length is taken as the size of the ring formed. Next all possible β- and γ-atoms, out from each α-atom, are identified as the possible reaction strands. At any time the only strand atoms considered are those defined as skeletal for the current iteration level. β-Atoms are those attached to α (but not identical with the other α-atom in the product). γ-Atoms are those attached to each β but not identical with the other α- or any β-atom. All identified atoms are checked to be sure they are present in both substrate and product.

The *h*-, σ-, π-, and *z*-values of the αβγ-atoms in each strand are recorded for both substrate and product, and for those that change in the reaction, the two Δzπ-lists are calculated, one for each active αβγ-strand. These are then identified as characterizing the two half-reactions that make up the construction of the bond (Table II). If there are changes in more than one β- or γ-atom out from an α-atom, the reaction is deleted as unclassifiable. When both strands are successfully characterized as half-reactions, the reaction entry number is recorded in the matrix array of Table IV; also recorded are the identity of the active strands, the σ-, *z*-, and π-values of the αβγ-atoms of each strand, and the ring size for any cyclization.

The same procedure is followed iteratively for each level of skeletal atom identity. Thus, first only carbons are taken as skeletal atoms and N, O, and S are recorded as *z*-values on attached carbons. In the second iteration, nitrogen is also a skeletal atom and O and S atoms are recorded as functionality (*z*-values). An addition to an imine would be recorded as a 21 half-reaction in the first iteration but as a 12 addition with skeletal β-nitrogen in the second pass. The total reaction count is not increased by this duplication, but the reaction can be retrieved either as a carbonyl addition or as an imine addition. There are actually four matrixes created in this way for SYNGEN retrieval use, but only the C–C constructions are illustrated by Table IV.

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Total Synthesis of 9-Dihydroerythronolide B Derivatives and of Erythronolide B

Johann Mulzer,*,† Holger M. Kirstein,†,‡ Jürgen Buschmann,§ Christian Lehmann,§ and Peter Luger§,‖

Contribution from the Institut für Organische Chemie, Takustrasse 3, und Institut für Kristallographie, Takustrasse 6, der Freien Universität Berlin, D-1000 Berlin 33, FRG.
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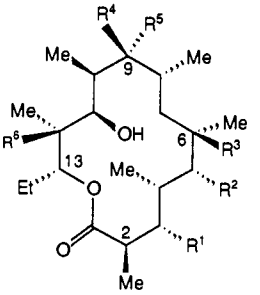
Abstract: A convergent total synthesis (22 steps on the longest linear route) of (−)-erythronolide B (**5**) and two 9-dihydro derivatives (**52** and **54**) thereof from (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**20**) as the only source of chirality is described. A key step of the synthesis is the regio- and stereocontrolled coupling of the allyl sulfide anion **39** and ketone **26**, which can be directed to either α-adduct **40** or **41** by an appropriate choice of the conditions (Scheme V, Table II). From **40** and **41** the seco acids **47** and **49** are prepared, which are smoothly macrolactonized to **50** and **51** according to a modified Yamaguchi procedure. Hydroboration of **50** and **51** proceeds under macrocyclic stereocontrol to afford the 9-dihydroerythronolide B derivatives **52** and **54**, of which **54** is converted into **5** by a known oxidation–deketalization sequence.

The stereocontrolled total synthesis of erythromycin macrolides (**1–6**) has been an evergreen in organic chemistry for more than



1 R^1= L-cladinosyl, R^2= D-desosaminyl, R^3= R^6= OH, R^4=R^5=O
(Erythromycin A)
2 R^1= L-cladinosyl, R^2= D-desosaminyl, R^3= OH, R^4=R^5=O, R^6= H
(Erythromycin B)
3 R^1=R^2=R^3= R^6= OH, R^4=R^5=O
(Erythronolide A)
4 R^1=R^2=R^3=R^4=R^6= OH, R^5= H
(9S-Dihydroxyerythronolide A)
5 R^1=R^2=R^3= OH, R^4=R^5= O, R^6= H
(Erythronolide B)
6 R^1=R^2= OH, R^3=R^6= H, R^4=R^5= O
(6-Deoxyerythronolide B)

one decade.[1] Whereas the diglycoside (erythromycin A, **1**) has been synthesized only once,[2] there are several syntheses of the aglycons erythronolide A (**3**)[3] erythronolide B (**5**)[4] and of 6-deoxyerythronolide B (**6**),[5] Additionally, a number of approaches to advanced synthetic intermediates has been reported, e.g., 9-(*S*)-dihydroerythronolide A (**4**)[6] and various seco acid derivatives

† Institut für Organische Chemie.
‡ Synthetic part of the work.
§ Institut für Kristallographie,
‖ X-ray analysis of compounds **46** and **52**.

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(3) (a) Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. B.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131. (b) Kinoshita, M.; Ohsawa, N.; Gomi, S. *Carbohydr. Res.* **1982**, *109*, 5. (c) Kinoshita, M.; Arai, M.; Tomooka, K.; Nakata, M. *Tetrahedron Lett.* **1986**, *27*, 1811. (d) Kinoshita, M.; Arai, M.; Ohsawa, N.; Nakata, M. *Tetrahedron Lett.* **1986**, *27*, 1815. (e) Kochetkov, N. K.; Sviridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V.; Borodkin, V. S. *Tetrahedron* **1989**, *45*, 5109,

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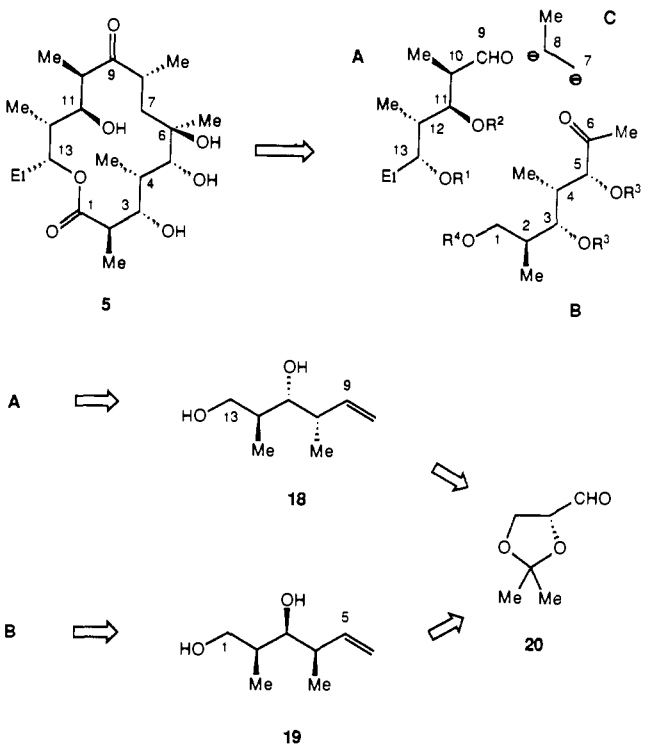
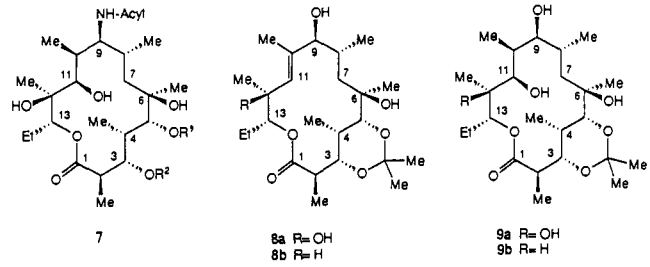
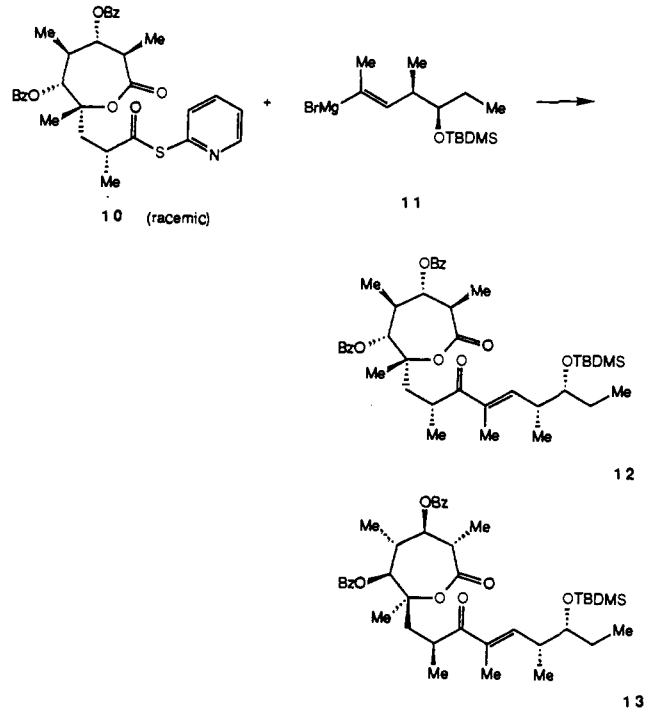
Scheme I. Retrosynthetic Disconnection



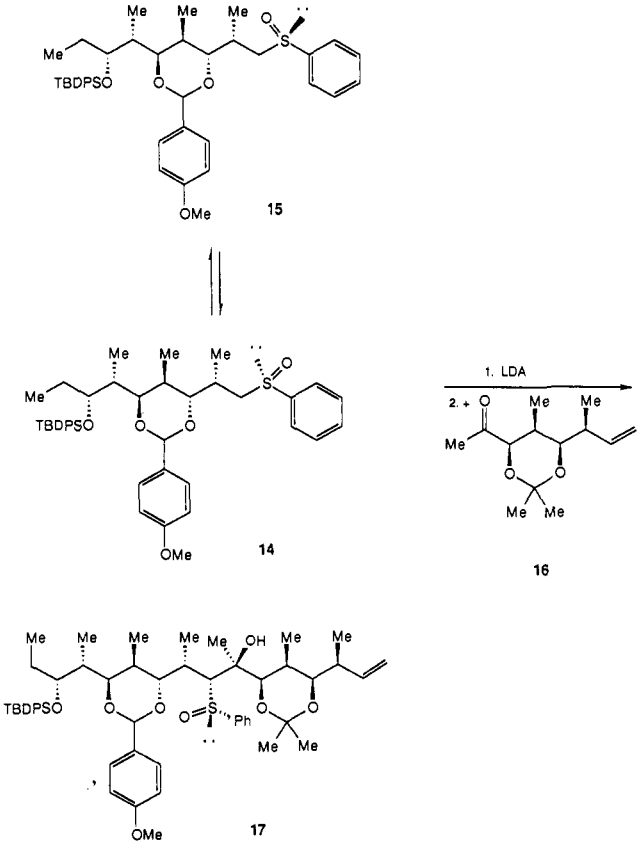
of **4**[7] and **5**.[8] A critical evaluation of the literature suggests that extensive use has been made of the "relay principle"; i.e., the synthetic sequence ended at some advanced intermediate, which was also accessible by degradation of the natural erythromycins on a reversible route ("natural product synthesis by working backward and forward"). In fact, most of the abovementioned syntheses proceed via intermediates like **7–9**, which have been developed in the course of degradation studies of **1** and **5**, respectively.[9]



We concentrated our attention on erythronolide B (**5**), which in contrast to erythronolide A (**3**) is a natural product and a biogenetic precursor on the route to erythromycins B and A.[1d] The syntheses of **5** reported so far,[4] though being landmarks in macrolide chemistry, have serious deficiencies. Both routes critically depend on the C,C coupling of the two halves of the target molecule in the key step. Corey[4a] added the optically active Grignard reagent **11** (obtained by resolution of racemic material)



to racemic thioester **10**. The subsequent separation of the two diastereomers inevitably results in the loss of >50% of the material. Kochetkov[4b] applied the addition of the sulfoxides **14**/**15** to ketone



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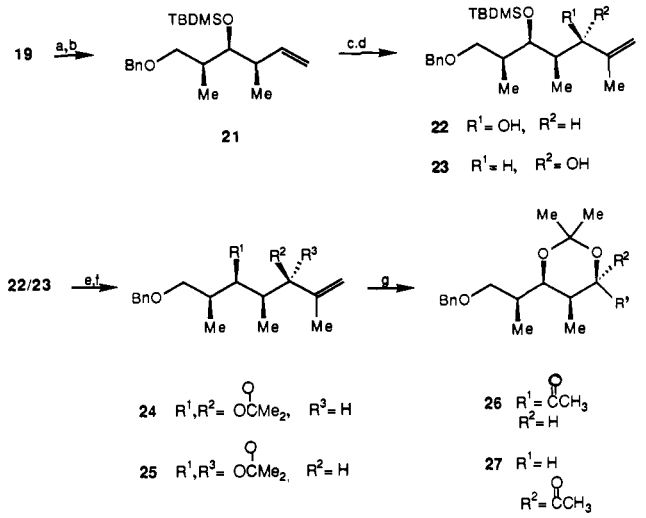
Scheme II. Synthesis of the C1–C6 Fragment (**26**)

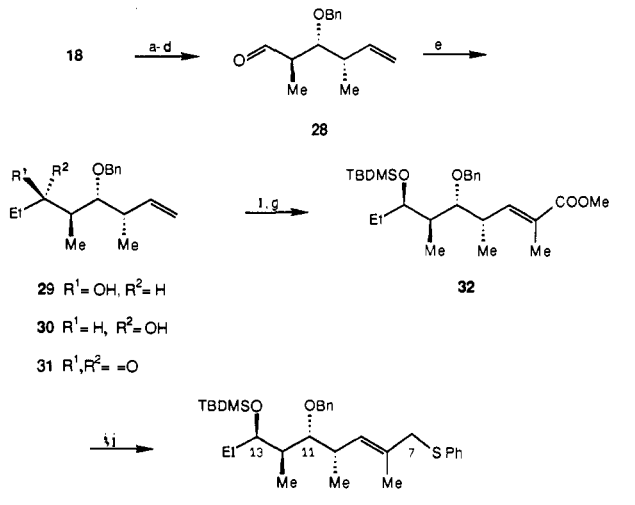


[a] Reagents and Conditions; (a) NaH, BnBr, DMF, −40 °C, (75%); (b) *t*-BuMe$_2$SiCl, imidazole, DMF, 60 °C (98%); (c) O_3, CH_2Cl_2, Ph_3P (88%); (d) $H_2C{=}C(Me)$–MgBr, THF (73%); (e) $(n\text{-}Bu)_4NF$, THF, (95%); (f) DMP, H^+, CH_2Cl_2, (97%); (g) O_3, CH_2Cl_2, Ph_3P; K_2CO_3, MeOH (91%).

