 1291, 1249, 1223, 1112, 863 837, 773, 668 cm^{-1}. HRMS: calcd. for $[M]^+$ 394.2539; found 394.2542. **Isomer 53a:** ^1H NMR (400 MHz, $CDCl_3$): δ = 12.29 (s, 1 H), 3.74 (s, 3 H), 3.61 (d, *J* = 7.4 Hz, 1 H), 2.92 (dd, *J* = 14.0, 8.2 Hz, 1 H), 2.65 (m, 1 H), 2.37 (dd, *J* = 10.9, 7.9 Hz, 1 H), 2.26 (m, 1 H), 2.07 (dd, *J* = 8.5, 7.5 Hz, 1 H), 1.88 (m, 1 H), 1.82 (m, 1 H), 1.49 (m, 1 H), 1.41 (m, 1 H), 1.33 (s, 3 H), 0.96 (s, 3 H), 0.91 (s, 3 H), 0.89 (s, 9 H), –0.073 (s, 3 H), –0.064 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7 (C), 173.4 (C), 100.6 (C), 82.3 (CH), 53.6 (CH_3), 51.7 (CH), 43.1 (CH), 42.6 (CH_2), 41.1 (C), 38.4 (C), 34.7 (CH), 32.7 (CH_2), 29.3 (CH_3), 27.3 (CH_2), 27.1 (CH_3), 26.9 (CH_3), 26.8 ($3\times CH_3$), 18.7 (C), –1.6 (CH_3), –3.0 (CH_3) ppm.

Methyl (4a*R*,7*S*,7a*S*,7b*R*)-7-(*tert*-Butyldimethylsilyloxy)-6,6,7b-trimethyl-4-oxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-cyclobuta[*e*]indene-3-carboxylate (54): A solution of β-oxo esters **53a** and **53b** (90 mg, 0.23 mmol) in THF (2 mL) was slowly added at –78 °C to a stirred solution of lithium diisopropylamide (0.25 M in THF, 0.57 mmol, 2.28 mL), and the mixture was allowed to warm to 0 °C. After the solution had been stirred for 45 min, a solution of phenylselenyl chloride (0.25 mmol, 48 mg) in THF (0.5 mL) was added, and the mixture was stirred for another 20 min. Addition of satd. aq. NH_4Cl quenched the mixture, which was diluted with Et_2O, and the aqueous phase was extracted three times with Et_2O. The combined organic phases were washed with brine and dried with $MgSO_4$. After concentration of the crude product in vacuo and filtration through a short pad of silica gel in order to separate the selenides from the excess of phenylselenyl chloride, a mixture of epimers (80 mg, 0.14 mmol, 63%) was obtained as yellow oil and used without further purification. Satd. aq. NH_4Cl (0.25 mL) and aq. H_2O_2 (30% by wt., 1.5 mL) were added at 0 °C to the crude mixture obtained above (20 mg, 0.036 mmol) in CH_2Cl_2 (2 mL). The biphasic mixture was stirred vigorously for 2 h at the same temperature. After dilution with H_2O (1 mL) and CH_2Cl_2 (2 mL), the phases were separated, the aqueous phase was extracted twice with CH_2Cl_2, and the combined organic phases were washed with aq. $Na_2S_2O_3$ (10%) and brine, dried with $MgSO_4$, and concentrated in vacuo. The semisolid product was purified by column chromatography (hexane/ethyl acetate 10:1) to provide only the de-