16. Of the two S–O diastereomers, only **14** (minor diastereomer) was reactive, so that **15** (major diastereomer) had to be epimerized and recycled. Additionally, in both syntheses the yields of the macrolactonization step were moderate, probably due to unfavorable nonbonding interactions of the O-protective groups.

In view of these considerations, we decided to develop our approach along the following principles. (1) The route should be connective with an efficient coupling of the fragments. These, in turn, should be available on a large scale (20 g and more) from inexpensive chiral starting materials by simple, easy to perform sequences. (2) To demonstrate that our synthesis does not have to resort to relay intermediates but proceeds unidirectionally from educt to product, we intended to prepare not only the natural product, but unnatural derivatives as well, which are not obtainable from degradation processes. The best positions in **5** to make this point clear are C6 (a tertiary alcohol that cannot be inverted) and C9 (which we wanted to be *R* configured in the corresponding carbinol precursor, as the reduction of **5** yields the 9*S* epimer). (3) A lot of recent efforts have been spent to increase the yield of the macrolactonization by optimizing the nature of the O-protective groups.[10] Like Paterson[6c] we realized that any reduction of the number of tetrahedral centers on the ring periphery would facilitate the cyclization, especially in the crucial[11] region around C9. Hence, an 8,9-anhydro seco acid seemed a suitable substrate for macrolactonization. Moreover, the 8,9-olefin moiety could be of advantage in connecting the halves of the molecule. In consequence, we envisaged a retrosynthetic disconnection of **5** between bonds C8–C9 and C7–C6 to generate two fragments A and B, both with terminal carbonyl functions (Scheme I). The carbon skeleton should then be assembled by coupling A and B across a vicinally dianionic two-carbon (C6/C7) synthon C. A and B should, in turn, be elaborated from the stereotriads[12] **18**/**19**, for which efficient routes have been developed starting from (*R*)-2,3-*O*-isopropylideneglyceraldehyde[13] (**20**), which was to be the only source of chirality in our synthesis; no other chiral auxiliaries or catalysts should be used. At that time it remained to be figured out what the nature of synthon C should be, especially with respect to the desired formation of an 8,9-olefinic bond in the coupling product. The presence of the methyl branching in C excluded the straightforward application of some acetylenic derivative.

Scheme III. Synthesis of the C7–C13 Fragment (**33**)

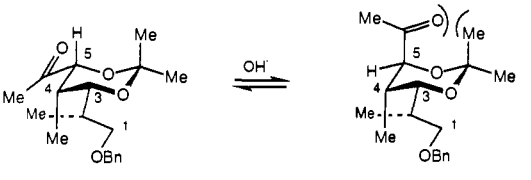


[a] Reagents and conditions: (a) TrCl, pyr, DMAP (95%); (b) NaH, BnBr, DMF (98%); (c) HCOOH, ether; KOH, MeOH (96%); (d) $(COCl)_2$, DMSO, CH_2Cl_2; $(Et)_3N$ (86%); (e) EtMgBr, ether (81%); (f) *t*-BuMe$_2$SiCl, imidazole, DMF (97%); (g) O_3, CH_2Cl_2, Ph_3P (86%); (h) Ph_3P–C(Me)COOMe, THF (95%); (i) DIBAL, toluene, −10 °C (95%); (j) *n*-Bu_3P, $(PhS)_2$, pyr (98%).

Table I. Reduction of Ketone **31** to the Alcohols **29** and **30**

reducing agent	ratio **29**/**30**	yield, %
L-Selectride	1:1	86
$Zn(BH_4)_4$	1:3.5	81
Red Al	1:1	82
$NaBH_4$	1:7	89
LAH	1:6	91
DIBAL	1:2	87

Preparation of the C1–C6 Fragment (Scheme II). **19** was monobenzylated at the primary position and the secondary hydroxyl group was then silylated to give **21**, which was ozonized to the aldehyde and then treated with isopropenylmagnesium bromide. The stereochemical course of this addition depended on the nature of the protective group at the 3-OH position. Thus, a 5:1 ratio of **22** to **23** was obtained from **21**, whereas the corresponding 3-OBn derivative gave a 2:1 mixture of the diastereomeric Grignard adducts. The silyl group obviously suppresses[14] a 1,3 chelated mechanism, which would induce the formation of the 1,3-anti diol.[15] Instead, the reaction follows the Felkin–Anh pathway[16] to give the 1,3-syn diastereomer **22** preferentially. To improve the syn selectivity even further, we resorted to a trick originally introduced by Stork and Paterson in their synthesis of **4**.[6a] Thus, the **22**/**23** mixture was converted to the acetonides **24**/**25**, which were oxidized to the ketones **26**/**27**. Due to the



26 **27**

chair conformation of the acetonide ring (which was confirmed later on, vide infra), **27** suffers from an unfavorable 1,3 diaxial interaction. Therefore, deprotonation and reprotonation at C5 with mild base leads to an equilibrium mixture in which **26** strongly predominates (ratio of **26**:**27** (HPLC analysis) = 94:6),

(10) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7.
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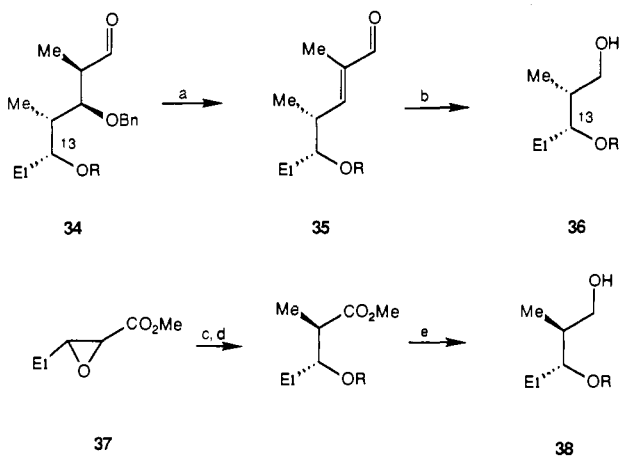
(15) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

Scheme IV. Configurational Assignment of C13 by Chemical Correlation (R = Me_2-*t*-BuSi)

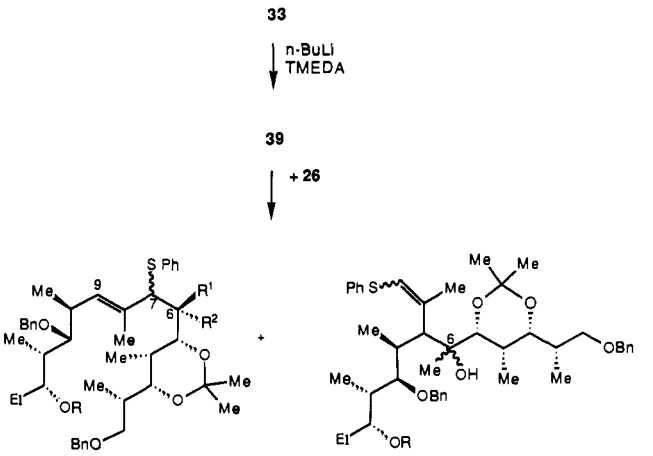


[a] Reagents and conditions: (a) LDA, THF, −20 °C (46%); (b) O_3/$NaBH_4$, MeOH (91%); (c) ref 23; (d) *t*-$BuMe_2SiCl$, imidazole, DMF (98%); (e) DIBAL, toluene, (96%).

In conclusion, fragment B in form of ketone **26** was prepared from **19** with almost complete stereoselectivity in an overall yield of 35% over seven steps in ~20 g/sequence.

Preparation of the C7–C13 Fragment (Scheme III). Diol **18** was converted into the 13-aldehyde **28** via a conventional protection–deprotection sequence and subsequent Swern oxidation. Addition of ethylmagnesium bromide to **28** proceeded with moderate selectivity and furnished **29**/**30** in a ratio of 3:1. All attempts to improve the stereocontrol, e.g., by using titanium reagents,[17] led to poor yields and even lower selectivity. A change of the O-protective group at C11 from benzyl to the more chelating MOM moiety resulted in extensive epimerization of aldehyde **28**. Consequently, **29**/**30** were separated by gravity column chromatography or by large-scale HPLC (2 g/injection). The undesired epimer **30** was recycled by Swern oxidation[18] to the ketone **31** and subsequent reduction with a variety of hydride-transfer reagents. Remarkably, the selectivity was always in favor of the 1,3-syn diol **30** (Table I), quite in analogy to earlier reports.[19] However, the use of L-Selectride, though producing only a 1:1 ratio of **29**/**30**, proved quite satisfactory, because after one cycle approximately 90% of the original mixture of **29**/**30** had been transformed into pure 13*R* alcohol **29**. In a different approach, aldehyde **28** was treated with Corey's sulfoxonium ylide to convert it into the epoxide, which should be opened with a methyl cuprate reagent to give **29**.[20] This experiment failed completely, as the ylide caused total decomposition of **28**. Nevertheless, multigram quantitites of **29** were easily procured by the route described above, and we could turn to the problem of attaching synthon C. After conversion of **30** into the TBDMS ether, the double bond was ozonized and the resulting aldehyde was submitted to an *E*-selective (>95%) Wittig condensation to furnish the ester **32**. Reduction with DIBAL and exchange of the OH function for a thiophenoxide group gave the allyl sulfide **33**. As such sulfides are known[21] to undergo clean deprotonation with strong base, we have, in effect, introduced synthon C in form of the Wittig phosphorane and subsequent "umpolung" of C7. In conclusion, **33** (fragment A in Scheme I) is available from **18** in 40% overall yield. Despite the recycling operation at the stage of **29**/**30** 20-g quantities of **33** may be conveniently prepared within 2 weeks' time.

Scheme V[a]



[a] Conditions: (A) *n*-BuLi, *n*-hexane, TMEDA, addition of **33** in THF at −78 °C, then addition of **26** at −40 °C. (B) *n*-BuLi, *n*-hexane, TMEDA, addition of **33** in THF at −78 °C, then HMPA + THF, −40 °C, 40 min, then addition of **26** in THF at −78 °C. (C) As in A, but **26** treated with BF_3·Et_2O (5 equiv) in THF at −78 °C and then added to **39**.

Table II. Product Distribution of **40**–**42** under Conditions A–C

condition	product ratio, %			total yield, %
	40	**41**	**42**	
A	6	34	60	90
B	86	14	<1	96
C	12	88	<1	93

Configurational Assignment of C13 (Scheme IV). Although we hoped to obtain some crystalline intermediate, suitable for X-ray analysis (which indeed came true later on), it was deciced for safety's sake to secure the configuration of C13 at this stage of the synthesis. Thus, aldehyde **34**, obtained from the ozonolysis of O-silylated **29**, was treated with LDA to give **35**, which was degraded to the known[22] diol derivative **36**. The reported[22] ^1H NMR data of **36**, although in accordance with those of our material, did not allow an unambiguous assignment of the relative configuration at C12/C13. We therefore prepared the "wrong" stereoisomer **38** from epoxy ester **37** on a stereodefined route[23] and found that **38** and **36** were clearly different with respect to their ^1H and ^{13}C NMR spectra.

Coupling of the Segments 26 and 33 (Scheme V). Having established efficient and reliable routes to both fragments **26** and **33** in sufficient quantities, we turned to the coupling process, which was envisaged as an addition of the anion **39** to the ketone **26**. Two problems had to be faced in this reaction: (1) a regioproblem resulting from the allylic delocalization of the negative charge in **33** and, hence, the potential formation of α- and γ-adducts, respectively;[21] (2) a stereoproblem with respect to C6, referring to the possibility of chelated and nonchelated mechanisms.[15] Only the chelated process would afford the "natural" configuration, and due to the tertiary substitution at C6, no easy way of correcting the configuration later on could be imagined. In keeping with our original intentions, we wanted an efficient access to both *R* and *S* configurations at C6.

After extensive experimentation, a set of conditions (A–C) was worked out offering regio- and stereoselection in form of various options (Table II). From the beginning we were limited by the fact that clean deprotonation of **33** with commercially available *n*-butyllithium (1.6 M in hexane) could only be achieved after adding THF and TMEDA. In this solvent system the γ-adduct **42** (generated as a mixture of two diastereomers **42a**/**b**, easily

(16) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.
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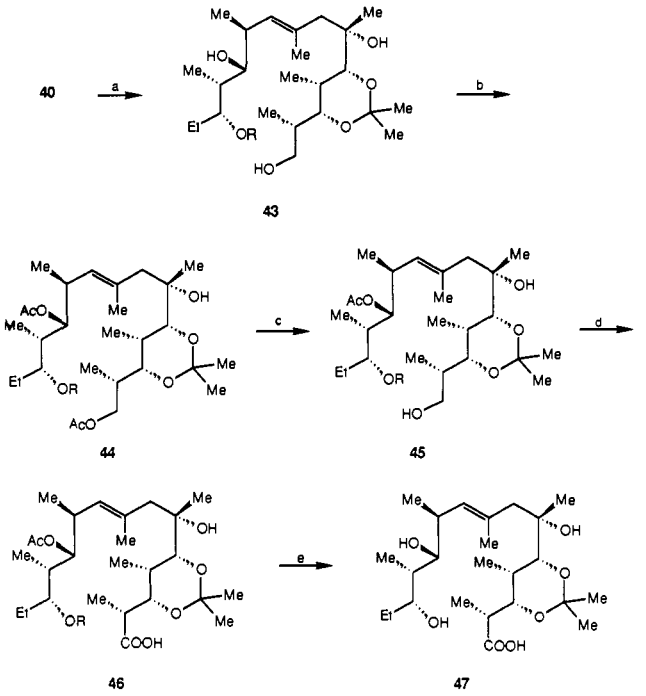
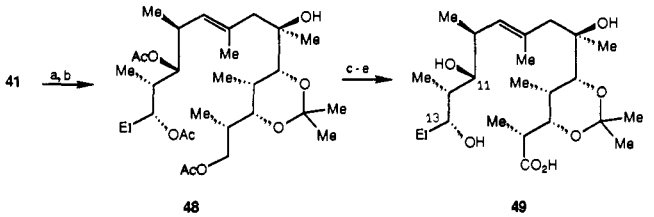
(23) Mulzer, J.; Lammer, O. *Chem. Ber.* **1986**, *119*, 2178.

Scheme VI[a]



[a] Reagents and conditions: (a) Li/EtNH$_2$, THF, 0 °C, (70%); (b) Ac$_2$O, pyr, DMAP (98%); (c) KO-*t*-Bu, THF (90%); (d) PDC, DMF, H$_2$O (85%); (e) *n*-Bu$_4$NF, THF, Δ (75%). R = TBDMS.

Scheme VII[a]

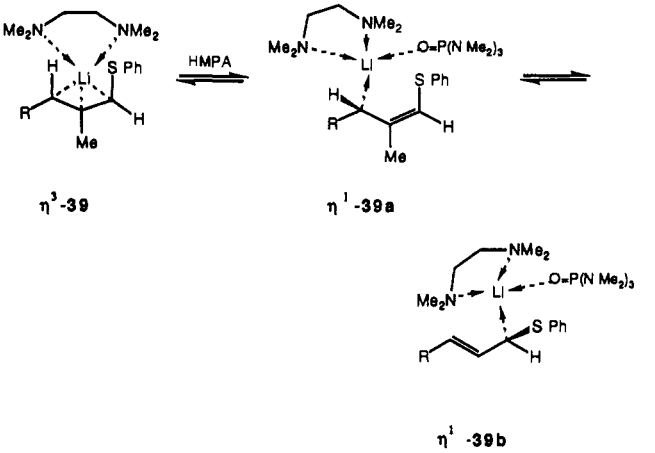


[a] Reagents and conditions: (a) Li/EtNH$_2$, THF, (71%); (b) Ac$_2$O, pyr, DMAP (93%); (c) KO-*t*-Bu, THF (92%); (d) PDC, DMF, H$_2$O (80%); (e) NaOH/MeOH (89%).

separable by chromatography) was the main product (conditions A). However, by addition of 5 equiv of HMPA to the hexane/THF/TMEDA solution of **39**, the formation of **42** could be suppressed almost completely, and the α-adduct **40** was now the major product (conditions B). The reaction medium leading to α-addition obviously induced an ion-pair separating effect on **39**. For the stereochemical outcome, this had the consequence that a chelate-controlled mechanism was unlikely. In fact, under conditions B the "unnatural" derivative **40** was generated selectively. In desperate efforts to force the addition mechanism over to a "chelated" pathway even in the presence of HMPA and TMEDA, a variety of complexing agents like MgBr$_2$, TiCl$_4$, etc. were tried. All attempts were in vain; either the addition led to the unnatural product **40** as before, but proceeded with a significantly lower yield, or the material was completely decomposed by the strong Lewis acid. Finally BF$_3$·Et$_2$O was used, for precomplexing ketone **26** before adding it to the solution of **39** (conditions C). Surprisingly, adduct **41** was now formed with good selectivity! With respect to C7, no stereocontrol was observed under conditions A–C, and the α-adducts were obtained as diastereomeric mixtures (**40a/b** and **41a/b**) at C7. This was without any consequence to the success of the synthesis, because the sulfur was removed in the next step anyhow, so that the mixtures of **40a/b** and **41a/b** could be used. For the sake of analytical characterization, however, all stereoisomers were separated by flash chromatography. The product distribution was kinetically controlled under conditions A–C; this was demonstrated by submitting the pure isomer **40a** to these conditions and reisolating it unchanged.

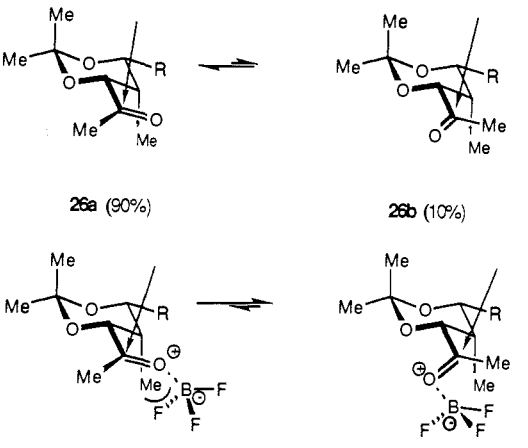
To get clean coupling products it was advisable to stop the reaction after ~50% conversion of the starting materials **26** and **33**, which could easily be recycled after workup. In this manner, the coupling reaction was performed in an effective yield of >80% over two cycles, leading to gram quantities of **40** and **41**, respectively.

Mechanistic Rationalizations. An interpretation of the regiochemical phenomena may be based on the crystal structure of a simpler lithiated allyl sulfide.[24] It was found that the allyl anion binds the lithium cation in form of a η^3-complex, which shows no significant preference toward α- or γ-addition.[25] Thus, **39** may be assumed to exist as η^3-**39** under conditions A. The effect



of the HMPA could then induce a change to the η^1-isomer (η^1-**39**) because the HMPA oxygen acts as an additional donor to the lithium. η^1-**39a** may be expected to be energetically preferred over η^1-**39b** due to vinyl sulfide conjugation, so that under conditions B and C **26** reacts with η^1-**39a** to form the α-adduct.

The stereochemical argumentation rests on the premise that **26** adopts a chair conformation with an axial 4-methyl substituent. This assumption appears justified as the NMR coupling constant of 4-H/5-H in **26** is 2,5 Hz, indicating a syn arrangement of these



hydrogens; additionally, the crystal structures of **46** and **52** both show cyclohexane chair conformations of the 3,5-acetonide ring with an axially located 4-Me group. (Figures 1 and 4). Thus, the bottom face of **26** is shielded by the axial substituent and the nucleophilic attack at the 6-CO function occurs from the top face only, which appears favorable in view of the antiperiplanar effect of the endocyclic C3–O bond. In the absence of chelate-forming reagents a Felkin–Anh-type mechanism[16] may be expected, proceeding via the reactive conformers **26a** and **b**, respectively. **26a** is sterically favored, so that **40** is formed as the major adduct.

The complexation with BF$_3$ (conditions C) will occur at the

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(25) Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277.

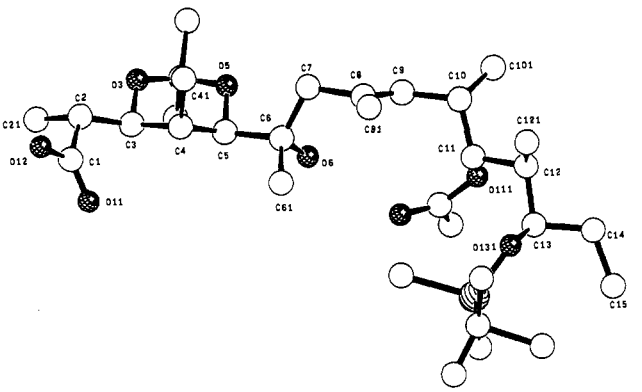


Figure 1. Crystal structure of seco acid **46**.

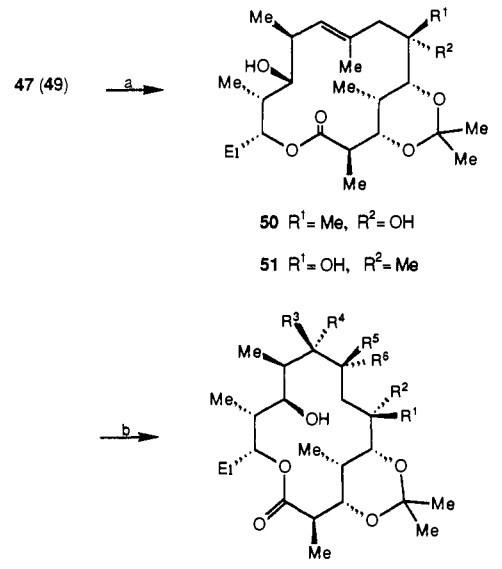
endocyclic oxygens and, to a minor extent, at the carbonyl oxygen, generating species **26c** and **d**. By the BF_3 ligand the effective size of the carbonyl oxygen is significantly enhanced, almost irrespective of the syn–anti geometry of the boron–oxygen complex.[26] This leads to repulsive interactions with the 4-methyl group. The conformational equilibrium will be shifted toward **26c** and enforce the formation of **41**. Gratifyingly the BF_3 addition did not change the α-regioselectivity of the overall reaction.

Synthesis of the Seco Acids 33/35 (Schemes VI and VII). The reduction of **40** with lithium in ethylamine led to desulfuration of the 7-position and to hydrogenolysis of the benzyl ethers at C1 and C11, so that triol **43** was formed in one step. Remarkably, no scrambling of the double bond from the 8,9- into the 7,8-position was observed, although allylic radicals or anions have to be assumed as intermediates in the desulfuration.[27] To differentiate between the primary and the secondary hydroxyl function, **43** was first diacetylated to give **44** and then monodeacetylated to form **45** with high (>95%) chemoselectivity. Oxidation with PDC in DMF in the presence of a small amount of water delivered the crystalline carboxylic acid **46**. Treatment with tetrabutylammonium fluoride not only removed the TBDMS group from O13, as expected, but also the acetate from O11, thus generating the 6,11,13-trihydroxy seco acid **47** in 40% overall yield from **40**. To secure the relative configurations at the newly created stereocenters C5, C6 and C13, along with the geometry of the 8,9 double bond, **46** was submitted to a X-ray analysis (Figure 1).

For the preparation of seco acid **49** (Scheme VII), the same sequence of operations was applied to **41**. In this case, the reduction with lithium immediately generated the tetrol, which was acetylated to **48**. Selective deblocking of the 1-OH group, oxidation, and deacetylation led to the seco acid **49** in 40% overall yield from **41**.

Macrolactonization/Hydroboration (Scheme VIII). In many macrolide syntheses so far, macrolactonization has been a particularly crucial step, requiring carefully selected reagents and elaborated conditions.[28] In our hands, as in some related cases,[28] Yamaguchi's protocol[29] proved extremely successful, converting both seco acids **47** and **49** into the macrolides **50** and **51**, respectively, in >85% isolated yields. Other lactonization methods, e.g., Corey's thiopyridyl activation,[30] failed completely, even under silver ion catalysis.[31] The exclusive formation of the 14-membered macrolides was clearly indicated by the multiplicity of the ^1H NMR signal of the deshielded (i.e., lactonized) C*H*O protons, which appear at 5.24 (**50**) and 5.28 ppm (**51**), respectively, as characteristic ddd multiplets. We were surprised at the extraordinarily smooth lactonization and also at the fact that absolutely no 12-membered lactone was formed, despite the presence

Scheme VIII[a]



50 R^1 = Me, R^2 = OH

51 R^1 = OH, R^2 = Me

	R^1	R^2	R^3	R^4	R^5	R^6
52	Me	OH	H	OH	H	Me
53	Me	OH	H	OH	Me	H
54	OH	Me	H	OH	H	Me
55	OH	Me	OH	H	Me	H

[a] Reagents and conditions: (a) 2,4,6-trichlorbenzoyl chloride, Et_3N, pyr, added after filtration as a 10^{-3} M solution in toluene to DMAP (30 equiv) in refluxing toluene over 5 h (89%); (b) $BH_3 \cdot Me_2S$ in THF, 0 °C, then $NaOH/H_2O_2$ (77%).

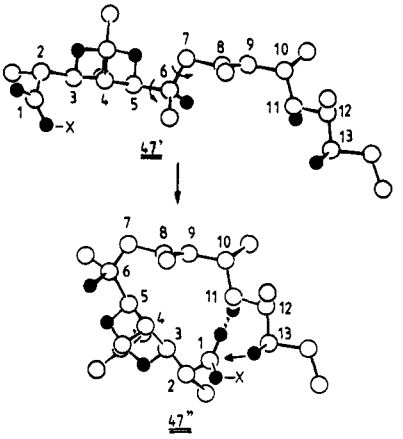


Figure 2. Hypothetical rotations of the activated species **47′** (X = 2,4,6-trichlorobenzoyl) to a prering conformer **47″** (empty circles, carbon; filled circles, oxygen).

of an unprotected 11-OH function. Obviously some favorable conformational effects had come to our assistance. To analyze the conformational situation in the activated species **47′** (Figure 2), we took the crystal structure of **46** as a model (Figure 1). **46** (and hence **47′**) can be dissected into three conformationally relatively rigid subsections; (i) the C1–C6 segment, in which the acetonide chair with its 1,3 diequatorial substitution pattern induces a roughly linear geometry of the carbon skeleton; (ii) the C7–C10 segment, which reveals an approximately perpendicular arrangement of the C6/C7 and C10/C11 bonds on the plane of the 8,9-olefin (dihedral angles; C6–C7–C8–C9 91°, and C8–C9–C10–C11 82°). This may be expected on the basis of the well-known preference of allylic hydrogens to adopt an ecliptic position with the olefinic bond. In the case of the C10/C11 bond an allylic 1,3-strain effect[32] may also be important. As a result, the molecule adopts a bent conformation well suited for a cy-

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(30) Corey, E. J.; Brunelle, D. J. *Tetrahedron Lett.* **1976**, 3409.
(31) Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1974**, *57*, 2661.