sired α,β-unsaturated β-keto ester **54** in 72% yield (31 mg, 0.079 mmol). R_f (hexane/ethyl acetate 4:1) = 0.27. $[\alpha]_D^{20}$ = –12.0 (*c* = 0.20, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.79 (d, *J* = 7.0 Hz, 1 H), 3.74 (s, 3 H) 3.32 (ddd~dt, *J* = 18.8, 9.2 Hz, 1 H), 3.19 (ddd, *J* = 18.9, 8.4, 4.0 Hz, 1 H), 3.08 (ddd~dt, *J* = 12.6, 7.4 Hz, 1 H), 2.66 (dd, *J* = 12.6, 7.0 Hz, 1 H), 2.20 (m, 1 H), 2.12 (ddd~dt, *J* = 10.4, 4.0 Hz, 1 H), 1.82 (dd, *J* = 13.0, 7.4 Hz, 1 H), 1.41 (t, *J* = 13.0 Hz, 1 H), 1.26 (s, 3 H), 1.03 (s, 3 H), 0.90 (s, 3 H), 0.89 (s, 9 H), –0.09 (s, 3 H), –0.04 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 197.3 (C), 184.6 (C), 163.4 (C), 123.9 (C), 81.2 (CH), 52.7 (CH), 51.9 (CH_3), 49.4 (CH), 45.6 (C), 43.1 (C), 40.3 (CH_2), 35.1 (CH_2), 30.6 (CH_2), 27.4 (CH_3), 26.2 (3 × CH_3), 23.7 (CH_3), 20.8 (CH_3), 18.4 (C), –3.4 (CH_3), –3.7 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 2927, 2363, 1734, 1561, 1256, 898 cm^{-1}. HRMS: calcd. for $[M]^+$ 392.2383; found 392.2395.

Methyl (4*S*,4a*R*,7*S*,7a*S*,7b*R*)-7-(*tert*-Butyldimethylsilyloxy)-4-hydroxy-6,6,7b-trimethyl-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-cyclobuta-[*e*]indene-3-carboxylate (55): A solution of β-oxo ester **54** (10 mg, 0.025 mmol) in MeOH (2 mL), together with $CeCl_3 \cdot 7H_2O$ (93 mg, 0.25 mmol), was stirred at 0 °C for 30 min. Sodium borohydride (2.8 mg, 0.075 mmol) was then added, and the reaction mixture was stirred at 0 °C for another 15 min. At this point, the reaction was quenched with water and diluted with ethyl acetate. The phases were separated, and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography, with elution with hexane/ethyl acetate (4:1), to yield alcohol **55** (8.9 mg, 0.023 mmol, 90%). R_f = 0.50 (hexane/ethyl acetate, 4:1). $[\alpha]_D^{20}$ = –29.0 (*c* = 0.10, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.28 (d, *J* = 1.4 Hz, 1 H), 4.19 (d, *J* = 8.7 Hz, 1 H), 3.74 (s, 3 H), 3.70 (d, *J* = 8.3 Hz, 1 H), 3.07 (m, 1 H), 2.98 (m, 1 H), 2.33 (m, 1 H), 2.22 (dd, *J* = 13.1, 8.2 Hz, 1 H), 2.03 (dd, *J* = 9.4, 3.0 Hz, 2 H), 1.92 (dd, *J* = 12.4, 7.4 Hz, 1 H), 1.20 (s, 3 H), 1.14 (t, *J* = 12.4 Hz, 1 H), 1.01 (s, 3 H), 0.91 (s, 3 H), 0.88 (s, 9 H), 0.09 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.6 (C), 168.4 (C), 121.8 (C), 82.1 (CH), 71.8 (CH), 52.4 (CH), 51.7 (CH_3), 46.2 (C), 45.5 (CH), 44.6 (CH_2), 42.5 (C), 36.3 (CH_2), 29.6 (CH_2), 27.7 (CH_3), 26.3 (3 × CH_3), 20.8 (CH_3), 20.4 (CH_3), 18.6 (C), –3.2 (CH_3), –3.6 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 2927, 2787, 1694, 1560, 1113, 887, 876, 612 cm^{-1}. HRMS: calcd. for $[M]^+$ 394.2539; found 394.2532.