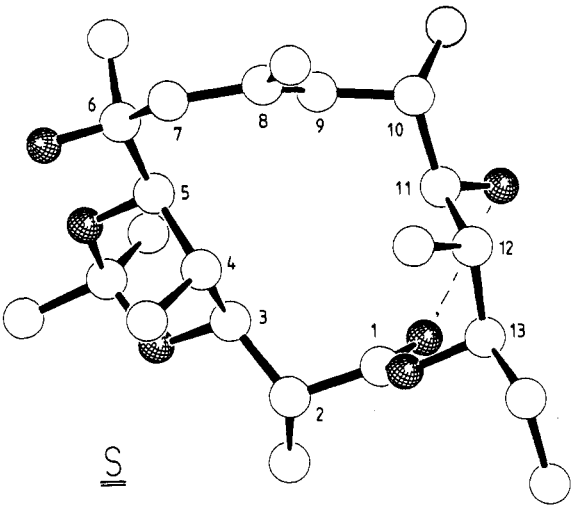


Figure 3. Calculated gobal minimum energy conformation of **50**.

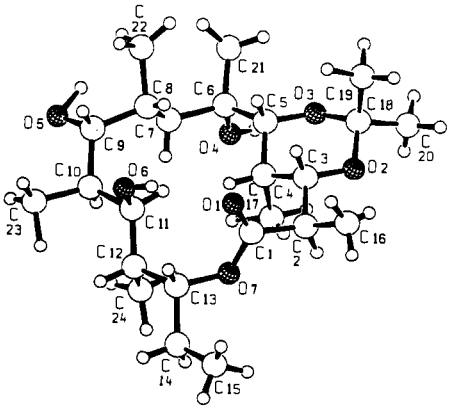


Figure 4. Crystal structure of compound **52**.

clization at the termini; (iii) the C11–C13 segment with a nearly all-anti (zig-zag) conformation.

Inspection of a Dreiding model suggests that mere rotations around the 5,6- and 6,7-axes without any conformational changes within the rigid segments converts **47'** into a prering conformer **47''** practically devoid of transannular repulsions (Figure 2). O13 and C1 fit nicely onto the Bürgi–Dunitz trajectory[33] required for carbonyl addition, whereas O11 and C1 can hardly meet. On the other hand, 11-OH may form a hydrogen bridge to the carbonyl O of the 1-C=O group, thus facilitating the addition of O13 to C1 (principle of "double activation"[30]).

We also analyzed the conformational situation in lactone **50** by performing molecular mechanics calculations.[34] Structure S was obtained as the global minimum energy conformation (Figure 3); it is obvious that S is highly similar to the conformer **47''**. Roughly the same conformational subsegments may be detected as in **46**; a difference lies in the dihedral angle C6–C7–C8–C9 which, due to ring effects, has now been reduced to ~60°. O11 and 1-C=O are close enough to form a hydrogen bridge.

Interestingly, the ^{1}H NMR signals of **50** and **51** are doubled in $CDCl_3$ up to 60 °C; the phenomenon disappears on changing the solvent to DMSO-d_6. Probably **50** and **51** exist in the form of two ring conformers, and in $CDCl_3$, but not in DMSO, a hydrogen bridge is formed that raises the barrier enough to make interconversion slow on the NMR time scale. In fact, a hydrogen bridge between 11-OH and 1-C=O is detected in the crystal

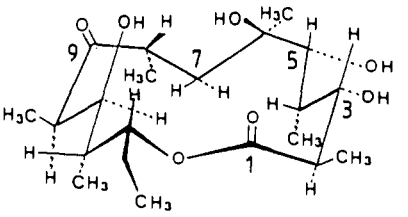
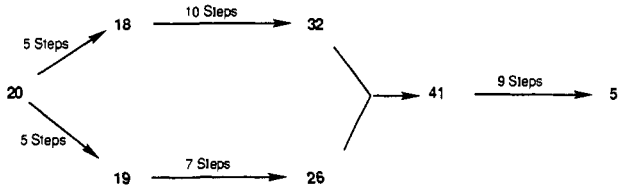


Figure 5. Perun model of **5**. (Egan, R. S.; Perun, T. J.; Martin, J. R.; Mitscher, L. A. *Tetrahedron* **1973**, *29*, 2525. Perun, T. J.; Egan, R. S.; Martin, J. R. *Tetrahedron Lett.* **1969**, 4501.)

Scheme IX. Overall Course of the Synthesis



structure of **52** (O–H–O distances 11-O-H 0.775 Å, 1-C=O···H 2.416 Å, O–H–O angle 154°; see Figure 4).

To introduce the missing oxygen function at C9 **50** was hydroborated with BH_3·SMe_2 to give **52**/**53** in a ratio of 9:1. Despite alkaline workup the lactone mainly remained intact. The structure of **52** was secured by X-ray analysis (Figure 4), which showed that the borane had attacked at the 8-*si*–9-*si* face of the double bond. Based on the assumption **50** reacts in the conformation shown in Figure 3, this stereochemical outcome may be interpreted in terms of an antiperiplanar effect of the C10–C11 bond.[35] High diastereofacial selectivities have been found for the alkylation of macrocyclic enolates[36] and the reduction of macrocyclic ketones,[37] The stereochemical outcome of these reactions was interpreted in terms of an attack from the peripheral face in the ground-state conformation. It appears, however, that antiplanar effects may be operative in these cases as well, Figure 4 shows some more interesting structural features. The macrocycle exists in a [3434] conformation[38] with two approximately parallel four-carbon units (C3–C6 and C10–C13) both in antiperiplanar (zig-zag) conformation. This indicates that the C9–C15 segment has probably maintained its conformation throughout all transformations from **40** to **52**! The substituents around the ring adopt equatorial and axial positions; 1,3 diaxial interactions (e.g., between 6- and 8-Me or 4-Me and 6-OH) are tolerated without inducing ring deformations.

On comparing the crystal structure of **52** (Figure 4) with the Perun model of **5** (Figure 5), one quickly detects the striking similarity of both conformations. Apparently neither the 3,5-acetonide bridge nor the 9(*R*)-OH function in **52** have a major effect on the conformational behavior of the macrolide ring.

Similar to **50**, lactone **51** was hydroborated to give an 8:1 mixture of **54**/**55**. The diastereofacial preference is the same as for **50**; this was confirmed by converting **54** into **5** (identical with the authentic material according to ^{1}H and ^{13}C NMR, mp, and optical rotation) by the reported[3e] oxidation–deketalization sequence. As in Corey's 9-dihydroerythronolide B[4a] derivatives the 9-H NMR signal is upfield in the 9*S* series (**53**, 3.06 ppm; **55**, 2.98 ppm) and downfield in the 9*R* series (**52**, 3.34 ppm; **54**, 3.34 ppm). Similarly, the 9*R* alcohols **52**/**54** have a lower R_f value on silica gel than the 9*S* isomers **53**/**55**.[4a]

Final Evaluation. In conclusion, an efficient synthesis of various members of the erythronolide B family, starting from the chiral precursor **20** has been accomplished. The overall approach is

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(38) Celmer, W. D. *Antimicrob. Agents Chemother.* **1965**, 144.

summarized in Scheme IX, which emphasizes our initial intention, to devise a synthesis that has both divergent (**20** → **18** + **19**) and convergent (**32** + **26** → **40** + **41**) phases. One main advantage of our route is its stereochemical flexibility. The stereotriads **18**/**19** are as well available in enantiomeric or diastereomeric forms[15] and the stereocenter at C6 can be introduced in both configurations. The only chiral center we were unable to control so far is C13; on the other hand, both 13-epimers may be obtained in pure form, which adds to the stereochemical potential of our synthesis. A second advantage of the synthesis is conciseness. Only 22 steps are required on the shortest linear route from **20** to **5**, which contrasts favorably with Corey's (29 steps + optical resolution) and Kochetkov's (36 steps) syntheses. Additional attractive features are the high yield of the macrolactonization and the efficient macrocyclic stereocontrol in the hydroboration of **50**/**51**. Apart from minimizing the total number of steps, it is also desirable in the synthesis of an optically active compound to introduce the stereocenters in a minimum number of steps, because each one of these steps may produce mixtures of stereoisomers. In our synthesis, 11 stereogenic operations are required, in contrast to Corey et al., who needed 17 such steps. Kochetkov's approach contains only one stereoambiguous reaction, namely, the coupling of fragments **14** and **16**; however, due to levoglucosan as the chiral starting material, the synthesis has to cope with an unusually large number of "unproductive", i.e., protection–deprotection and functional group interchanging, transformations. As a result of the general progress in synthetic methodology, the synthesis of **5**, which required the combined effords of large groups just a couple of years ago,[4] has now been reduced to the subject of a 3 years' Ph.D. thesis.[39]

Experimental Section

Infrared spectra (IR) were obtained with a Perkin-Elmer IR 580B spectrometer. Nuclear magnetic resonance spectra (NMR) were recorded with a Bruker WH 270 or AC 250 spectrometer in $CDCl_3$ and are reported in ppm downfield of internal tetramethylsilane (δ units). Optical rotations were determined in $CHCl_3$ (unless stated otherwise) with a Perkin-Elmer 121 polarimeter at a wavelength of 589 nm at 20 °C. Mass spectra (MS) were recorded with a Varian MAT 711 spectrometer. HPLC separations were performed on 7- (preparative separations) and 5-μm (analytical separations) Nucleosil 50. All reactions were performed in purified solvents and monitored by TLC plates (Merck 5554). Preparative column chromatography was performed on silica gel Merck 60, 230–400 mesh.

(2*S*,3*S*,4*R*)-1-*O*-Benzyl-3-*O*-(*tert*-butyldimethylsilyl)-2,4-dimethyl-5-hexene-1,3-diol (21). Sodium hydride (11.5 g, 80% suspension in mineral oil) was washed with hexane, dried, and suspended in DMF (200 mL). (2*S*,3*S*,4*R*)-2,4-Dimethyl-5-hexane-1,3-diol (**19**;[15] 50.0 g, 346.5 mmol) in DMF (200 mL) was added dropwise at 0 °C. After the evolution of hydrogen had ceased, benzyl bromide (60.0 g, 351 mmol) in DMF (150 mL) was added at −50 °C and the mixture was allowed to reach room temperature overnight. Water (10 mL) was added and the mixture was extracted with hexane, washed with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (3:1 hexane/ethyl acetate) furnished 55.0 g (70%) of the primary monobenzyl ether, 14.0 g (13%) of the dibenzyl ether, and 5.0 g of the secondary monobenzyl ether in addition to 6.0 g (12%) of unreacted starting material. The primary monobenzyl ether (50.0 g, 213 mmol), imidazole (35.0 g, 514 mmol), and *tert*-butyldimethylsilyl chloride (42.0 g, 279 mmol) were stirred in DMF (150 mL) at 60 °C for 2 days. After cooling to 0 °C, hexane (300 mL) and water (100 mL) were added. The organic phase was washed with water, dried over $MgSO_4$, and concentrated in vacuo to afford **21** (72.9 g, 98%) as a colorless oil: $[\alpha]^{20}_D$ = +7.8° (*c* 2); ^{1}H NMR δ 0.00 (s, 3 H, SiCH_3), 0.04 (s, 3 H, SiCH_3), 0.86 (d, *J* = 6.5 Hz, 3 H, 2-CH_3), 0.88 (s, 9 H, SiC(CH_3)$_3$), 0.98 (d, *J* = 7.5 Hz, 3 H, 4-CH_3), 2.00 (mc, 1 H, 2-H), 2.34 (mc, 1 H, 4-H), AB part of an ABX system (δ_A = 3.22, δ_B = 3.39, J_{AB} = 9.7 Hz, J_{AX} = 6.3 Hz, J_{BX} = 7.6 Hz, 2 H, 1-H), 3.74 (dd, $J_{3,2}$ = 2.7 Hz, $J_{3,4}$ = 8.1 Hz, 1 H, 3-H), AB system (δ_A = 4.45, δ_B = 4.54, J_{AB} = 12.1 Hz, 2 H, OCH_2Ph), 4.93 (d, *J* = 10.2 Hz, 1 H, 6-H), 4.98 (d, *J* = 17.8 Hz, 1 H, 6-H), 5.80 (ddd, J_{trans} = 17.8 Hz, J_{cis} = 10.2 Hz, $J_{5,4}$ = 7.5 Hz, 1 H, 5-H), 7.24–7.40 (m, 5 H, aryl-H); ^{13}C NMR δ −4.16, −3.64, 11.15, 16.88, 18.45, 26.16, 36.59, 42.72, 72.79, 73.75, 75.59, 113.48, 127.39, 127.52, 128.28, 138.78, 142.11; IR (film) 3080 m, 3040 m, 2960 vs, 2940 vs, 2890 s, 2860 vs, 2800 w, 2750 w, 2720 w, 1640 w, 1610 w, 1590 w, 1500 m, 1470 s, 1460 s, 1455 s, 1410 m, 1390 m, 1360 s, 1255 vs, 1245 s, 1120–1090 vs, 1055 vs, 1005 s, 965 m, 940 m, 915 s, 855 s, 840 vs, 810 s, 775 vs, 735 s, 700 s, 675 m cm^{-1}; MS (CI, isobutane, 160 eV, 120 °C) *m*/*e* (relative intensity) 349.1 (15, (M + H)$^+$), 294.1 (7.5, ((M + H) − C_4H_7)$^+$), 293 (40), 217 (47), 131 (6, OTBDMS)$^+$), 115 (4, (TBDMS)$^+$), 91 (100, (CH_2 − C_6H_5)$^+$).

(2*S*,3*R*,4*R*,5*S*)- and (2*S*,3*R*,4*R*,5*R*)-1-*O*-Benzyl-3-*O*-(*tert*-butyldimethylsilyl)-2,4,6-trimethyl-6-heptene-1,3,5-triol (22) and (23). Olefin **21** (70 g, 201 mmol) in dichloromethane (4200 mL) was treated with ozone at −78 °C with sudane III as an indicator, until the solution was decolorized. Triphenylphosphane (60.7 g, 231 mmol) was added, and the mixture was allowed to warm to room temperature and then concentrated in vacuo. On dilution with ether, the phosphane oxide was precipitated and removed by filtration. Flash chromatography of the filtrate (10:1 hexane/ethyl acetate) furnished the aldehyde (61.6 g, 88%) as a colorless oil, which was dissolved in ether (500 mL) and treated dropwise at 0 °C with a solution of isopropenylmagnesium bromide (1 M in ether, 195 mL). After the mixture was stirred at 22 °C for 2 h, 1 N H_2SO_4 was added dropwise until a clear suspension was formed. The inorganic salts were removed by filtration, and the filtrate was dried over $MgSO_4$ and evaporated to dryness to give, after flash chromatography (10:1 hexane/ethyl acetate), **22** (41,8 g, 61%) and **23** (8.3 g, 12%) as clear colorless oils. **22**: $[\alpha]^{20}_D$ = −9.3° (*c* 2); ^{1}H NMR δ −0.04 (s, 3 H, SiCH_3), 0.06 (s, 3 H, SiCH_3), 0.79 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 7.0 Hz, 3 H), (2-CH_3, 4-CH_3), 0.86 (s, 9 H, SiC(CH_3)$_3$), 1.62 (s, 3 H, 6-CH_3), 1.75 (mc, 1 H), 2.07 (mc, 1 H), (2-H, 4-H), 1.93 (d, *J* = 4 Hz, 1 H, OH), AB part of an ABX system (δ_A = 3.24, δ_B = 3.47, J_{AB} = 6.3 Hz, J_{AX} = 8.1 Hz, J_{BX} = 10 Hz, 2 H, 5-H), 3.80 (dd, *J* = 5.8 Hz, *J* = 3 Hz, 1 H, 3-H), 4.06 (mc, 1 H, 5-H), AB system (δ_A = 4.44, δ_B = 4.49, J_{AB} = 10.8 Hz, 2 H, OCH_2Ph), 4.88 (s, 1 H, 7-H), 4.98 (s, 1 H, 7-H), 7.22–7.38 (m, 5 H, aryl H); ^{13}C NMR δ −3.89, −3.85, 9.09, 12.16, 18.41, 19.11, 26.14, 38.11, 38.59, 72.92, 73.37, 75.01, 76.41, 110.82, 127.43, 127.56, 128.29, 138.61, 146.50; IR (KBr, film) 3460 s, 3100 m, 3070 m, 3040 m, 2965 vs, 3935 vs, 2890 vs, 2860 vs, 2750 w, 2720 w, 1810 w, 1725 w, 1650 m, 1610 w, 1590 w, 1500 m, 1475 s, 1455 s, 1410 m, 1390 s, 1380 s, 1365 s, 1330 w, 1310 m, 1255 s, 1210 m, 1190 m, 1145 s, 1100 vs, 1050–1030 vs, 1010 s, 985 s, 940 m, 900 s, 825 s, 840 vs, 810 s, 775 vs, 740 s, 700 s, 680 s cm^{-1}; MS (CI, isobutane, 160 eV, 150 °C) *m*/*e* (relative intensity) 393.2 (14, (M + H)$^+$), 375.2 (18, ((M + H) − H_2O)$^+$), 293.1 (73, ((M + H) − $C_6H_{12}O$)$^+$), 261.3 (19), 243.1 (28), 99.1 (22), 91 (100), (CH_2 − C_6H_5)$^+$). Anal. Calcd for $C_{23}H_{40}O_3Si$: C, 70.35; H, 10.27. Found: C, 70.19; H, 10.15.

(2*S*,3*R*,4*S*,5*R*)-1-*O*-Benzyl-3,5-*O*-isopropylidene-2,4,6-trimethyl-6-heptene-1,3,5-triol (24). The protected triol **22** (40.0 g, 102 mmol) in THF (140 mL) was added to a 1 M solution of tetra-*n*-butylammonium fluoride in THF (100 mL, 100 mmol) and the resultant mixture was stirred at 22 °C for 15 h. The mixture was concentrated in vacuo and purified by flash chromatography (5:1 hexane/ethyl acetate) to afford the benzyloxy diol (26.5 g, 95%) as a colorless oil, which was dissolved in dichloromethane (45 mL). *p*-Toluenesulfonic acid was added until pH 3; then 2,2-dimethoxypropane (20.5 g, 200 mmol) in dichloromethane (25 mL) was added dropwise and the mixture was stirred overnight at 22 °C. After neutralization with aqueous sodium bicarbonate the organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo to give, after flash chromatography (10:1 hexane/ethyl acetate), **24** (29.5 g, 97%) as a clear colorless oil. Alternatively, the reaction was performed with a mixture of **22** and **23** to give **24** and **25** without chromatographic separation. **24**: $[\alpha]^{20}_D$ = +1.4° (*c* 2); ^{1}H NMR δ 0.75 (d, *J* = 7.1 Hz, 2-CH_3), 1.10 (d, *J* = 6.2 Hz, 4-CH_3), 1.44 (s, 3 H, isopropylidene CH_3), 1.46 (s, 3 H, isopropylidene CH_3), 1.60 (mc, 1 H, 2-H), 1.64 (s, 3 H, 6-CH_3), 3.38 (d, *J* = 5.1 Hz, 2 H, 1-H), 1.88 (mc, 1 H, 4-H), 3.74 (dd, *J* = 9.5, 2.5 Hz, 1 H, 3-H), 4.62 (s, 1 H, 5-H), AB part of an ABX system (δ_A = 4.46, δ_B = 4.56, J_{AB} = 12.1 Hz, 2 H, 1-H), 4.92 (s, 1 H, 7-H), 5.07 (s, 1 H, 7-H), 7.28–7.40 (m, 5 H, aryl H); ^{13}C NMR δ 5.33, 14.59, 19.11, 19.95, 29.99, 32.10, 35.53, 72.04, 73.28, 75.62, 75.74, 98.89, 110.13, 127.46, 127.53, 128.28, 138.72, 142.83; IR (film) 3100 w, 3070 m, 3040 m, 3000 s, 2980 s, 2940 s, 2920 s, 2880 s, 2860 s, 1950 w, 1870 w, 1810 w, 1655 m, 1605 w, 1590 w, 1500 m, 1480 m, 1455 s, 1380 s, 1360 s, 1330 w, 1310 m, 1295 m, 1260 s, 1200 vs, 1180 s, 1160 s, 1105 vs, 1065 s, 1020 s, 1000 s, 935 s, 900 s, 870 s, 845 m, 830 w, 800 w, 740 s, 700 s; MS (CI, isobutane, 160 eV, 120 °C) *m*/*e* (relative intensity) 319.2 (11, (M + H)$^+$), 261.2 (87, ((M + H) − C_3H_7O)$^+$), 179.1 (100, ((M + H) − $C_9H_{16}O$)$^+$), 91 (84, (CH_2 − C_6H_5)$^+$).

(3*R*,4*S*,5*R*,6*S*)-7-(Benzyloxy)-3,5-(isopropylidenedioxy)-4,6-dimethyl-2-heptanone (26). Olefin **24** (25.0 g, 78.5 mmol) was ozonized in dichloromethane (1.0 L) as described for **21** to give, after flash chromatography (10:1 hexane/ethyl acetate), ketone **26** (22.9 g, 91%) as a colorless oil. If the mixture of **24**/**25** had been used for the ozonolysis, the crude ketone was dissolved in methanol and a saturated

(39) Kirstein, H. M. Ph.D. Thesis, FU-Berlin, 1990.

solution of Na_2CO_3 in methanol was added. The mixture was stirred at 22 °C for 12 h, neutralized with 1 M HCl, and extracted with ether. The organic phase was washed with water, dried over $MgSO_4$, and evaporated in vacuo to give pure ketone **26** after chromatographic purification (10:1 hexane/ethyl acetate) as colorless needles: mp 40–41 °C; $[\alpha]^{20}_D$ = +33.6° (*c* 2); ^{1}H NMR δ 0.80 (d, *J* = 6.7 Hz), 1.04 (d, *J* = 6.8 Hz), (4-CH_3, 6-CH_3), 1.38 (s, 3 H, isopropylidene CH_3), 1.47 (s, 3 H, isopropylidene CH_3), 1.84 (mc, 1 H, 4-H), 2.02 (mc, 1 H, 2-H), 2.13 (s, 3 H, 1-H), AB part of an ABX system (δ_A = 3.31, δ_B = 3.36, J_{AB} = 8.4 Hz, J_{AX} = 5.1 Hz, J_{BX} = 4.6 Hz, 2 H, 7-H), 3.71 (dd, *J* = 9.4, 2.5 Hz, 1 H, 5-H), 4.25 (d, *J* = 3 Hz, 1 H, 3-H), 4.47 (s, 2 H, OCH_2Ph), 7.24–7.36 (m, 5 H, aryl H); ^{13}C NMR δ 6.20, 14.31, 19.01, 26.80, 29.63, 32.16, 34.77, 71.12, 72.99, 75.03, 79.22, 99.12, 127.29, 128.11, 138.20, 200.26. IR (film) 3100 w, 1070 m, 3040 m, 3000 s, 2940 s, 2880 s, 1950 w, 1855 w, 1810 w, 1715 vs, 1600 w, 1585 w, 1500 m, 1455 s, 1415 m, 1385 vs, 1355 s, 1315 m, 1270 s, 1255 s, 1205 vs, 1160 vs, 1110 vs, 1065 s, 1020 vs, 990 s, 945 m, 920 s, 870 s, 830 w, 815 w, 795 w, 750 s, 740 s, 700 s, 670 w, 655 w cm^{-1}; MS (CI, isobutane, 160 eV, 120 °C) *m/e* (relative intensity) 321.3 (16, $(M + H)^+$), 264.2 (17, $((M + H) - C_3H_5O)^+$), 263.2 (84.37, $((M + H) - C_3H_6O)^+$), 245.3 (71), 179.1 (100, $((M + H) - C_9H_{16}O)^+$), 155.2 (56), 91 (100, $(CH_2 - C_6H_5)^+$). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.07; H, 8.79.

(2*R*,3*R*,4*S*)-3-(Benzyloxy)-2,4-dimethyl-5-hexenal (28), (2*S*,3*R*,4*S*)-2,4-Dimethyl-5-hexene-1,3-diol (**18**;[14] 50.0 g, 347 mmol) in pyridine (50 mL) was added to trityl chloride (106.3 g, 381 mmol) in pyridine (300 mL). DMAP (1 g) was added and the mixture was stirred at 22 °C for 2 days. Then crushed ice (250 g) was added and the mixture was concentrated in vacuo to remove the pyridine. The residue was repeatly extracted with dichloromethane. The combined organic phases were washed with water, dried over $MgSO_4$, and evaporated. Flash chromatography (5:1 hexane/ethyl acetate) furnished the 1-trityl derivative (127 g, 95%) as a clear colorless oil, which was benzylated with NaH/benzyl bromide in DMF at 0 °C as described for **19** to give, after flash chromatography (10:1 hexane/ethyl acetate), the 1-trityl-3-benzyl derivative (151 g, 98%) as a colorless oil. For detritylation, the protected diol (150 g, 313 mmol) was stirred with formic acid (750 mL) in ether (450 mL) at 22 °C overnight. Ether (750 mL) and water (400 mL) were added, the aqueous layer was extracted 4 times with ether (500 mL), and the combined organic layers were neutralized with K_2CO_3. KOH (50 mL, 10% in methanol) was added and the mixture was stirred for 10 min and evaporated to dryness, The residue was diluted with hexane, and the solid impurities were removed by filtration. The filtrate was dried with $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (10:1 hexane/ethyl acetate) to afford the detritylated alcohol (70.5 g, 96%) as a clear oil. It was oxidized to the aldehyde **28** by dissolving it in dichloromethane (300 mL) and adding this solution dropwise to the Swern reagent[35] prepared from oxalyl chloride (53 g, 420 mmol) and DMSO (43.8 g, 550 mmol) in dichloromethane (1100 mL) at −78 °C. After the mixture was stirred at −78 °C for 20 min, triethylamine (142 g, 1.4 mol) was added dropwise and the temperature was slowly raised to room temperature. Dichloromethane (500 mL) and water (150 mL) were added and the organic phase was washed with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography was performed on a small scale (1 g) and showed that the aldehyde epimerized under chromatographic conditions to give a 92:8 mixture of **28** and the 2*S* epimer. Therefore, the crude aldehyde (60.0 g, 86%) was used in the next step. **28**: $[\alpha]^{20}_D$ = −45.1° (*c* 2); ^{1}H NMR δ 1.12 (d, *J* = 7.5 Hz, 3 H), 1.14 (d, *J* = 7.5 Hz, 3 H, 2-CH_3, 4-CH_3), 2.56 (mc, 1 H, 4-H), 2.72 (mc, 1 H, 2-H), 3.56 (dd, J_1 = 6.8 Hz, J_2 = 5.4 Hz, 1 H, 3-H), 3.70–3.78 (m, 1 H, 4-H), AB system (δ_A = 4.56, δ_B = 4.63, J_{AB} = 10.8 Hz, 2 H, OCH_2Ph), 5.08 (d, J_{cis} = 10.0 Hz, 1 H, 6-H), 5.08 (d, J_{trans} = 17.5 Hz, H, 6-H), 5.80 (ddd, J_{trans} = 17.5 Hz, J_{cis} = 10.0 Hz, $J_{4,5}$ = 7.5 Hz, 1 H, 5-H), 7.28–7.40 (m, 5 H, aryl H), 9.78 (d, *J* = 2.3 Hz, 1 H, CHO); ^{13}C NMR δ 10.99, 15.22, 40.49, 48.41, 73.54, 84.44, 115.53, 127.38, 127.76, 127,83, 128.06, 128,21, 137.96, 140.44, 203.71; IR (film) 3440 m, 3070 m, 2975 vs, 2940 vs, 2880 vs, 2740 m, 1720 vs, 1640 m, 1500 m, 1455 s, 1420 m, 1395 m, 1370 m, 1350 m, 1310 m, 1260 s, 1210 m, 1100–1060 vs, 950 m, 920 s, 805 s, 740 s, 700 vs.