Pasteurestin B (2): Alcohol **55** (5.9 mg, 0.015 mmol) was dissolved in THF (1 mL) in a polyethylene vessel and the solution was cooled to 0 °C. HF·pyridine complex (70%, 0.07 mL, 0.50 mmol) was added, and the reaction mixture was stirred at room temp. overnight. It was quenched by addition of satd. aq. $NaHCO_3$ (2 mL) and diluted with CH_2Cl_2 (5 mL). The phases were separated, the aqueous phase was extracted three times with CH_2Cl_2 (2 mL), and the combined organic extracts were washed with HCl (2 M, 2 mL) and subsequently with satd. aq. $NaHCO_3$. The organic phase was then dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was then dissolved in THF (1.4 mL). An aliquot was taken from this mixture for mass analysis. H_2O (0.6 mL) was added to the reaction mixture. After the addition of $LiOH \cdot H_2O$ (4 mg, 0.095 mmol), the reaction mixture was stirred overnight. When TLC analysis showed the hydrolysis to be complete, HCl (2 M, 0.5 mL) was added. The reaction mixture was again diluted with CH_2Cl_2 (5 mL), and after phase separation, the aqueous phase was extracted three times with CH_2Cl_2 (2 mL). The organic phases were washed with satd. aq. $NaHCO_3$, dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (hexane/ethyl acetate, 1:1 → 0:1) delivered **2** (2.5 mg, 0.009 mmol, 59%) as a semisolid colorless oil. R_f = 0.10 (ethyl acetate). $[\alpha]_D^{20}$ = –42 (*c* = 0.10, MeOH). ^{1}H NMR (600 MHz, CD_3OD): δ = 4.17 (ddd, *J* = 9.0, 3.2, 2.0 Hz, 1 H, (CO_2H)CC*H*OH), 3.65 (d, *J* = 9.7 Hz, 1 H, C(CH_3)CHC*H*OH), 3.17 (dddd, *J* = 17.3, 8.3, 3.9, 2.0 Hz, 1 H, C(CO_2H)CC*H*H), 3.04 (ddd, *J* = 17.3, 9.4, 3.6 Hz, 1 H, C(CO_2H)CCH*H*), 2.29 (dddd, *J* = 12.6, 10.2, 9.0, 7.7 Hz, 1 H, C(CO_2H)CH(OH)C*H*), 2.21 (dd, *J* = 12.6, 9.7 Hz, 1 H, CH(OH)C*H*CH), 2.07 (ddd, *J* = 19.4, 8.3, 3.6 Hz, 1 H, CCH_3CHHCH_2), 2.05 (ddd, *J* = 19.4, 9.4, 3.9 Hz, 1 H, CCH_3CHHCH_2), 1.87 (dd, *J* = 12.8, 7.7 Hz, 1 H, CH(OH)CHC*H*H), 1.31 (s, 3 H, CHCC*H*$_3$), 1.20 (dd, *J* = 12.8, 10.2 Hz, 1 H, CH(OH)CHCH*H*), 1.06 (s, 3 H, CC*H*$_3$CH$_3$), 0.95 (s, 3 H, CCH_3CH_3) ppm. ^{13}C NMR (150 MHz, CD_3OD): δ = 171.8 (C), 170.3 (C), 123.7 (C), 82.5 (CH), 73.9 (CH), 52.6 (CH), 47.8 (C), 47.3 (CH), 45.2 (CH_2), 43.3 (C), 38.3 (CH_2), 31.2 (CH_2), 28.1 (CH_3), 21.4 (CH_3), 21.0 (CH_3) ppm. IR (thin film): $\tilde{\nu}$ = 3369 (br.), 2930, 2854, 1687, 1651, 1463, 1248, 1036, 895, 862 cm^{-1}. HRMS: calcd. for $[M]^+$ 280.1675; found 280.1679 (methyl ester).

Supporting Information (see footnote on the first page of this article): MIC data for pasteurestin A, pasteurestin B, and *ent*-pasteurestin B, NMR data for compounds **1**, **2**, **4**, **5**, **6a**, **6b**, **7**, **22a**, **23**, **40**, **54**, and **55**.

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