(3*R*,4*S*,5*R*,6*S*)- and (3*S*,4*S*,5*R*,6*S*)-5-*O*-Benzyl-4,6-dimethyl-7-octene-3,5-diol (29 and 30). Crude, nonepimerized aldehyde **28** (56.0 g, 243 mmol) in ether (500 mL) was added dropwise to a 1 M solution of ethylmagnesium bromide in ether (292 mL, 292 mmol) at 0 °C. The mixture was stirred at 22 °C for 2 h and then quenched with 2 N sulfuric acid (150 mL). The organic phase was washed with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (10:1 hexane/ethyl acetate) or HPLC (7-μm Nucleosil) furnished **29** (38.9 g, 62%) and **30** (12.4 g, 19%) as clear oils. **29**: $[\alpha]^{20}_D$ = −8.5° (*c* 3); ^{1}H NMR δ 0.88 (t, *J* = 7.5 Hz, 3 H, 1-H), 1.02 (d, *J* = 7.5 Hz, 3 H), 1.15 (d, *J* = 7.5 Hz, 3 H, 4-CH_3, 6-CH_3), 1.32 (mc, 1 H, 2-H), 1.52 (mc, 1 H, 2-H), 1.82 (mc, 1 H, 4-H), 2.65 (mc, 1 H, 6-H), 3.23 (s, 1 H, OH), 3.33 (dd, J_1 = 7.5 Hz, J_2 = 3.5 Hz, 1 H, 5-H), 3.92 (t, *J* = 7.5 Hz, I H, 3-H), AB system (δ_A = 4.60, δ_B = 4.68, J_{AB} = 11 Hz, 2 H, OCH_2Ph), 5.02 (d, J_{cis} = 10.5 Hz, H, 8-H), 5.08 (d, J_{trans} = 17.5 Hz, 1 H, 8-H), 5,77 (ddd, J_{trans} = 17.5 Hz, J_{cis} = 10.5 Hz, $J_{4,5}$ = 7.5 Hz, 1 H, 7-H), 7.26–7.38 (m, 5 H, aryl H); ^{13}C NMR δ 10.58, 11.50, 16.45, 27.30, 37.70, 41.35, 71.97, 75.90, 89.32, 114.65, 127.60, 127.67, 127.75, 128.41, 137.98, 141.36; IR (film) 3500 s, 3070 m, 3040 m, 2960 vs, 2940 vs, 2880 vs, 1640 m, 1495 s, 1455 vs, 1420 s, 1380 s, 1350 s, 1260 m, 1210 m, 1110–1055 vs, 1030 s, 995 m, 950 s, 908 s, 805 s, 755 s, 735 s, 700 s; MS (EI, 80 eV, 40 °C) *m/e* 207.3 ($M^+ - C_4H_7$), 149.2 ($M^+ - (C_4H_7, C_3H_6O)$). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.81; H, 9.98. Found: C, 77.83; H, 9.69. **30**; $[\alpha]^{20}_D$ = −34.2° (*c* 3); ^{1}H NMR δ 0.97 (t, *J* = 7.5 Hz, 3 H, 1-H), 0.88 (d, *J* = 7.5 Hz, 3 H), 1.10 (d, *J* = 7.5 Hz, 3 H, 4-CH_3, 6-CH_3), 1.34 (mc, 1 H, 2-H), 1.58 (mc, 1 H, 2-H), 1.84 (mc, 1 H, 4-H), 2.54 (mc, 1 H, 6-H), 3.28 (s, 1 H, OH), 3.35 (dd, J_1 = 7.5 Hz, J_2 = 3.8 Hz, 1 H, 5-H), 3.60 (dt, *J* = 7.5, 2.7 Hz, 1 H, 3-H), AB system (δ_A = 4.52, δ_B = 4.66, J_{AB} = 11.0 Hz, 2 H, OCH_2Ph), 5.03 (d, J_{cis} = 10.0 Hz, H, 8-H), 5.08 (d, J_{trans} = 17.5 Hz, 1 H, 8-H), 5.92 (ddd, J_{trans} = 17.5 Hz, J_{cis} = 10.0 Hz, $J_{4,5}$ = 7.5 Hz, 1 H, 7-H), 7.20–7.32 (m, 5 H, aryl H); ^{13}C NMR δ 9.58, 13.96, 14.18, 26.46, 40.92, 41.19, 74.49, 74.90, 88.01, 114.03, 127.63, 128.04, 128.28, 138.12, 142.59.

(4*R*,5*R*,6*S*)-5-(Benzyloxy)-4,6-dimethyl-7-octen-3-one (31), Oxalyl chloride (8.3 g, 65 mmol) in dichloromethane (160 mL) was treated dropwise at −78 °C with DMSO (6.7 g, 85 mmol) in dichloromethane (50 mL). After 20 min, alcohol **30** (12 g, 76 mmol) in dichloromethane (40 mL) was added. After the mixture was stirred at −78 °C for 20 min, ethylamine (21.8 g, 0.21 mmol) was added dropwise and the temperature was allowed to reach room temperature. Dichloromethane (80 mL) and water (25 mL) were added and the organic phase was washed with water, dried over $MgSO_4$, and concentrated in vacuo to give, after flash chromatography (10:1 hexane/ethyl acetate), ketone **31** (11.1 g, 93%) as a clear oil. $[\alpha]^{20}_D$ = −43.3° (*c* 1); ^{1}H NMR δ 0.99 (t, *J* = 7.5 Hz, 3 H, 1-H), 1.02 (d, *J* = 7.0 Hz, 3 H, 6-CH_3), 1.08 (d, *J* = 7.0 Hz, 3 H, 4-CH_3), 2.40 (mc, 1 H, 6-H), 2.46 (q, *J* = 7.5 Hz, 2 H, 2-H), 2.86 (dq, 1 H, *J* = 9.5, 7.5 Hz, 1 H, 4-H), 3.86 (dd, *J* = 8.0, 4.0 Hz, 1 H, 5-H), AB system (δ_A = 4.32, δ_B = 4.54, J_{AB} = 10.5 Hz, 2 H, OCH_2Ph), 5.02 (d, J_{cis} = 10.0 Hz, 1 H, 8-H), 5.10 (d, J_{trans} = 17.5 Hz, 1 H, 8-H), 5.94 (ddd, J_{trans} = 17.5, J_{cis} = 10.0 Hz, *J* = 7.0 Hz, 1 H, 7-H), 7.16–7.31 (m, 5 H, aryl H); ^{13}C NMR δ 7.25, 12.78, 13.52, 36.86, 39.37, 48.03, 74.31, 85.25, 114.13, 127.18, 127.39, 128.06, 138.52, 141.79, 213.99. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.79; H, 9.21,

Ketone **31** (10.0 g, 38 mmol) in THF (200 mL) was treated dropwise at −78 °C with L-Selectride (1 M solution in THF, 45 mL). The mixture was allowed to warm to room temperature overnight and then quenched with water (1 mL). Workup as described for the preparation of **29**/**30**, including flash chromatography, furnished a 1:1 mixture of the alcohols **29** and **30** (9.4 g, 94%).

Configurational Assignment of C13. Alcohol **29** (4.13 g, 15.96 mmol) was silylated with TBDMS-Cl as described to give the 3-O-silyl ether (5.71 g, 97%). Ozonolysis as described furnished the crude aldehyde (5.7 g), which was dissolved in THF (10 mL) and added dropwise to a solution of lithium diisopropylamide prepared from diisopropylamine (2.24 g, 21.88 mmol) in THF (50 mL) and *n*-butyllithium (1.6 M, in hexane, 13 mL, 20.8 mmol). The mixture was stirred at −78 °C for 2 h and allowed to warm to room temperature. Sulfuric acid (2 N) was added for neutralization, the phases were separated, and the organic phase was washed with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (10:1 hexane/ethyl acetate) furnished the unsaturated aldehyde **35** (1.91 g, 46%): $[\alpha]^{20}_D$ = +3.2° (*c* 2); ^{1}H NMR δ 0.04 (s, 3 H, SiCH_3), 0.06 (s, 3 H, SiCH_3), 0.87 (t, *J* = 8.0 Hz, 3 H, 7-H), 0.90 (s, 9 H, SiC(CH_3)$_3$), 1.04 (d, 3 H, *J* = 6.8 Hz, 4-CH_3), 1.58–1.65 (m, 2 H, 6-H), 1.78 (s, 3 H, 2-CH_3), 2.74–2.90 (m, 1 H, 4-H), 3.56 (dt, 1 H, J_1 = J_2 = 5.5 Hz, 5-H), 6.41 (dd, *J* = 10, 1.5 Hz, 1 H, 3-H), 9.39 (s, 1 H, CHO).

A solution of sudane III (50 mg) and the aldehyde **35** (1.00 g, 3.40 mmol) in methanol (160 mL) was treated with ozone at −78 °C until the red color had disappeared. Then solid sodium borohydride (1.40 g, 37.01 mmol) was added at −78 °C and the mixture was allowed to warm to room temperature. The mixture was neutralized with 2 N sulfuric acid, concentrated under reduced pressure, and diluted with water. Extraction with ether and the usual workup delivered the crude alcohol **36** (780 mg, 91%), which was purified by HPLC to give an analytically pure sample; $[\alpha]^{20}_D$ = +2.4° (*c* 2); ^{1}H NMR δ 0.08 (s, 3 H, SiCH_3), 0.10 (s, 3 H, SiCH_3), 0.82 (d, 3 H, *J* = 7.0 Hz, 2-CH$_3$), 0.90 (s, 9 H, SiC(CH_3)$_3$), 0.90 (t, *J* = 7.5 Hz, 3 H, 5-H), 1.52 (dq, J_1 = J_2 = 7.0 Hz, 2 H, 4-H), 1.87–2.01 (m, 1 H, 2-H), 2.76 (br s, 1 H, OH), 3.45–3.57 (m, 1 H, 3-H), 3.63–3.74 (m, 2 H, 1-H); ^{13}C NMR δ −4.58, −4.41, 10.64, 11.65, 17.99, 25.38, 25.84, 39.26, 65.96, 76.90.

Racemic hydroxy ester **37a** was prepared from the epoxy ester as described[22] on a 10-mmol scale. Silylation of **37a** (700 mg, 4,79 mmol)

furnished **37b** (1.24 g, 98%). **37b** (1.23 g, 4.72 mmol) in ether (25 mL) was treated dropwise with DIBAL (1.6 M solution in toluene, 10 mL, 16 mmol) at −30 °C. The mixture was stirred at −30 °C for 90 min and then allowed to warm to −10 °C. Sodium fluoride (1.60 g) and water (2 mL) were added and the mixture was stirred at room temperature for 14 h. After filtration the organic phase was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (5:1 hexane/ethyl acetate) to give pure alcohol **38** (1.05 g, 96%); ^1H NMR δ 0.00 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$), 0.79 (t, J = 7.0 Hz, 3 H, 5-H), 0.82 (s, 9 H, $SiC(CH_3)_3$), 0.94 (d, J = 7.1 Hz, 3 H, 2-CH_3), 1.44–1.60 (m, 2 H, 4-H), 1.70 (mc, 1 H, 2-H), 2.88 (t, 1 H, J = 5.0 Hz, 1 H, OH), AB system (δ_A = 3.50, δ_B = 3.71, J_{AB} = 10.8 Hz, J_{AX} = J_{BX} = 5.0 Hz, 2 H, 1-H), 3.60 (dd, J = 17.0, 5.4 Hz, 1 H, 3-H); ^{13}C NMR δ −4.82, −4.60, 8.98, 14.46, 17.95, 25.82, 27.27, 37.56, 65.37, 78.22.

Methyl (4*S*,5*R*,6*R*,7*R*)-5-(Benzyloxy)-7-[(*tert*-butyldimethylsilyl)-oxy]-2,4,6-trimethyl-2(*E*)-nonenoate (32). Alcohol **29** was silylated as described for **21** to give the TBDMS ether **34**.6 g, 97%) as a colorless oil, which was ozonized as described for **21** to afford the aldehyde (42.5 g), which epimerized on chromatography and was therefore used without purification in the next step. Thus, the crude aldehyde (40 g) was stirred with carbomethoxymethylene-triphenylphosphorane (96 g, 276 mmol) in THF (40 mL) at 22 °C for 3 days. The mixture was concentrated in vacuo, diluted with hexane (160 mL), filtered, and purified by flash chromatography (10:1 hexane/ethyl acetate) to furnish the unsaturated ester **32** (31.7 g, 74% based on **29**) as a colorless oil: $[\alpha]^{20}_D$ = +22.2° (*c* 1); ^1H NMR δ = −0.04 (s, 3 H, $SiCH_3$), −0.02 (s, 3 H, $SiCH_3$), 0.70 (t, J = 7.5 Hz, 3 H, 9-H), 0.78 (d, J = 7.5 Hz, 3 H, 6-CH_3), 0.84 (s, 9 H, $SiC(CH_3)_3$), 1.00 (d, J = 7.5 Hz, 3 H, 4-CH_3), 1.50 (mc, 2 H, 8-H), 1.76 (mc, 1 H, 6-H), 1.88 (s, 3 H, 2-CH_3), 2.72 (mc, 1 H, 4-H), 3.36 (dd, J_1 = 8.7 Hz, J_2 = 3 Hz, 5-H), 3.70 (s, 3 H, OCH_3), 3.88 (mc, 1 H, 7-H), 4.50 (s, 2 H, OCH_2Ph), 6.82 (d, J = 11 Hz, 1 H, 3-H), 7.24 (m, 5 H, aryl H); ^{13}C NMR δ −4.38, −3.35, 9.54, 12.51, 13.34, 18.25, 25.98, 28.19, 35.19, 39.18, 51.67, 72.89, 74.52, 83.41, 125.91, 127.33, 127.41, 128.24, 138.85, 146.93, 168.66; IR (film) 3090 w, 3060 w, 3030 m, 2950 vs, 2930 vs, 2880 vs, 2850 vs, 1710 vs, 1640 m, 1490 m, 1470 s, 1450 s, 1430 s, 1380 m, 1360 m, 1340 m, 1250 vs, 1190 m, 1140 s, 1060 vs, 1025 vs, 1000 s, 970 m, 930 m, 900 m, 870 m, 830 vs, 770 vs, 750 s, 730 m, 695 s, 670 m; MS (CI, isobutane, 160 eV, 130 °C) *m/e* (relative intensity) 449 (68, $(M + H)^+$), 317 (27, $(M - HOTBDMS)^+$), 247 (23), 225 (28), 209 (51), 173 (100, $(C_3H_6OTBDMS)^+$), 91 (72, $(CH_2-C_6H_5)^+$). Anal. Calcd for $C_{26}H_{44}O_4Si$: C, 69.59; H, 10.12. Found: C, 68.93; H, 10.15.

(3*R*,4*R*,5*R*,6*S*)-5-*O*-Benzyl-3-*O*-(*tert*-butyldimethylsilyl)-4,6,8-trimethyl-9-(thiophenoxy)-7-(*E*)-nonene-3,5-diol (33). Ester **32** (27.0 g, 60 mmol) in toluene (600 mL) was treated dropwise with DIBAL (1.2 M in toluene, 120 mL, 144 mmol) at −10 °C. The mixture was stirred vigorously for 15 min and then quenched with water (2 mL). The mixture was allowed to warm to 0 °C and NaOH (15% aqueous solution, 2 mL) was added. After being warmed to room temperature, the mixture was treated with water (2 mL). By this procedure an almost quantitative crystallization of the aluminum salts was accomplished. The mixture was filtered, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (10:1 hexane/ethyl acetate) afforded pure allylic alcohol (24.0 g, 95%) as a viscous oil, which was diluted with pyridine (10 mL) and added dropwise to a mixture of diphenyl disulfide (14.5 g, 67 mmol) and tri-*n*-butylphosphane (13.4 g, 67 mmol) in pyridine (10 mL) at 22 °C. The mixture was stirred overnight and concentrated in vacuo. Flash chromatography (10:1 hexane/ethyl acetate) gave the allyl sulfide **33** (30.1 g, 98%) as a clear viscous oil: $[\alpha]^{20}_D$ = +12.1° (*c* 1); ^1H NMR δ −0.05 (s, 3 H, $SiCH_3$), −0.03 (s, 3 H, $SiCH_3$), 0.80 (d, J = 7.5 Hz, 3 H, 4-CH_3), 0.84 (t, J = 7.5 Hz, 3 H, 1-H), 0.87 (d, J = 7.5 Hz, 3 H, 6-CH_3), 0.91 (s, 9 H, $SiC(CH_3)_3$), 1.51 (mc, 2 H, 2-H), 1.71 (mc, 1 H, 4-H), 1.78 (s, 3 H, 8-CH_3), 2.60 (mc, 1 H, 6-H), 3.28 (dd, J = 8.8, 3 Hz, 1 H, 5-H), 3.48 (s, 2 H, 9-H), 3.92 (mc, 1 H, 3-H), 4.40 (s, 2 H, OCH_2Ph), 5.33 (d, J = 8.75 Hz, 1 H, 7-H), 7.20–7.40 (m, 10 H, aryl H); ^{13}C NMR δ −4.28, −3.28, 9.68, 9.80, 13.89, 15.40, 18.24, 25.90, 26.03, 34.46, 39.25, 44.27, 73.04, 74.26, 84.05, 125.49–129.46, 130.47, 133.99, 136.40, 139.37; IR (film) 3060 m, 3030 m, 2950 vs, 2920 vs, 2880 vs, 1580 m, 1490 m, 1470 s, 1460 s, 1435 s, 1380 s, 1360 m, 1340 m, 1300 w, 1250 s, 1200 m, 1140 m, 1090 vs, 1070 vs, 1025 vs, 1000 s, 965 m, 940 m, 870 m, 830 vs, 770 vs, 740 vs, 690 s, 670 m; MS (CI, isobutane, 160 eV, 200 °C) *m/e* (relative intensity) 513.2 (23, $(M + H)^+$, 405.2 (4.5), 381.2 (9, $(M - HOTBDMS)^+$), 321.2 (4, $((M + H) - C_6H_{11}SC_6H_5)^+$), 273.2 (15), 191.1 (12), 173.2 (100, $(C_3H_6OTBDMS)^+$), 91.1 (18, $(CH_2-C_6H_5)$). Anal. Calcd for $C_{31}H_{48}O_2SSi$: C, 72.60; H, 9.43. Found: C, 72.74; H, 9.29.

Coupling of the Fragments 33 and 26. Conditions A. TMEDA (6.0 g, 52 mmol) in hexane (15 mL) was treated dropwise at −78 °C with *n*-butyllithium (1.6 M in hexane, 24 mL, 38 mmol). The mixture was allowed to warm to −40 °C and stirred for 30 min at this temperature, Then **33** (9.85 g, 19 mmol) in hexane (20 mL) was added dropwise at −40 °C. The deep red solution was stirred for another 30 min. Then THF (10 mL) was added and the clear red solution was cooled to −78 °C. Ketone **26** (6.4 g, 20 mmol) in THF (10 mL) was added dropwise, whereupon the color disappeared. After another 20 min at −78 °C, ethanol (10 mL) was added and the mixture was warmed to room temperature, diluted with ammonium chloride, concentrated in vacuo, and diluted with ether. The organic phase was washed with water, dried over $MgSO_4$, and evaporated in vacuo. Flash chromatography (10:1 hexane/ethyl acetate) afforded (with decreasing R_f values) the following: unreacted ketone **26** (2.4 g), unreacted sulfide **33** (3.05 g), **42a/b** (6.24 g, 57%), **40a** (2.65 g, 24%), **40b** (880 mg, 8%), **41a** (370 mg, 3%), and **41b** (250 mg, 2%). All yields are based on consumed **33**.

Conditions B. TMEDA (4.0 g, 34 mmol) in hexane (7 mL) was treated dropwise at −78 °C with *n*-butyllithium (1.6 M in hexane, 20 mL, 32 mmol). The mixture was stirred at −40 °C for 30 min. Then **33** (7.50 g, 14.6 mmol) in hexane (5 mL) was added dropwise. After 30 min, THF (20 mL) and HMPA (13.4 g, 75 mmol) were added dropwise and the resulting clear red solution was cooled to −78 °C. Ketone **26** (5.0 g, 15.6 mmol) in THF (5 mL) was added dropwise and the mixture was decolorized immediately. After another 2 min at −78 °C the reaction was quenched with ethanol (10 mL) and worked up as described in A. Flash chromatography furnished **26** (1.90 g), **33** (2.48 g), **40a** (4.81 g, 62%), **40b** (1.61 g, 21%), **41a** (650 mg, 8%), and **41b** (450 mg, 5%).

Conditions C. The deprotonation of **33** (7.50 g, 14.6 mmol) was performed as in B. Ketone **26** (6.0 g, 18.8 mmol) in ether (15 mL) was placed in a precooled (−40 °C) dropping funnel and $BF_3{\cdot}Et_2O$ (26.54 g, 187 mmol) was added under stirring. This mixture was then added dropwise to the solution of anion **39** at −78 °C. After 2 min the reaction was quenched with ethanol and worked up as before to furnish **26** (2.16 g), **33** (3.38 g), **40a** (451 mg, 8%), **40b** (145 mg, 2%), **41a** (2.93 g, 48%), and **41b** (1.95 g, 32%).

(2*S*,3*R*,4*S*,5*R*,6*R*,7*R*/*S*,10*S*,11*R*,12*R*,13*R*)-1,11-Di-*O*-benzyl-13-*O*-(*tert*-butyldimethylsilyl)-2,4,6,8,10,12-hexamethyl-3,5-*O*-isopropylidene-7-(thiophenoxy)-8(*E*)-pentadecene-1,3,5,6,11,13-hexol (40a/b). **40a**: $[\alpha]^{20}_D$ = +16.6° (*c* 4); ^1H NMR δ −0.06 (s, 3 H, $SiCH_3$), −0.03 (s, 3 H, $SiCH_3$), 0.76 (t, J = 7.6 Hz, 3 H, 15-H), 0.78 (d, J = 6.8 Hz, 3 H), 0.88 (d, J = 7.8 Hz, 3 H), 0.98 (d, J = 7.1 Hz, 3 H), 1.04 (d, J = 6.5 Hz, 3 H, 2-CH_3, 4-CH_3, 10-CH_3, 12-CH_3), 0.86 (s, 9 H, $SiC(CH_3)_3$), 1.24 (s, 3 H, 6-CH_3), 1.42 (s, 6 H, isopropylidene CH_3), 1.47 (mc, 2 H, 14-H), 1.65 (mc, 1 H), 1.82 (mc, 1 H), 1.90 (mc, 1 H, 2-H, 4-H, 12-H), 1.92 (s, 3 H, 8-CH_3), 2.48 (s, I H, 6-OH), 2.68 (mc, 1 H, 10-H), AB part of an ABX system (δ_A = 3.14, δ_B = 3.17, J_{AB} = 10.3 Hz, J_{AX} = 5.4 Hz, J_{BX} = 4.7 Hz, 2 H, 1-H), 3.34 (dd, J = 8.6, 2.5 Hz, 1 H), 3.62 (d, J = 9.7 Hz, 1 H, 3-H, 11-H), 3.81 (s, 1 H, 7-H), 3.93 (t, J = 7 Hz, 1 H, 13-H), 3.96 (d, J = 2.2 Hz, 1 H, 5-H), AB system (δ_A = 4.06, δ_B = 4.18, J_{AB} = 11.9 Hz, 2 H, OCH_2Ph), AB system (δ_A = 4.23, δ_B = 4.54, J_{AB} = 11.4 Hz, 2 H, OCH_2Ph), 5.66 (d, J = 8.6 Hz, 1 H, 9-H), 7.04–7.32 (m, 15 H, aryl H); ^{13}C NMR δ −4.32, −3.33, 7.04, 9.30, 10.15, 13.22, 14.75, 17.39, 18.31, 19.86, 22.90, 26.08, 28.49, 29.90, 30.61, 34.30, 34.52, 39.36, 60.14, 71.64, 72.92, 73.07, 74.11, 76.16, 76.86, 76.95, 83.73, 99.65, 125.93, 126.81, 126.98, 127.20, 127.30, 127.97, 128.19, 128.72, 129.26, 130.03, 136.24, 137.54, 138.57, 139.81; IR (film) 3560 m, 3090 m, 3070 m, 3030 s, 2960 vs, 2930 vs, 2880 vs, 2860 vs, 2800 m, 2740 w, 2720 w, 1945 w, 1865 w, 1805 w, 1745 w, 1690 w, 1605 w, 1585 m, 1495 s, 1480 s, 1470 s, 1460 s, 1455 vs, 1440 s, 1380 vs, 1370 s, 1360 s, 1340 s, 1330 s, 1315 m, 1290 m, 1260 vs, 1200 vs, 1180 s, 1155 s, 1105 vs, 1090 vs, 1065 vs, 1030 vs, 1015 vs, 980 s, 945 s, 910 s, 870 s, 835 vs, 815 m, 790 s, 775 s, 760 s, 735 vs, 695 vs, 670 m; MS (EI, 80 eV, 120 °C) *m/e* (relative intensity) 817 (0.34, $(M - CH_3)^+$), 717.1 (0.2, $(M - TBDMS)^+$), 512.1 (0.6, $(M - (C_6H_{11}OTBDMS - OCH_2C_6H_5)^+$), 455.2 (2), 404 (3.5), 321.3 (8, $(C_6H_{11}OTBDMS - OCH_2C_6H_5)^+$), 173.2 (100, $(C_3H_6OTBDMS)^+$), 91 (95.5, $(CH_2C_6H_5)^+$). Anal. Calcd for $C_{50}H_{76}O_6SiS$: C, 72.07; H, 9.19. Found: C, 72.55; H, 9.51.

40b: $[\alpha]^{20}_D$ = −7.7° (*c* 3); ^1H NMR δ 0.01 (s, 6 H, $SiCH_3$), 0.78 (t, J = 7.8 Hz, 3 H, 15-H), 0.80 (d, J = 7 Hz, 3 H), 0.92 (d, J = 7 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H), 1.02 (d, J = 6.5 Hz, 3 H, 2-CH_3, 4-CH_3, 10-CH_3, 12-CH_3), 0.91 (s, 9 H, $SiC(CH_3)_3$), 1.16 (s, 3 H, 6-CH_3), 1.25 (s, 3 H, isopropylidene CH_3), 1.39 (s, 3 H, isopropylidene CH_3), 1.48 (mc, 2 H, 14-H), 1.64 (mc, 1 H), 1.76–1.95 (m, 2 H, 2-CH_3, 4-CH_3, 12-CH_3), 1.84 (s, 3 H, 8-CH_3), 2.20 (s, 1 H, 6-OH), 2.65 (mc, 1 H, 10-H), 3.21 (dd, J = 8.6, 2.4 Hz, 1 H), 3.50 (d, J = 10.8 Hz, 1 H, 3-H, 11-H), AB part of an ABX system (δ_A = 3.24, δ_B = 3.33, J_{AB} = 8.5 Hz, J_{AX} = 5.4 Hz, J_{BX} = 4.6 Hz, 2 H, 1-H), 3.77 (s, 1 H, 7-H), 3.91 (t, J = 6.8 Hz, 1 H, 13-H), 4.10 (d, J = 2 Hz, 1 H, 5-H), AB system (δ_A = 4.11, δ_B = 4.21, J_{AB} = 11.4 Hz, 2 H, OCH_2Ph), AB system (δ_A = 4.38, δ_B = 4.46, J_{AB} = 12.4 Hz, 2 H, OCH_2Ph), 5.30 (d, J = 9.4 Hz, 1 H, 9-H), 7.00–7.44 (m, 15 H, aryl H); ^{13}C NMR δ −4.42, −3.46, 7.46, 9.50, 9.87, 13.38, 13.90, 14.11, 14.59, 18.13, 19.28, 22.44, 25.91, 28.26, 29.72,

31.28, 33.99, 34.48, 39.08, 70.11, 71.18, 72.84, 72.94, 74.13, 76.14, 76.37, 76.84, 83.43, 99.07, 126,82, 126.88, 126.95, 127.27, 127.34, 127.88, 128.11, 128.70, 131.67, 132.03, 135.14, 135.93, 138.42, 139.25.

(2*S*,3*R*,4*S*,5*R*,6*S*,7*R*/*S*,10*S*,11*R*,12*R*,13*R*)-1,11-Di-*O*-benzyl-13-*O*-(*tert*-butyldimethylsilyl)-2,4,6,8,10,12-hexamethyl-3,5-*O*-isopropylidene-7-(thiophenoxy)-8(*E*)-pentadecene-1,3,5,6,11,13-hexol (41a/b), 41a: $[\alpha]^{20}_D$ = +1.5° (*c* 1); ^{1}H NMR δ 0.01 (s, 3 H, SiCH_3), 0.03 (s, 3 H, SiCH_3), 0.70 (d, *J* = 7.3 Hz, 3 H), 0.78 (d, *J* = 7.4 Hz, 3 H), 0.90 (d, *J* = 7.6 Hz, 3 H), 1.03 (d, *J* = 6.5 Hz, 3 H, 2-CH_3, 4-CH_3, 10-CH_3, 12-CH_3), 0.79 (t, *J* = 7.4 Hz, 3 H, 15-H), 0.89 (s, 9 H, SiC(CH_3)$_3$), 1.24 (s, 3 H, 6-CH_3), 1.42 (s, 3 H, isopropylidene CH_3), 1.45 (s, 3 H, isopropylidene CH_3), 1.50 (mc, 2 H, 14-H), 1.68 (mc, 1 H), 1.82–1.96 (m, 2 H, 2-H, 4-H, 12-H), 1.85 (s, 3 H, 8-CH_3), 2.55 (mc, 1 H, 10-H), 2.70 (s, 1 H, 6-OH), 3.28–3.38 (m, 3 H), 3.64 (d, *J* = 9.2 Hz, 1 H, 1-H, 3-H, 11-H), 3.58 (s, 1 H, 7-H), 3.94 (t, *J* = 5.9 Hz, 1 H, 13-H), 4.22 (s, 1 H, 5-H), AB system (δ$_A$ = 4.43, δ$_B$ = 4.46, *J*$_{AB}$ = 10.8 Hz, 2 H, OCH_2Ph), AB system (δ$_A$ = 4.51, δ$_B$ = 4.59, *J*$_{AB}$ = 12.5 Hz, 2 H, OCH_2Ph), 5.11 (d, *J* = 9.7 Hz, 1 H, 9-H), 7.08–7.40 (m, 15 H, aryl H); ^{13}C NMR δ −4.58, −3.39, 6.77, 9.30, 9.92, 12.90, 14.59, 18.07, 19.74, 22.02, 26.05, 28.21, 29.70, 31.09, 33.88, 34.43, 39.13, 66.73, 71.75, 72.91, 74.12, 76.34, 77.15, 77.79, 84.14, 99.43, 126.37, 126.65, 126.86, 126.95, 127.18, 127.26, 127.84, 127.98, 128.09, 128.01, 128.24, 128.62, 130.98, 132.92, 135.53, 136.51, 138.23, 139.20.

41b: $[\alpha]^{20}_D$ = +22.3° (*c* 1); ^{1}H NMR δ 0.04 (s, 3 H, SiCH_3), 0.06 (s, 3 H, SiCH_3), 0.76 (t, *J* = 7.5 Hz, 3 H, 15-H), 0.08 (d, *J* = 6.0 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 1.03 (d, *J* = 6.2 Hz, 3 H), 1.06 (d, *J* = 7.6 Hz, 3 H, 2-CH_3, 4-CH_3, 10-CH_3, 12-CH_3), 0.92 (s, 9 H, OSiC(CH_3)$_3$), 1.26 (s, 3 H, 6-CH_3), 1.36 (s, 3 H, isopropylidene CH$_3$), 1.42 (s, 3 H, isopropylidene CH$_3$), 1.48 (mc, 2 H, 14-H), 1.60 (m, 2 H), 1.84 (mc, 1 H, 2-H, 4-H, 12-H), 1.90 (s, 3 H, 8-CH_3), 2.62 (s, 1 H, 6-OH), 2.68 (mc, 1 H, 10-H), 3.20 (d, *J* = 8.6 Hz, 1 H), 3.66 (d, *J* = 10.3 Hz, 1 H, 3-H, 11-H), 3.33 (d, *J* = 5.1 Hz, 2 H, 1-H), 3.92 (mc, 1 H, 13-H), 3.93 (s, 1 H), 4.23 (s, 1 H, 5-H, 7-H), AB system (δ$_A$ = 4.06, δ$_B$ = 4.20, *J*$_{AB}$ = 11.6 Hz, 2 H, OCH_2Ph); AB system (δ$_A$ = 4.38, δ$_B$ = 4.54, *J*$_{AB}$ = 12.1 Hz, 2 H, OCH_2Ph), 5.36 (d, *J* = 8.4 Hz, 1 H, 9-H), 6.96–7.39 (m, 15 H, aryl H); ^{13}C NMR δ −4.00, −3.15, 6.93, 9.73, 10.21, 13.64, 14.90, 15.50, 18.38, 19.69, 20.18, 26.22, 28.62, 29.14, 29.96, 34.52, 34.70, 39.39, 67.21, 71.59, 73.23, 74.46, 75.01, 75.78, 77.24, 77.71, 83.71, 99.64, 126.88, 127.13, 127.21, 127.56, 128.12, 128.40, 128.82, 128.95, 131.52, 132.04, 132.29, 136.18, 136,61, 138.58, 139.56.

(2*S*,3*R*,4*S*,5*R*,6*R*/*S*,7*R*/*S*,8*S*,9*S*,10*R*,11*R*)-1,9-Di-*O*-benzyl-3,5-*O*-isopropylidene-7-[1-methyl-2-(thiophenoxy)-(*E*/*Z*)-ethenyl]-2,4,6,8,10-pentamethyltredecane-1,3,5,6,9,11-hexol (42a/b). 42a: ^{1}H NMR δ 0.05 (s, 6 H, SiCH_3), 0.86 (t, *J* = 7.5 Hz, 3 H, 13-H), 0.91 (s, 9 H, SiC(CH_3)$_3$), 0.79 (d, *J* = 7.0 Hz, 3 H), 0.89 (d, *J* = 7.0 Hz, 3 H), 1.13 (d, *J* = 7.0 Hz, 3 H), 1.32 (d, *J* = 7.0 Hz, 3 H, 2-CH_3, 4-CH_3, 8-CH_3, 10-CH_3), 1.28 (s, 3 H, 6-CH_3), 1.39 (s, 3 H, isopropylidene CH_3), 1.44 (s, 3 H, isopropylidene CH_3), 1.53–1.82 (m, 4 H), 2.03–2.09 (m, 2 H, 2-H, 4-H, 8-H, 10-H, 12-H), 2.03 (s, 3 H, 1-CH_3), 2.93 (s, 1 H, 6-OH), AB part of an ABX system (δ$_A$ = 3.20, δ$_B$ = 3.27, *J*$_{AB}$ = 8.5 Hz, *J*$_{AX}$ = 4.5 Hz, *J*$_{BX}$ = 3,0 Hz, 2 H, 1-H), 3.53 (d, *J* = 11.0 Hz, 1 H, 7-H), 3.60 (d, *J* = 9.5 Hz, 1 H), 3.73 (d, *J* = 9.5 Hz, 1 H, 3-H, 9-H), 3.90 (d, *J* = 1 Hz, 1 H, 5-H), AB system (δ$_A$ = 3.85, δ$_B$ = 3.95, *J*$_{AB}$ = 11.0 Hz, 2 H, OCH_2Ph), 4.04 (dd, *J* = 8.0, 5.5 Hz, 1 H, 11-H), AB system (δ$_A$ = 4.55, δ$_B$ = 4.93, *J*$_{AB}$ = 10.8 Hz, 2 H, OCH_2Ph), 6.30 (d, *J* = 1 Hz, 1 H, 2′-H), 7.20–7.36 (m, 15 H, aryl H); ^{13}C NMR δ −4.23, −2.99, 7.07, 9.00, 10.47, 11.86, 14.75, 18.23, 19.87, 22.96, 23.12, 26.07, 28.50, 29.81, 31.28, 34.06, 34.43, 39.49, 48.27, 71.10, 72.54, 73.28, 75.26, 76.89, 78.71, 81.00, 99.70, 123.40, 124.84, 125.68, 126.32, 126.94, 127.03, 127.39, 127.68, 127.93, 128.06, 128.13, 128.35, 128.71, 131.90, 137.50, 138.87, 139.31, 139.90.

42b: ^{1}H NMR δ 0.05 (s, 6 H, SiCH_3), 0.81 (t, *J* = 7.5 Hz, 3 H, 13-H), 0.93 (s, 9 H, SiC(CH_3)$_3$), 0.87 (d, *J* = 7.0 Hz, 3 H), 1.03 (d, *J* = 7.0 Hz, 3 H), 1.05 (d, *J* = 7.0 Hz, 3 H), 1.12 (d, *J* = 7.0 Hz, 3 H, 2-CH_3, 4-CH_3, 8-CH_3, 10-CH_3), 1.36 (s, 3 H, 6-CH_3), 1.43 (s, 3 H, isopropylidene CH_3), 1.46 (s, 3 H, isopropylidene CH_3), 1.51–1.87 (m, 5 H), 2.16 (mc, 1 H, 2-H, 4-H, 8-H, 10-H, 12-H), 1.96 (s, 3 H, 1′-CH_3), 2.49 (s, 1 H, 6-OH), 3.16 (d, *J* = 11.0 Hz, 1 H, 7-H), 3.35 (d, *J* = 4.5 Hz, 2 H, 1-H), 3.47 (d, *J* = 9.5 Hz, 1 H), 3.65 (d, *J* = 9.5 Hz, 1 H, 3-H, 9-H), 4.01 (d, *J* = 1 Hz, 1 H, 5-H), 3.95 (dd, *J* = 8.0, 5.5 Hz, 1 H, 11-H), AB system (δ$_A$ = 4.34, δ$_B$ = 4.44, *J*$_{AB}$ = 12.5 Hz, 2 H, OCH_2Ph), AB system: (δ$_A$ = 4.47, δ$_B$ = 4.83, *J*$_{AB}$ = 11.5 Hz, 2 H, OCH_2Ph), 6.28 (d, *J* = 1 Hz, 1 H, 2′-H), 7.02–7.36 (m, 15 H, aryl H); ^{13}C NMR δ −4.34, −3.06, 7.13, 9.03, 10.35, 13.30, 14.83, 18.29, 19.90, 22.00, 24.86, 26.11, 28.47, 29.73, 31.92, 33.62, 34.53, 39.25, 54.97, 71.41, 73.12, 73.23, 73.74, 75.51, 76.17, 77.22, 81.40, 99.54, 124.03, 125.49, 126.34, 126.52, 127.37, 127.50, 127.56, 127.87, 128.30, 128.78, 137.47, 138.53, 140.08, 140.14.

(2*S*,3*R*,4*S*,5*R*,6*S*,10*S*,11*R*,12*R*,13*R*)-13-*O*-(*tert*-butyldimethylsilyl)-2,4,6,8,10,12-hexamethyl-3,5-*O*-isopropylidene-8(*E*)-pentadecene-1,3,5,6,11,13-hexol (43). Isomerically pure thiophenoxide **41a** (300 mg, 0.36 mmol) in THF (2 mL) was treated with ethylamine (2 mL). Lithium (100 mg, 14.3 mmol) was added in one piece at 0 °C under vigorous stirring. The solution turned red after some minutes and then blue. When the change of the color was completed, ethanol (1 mL) was added and the unreacted lithium was removed from the solution with a pair of tweezers. Saturated aqueous NH_4Cl was added (1 mL), and the mixture was concentrated in vacuo and diluted with dichloromethane. The phases were separated and the organic phase was dried over $MgSO_4$ and evaporated. Flash chromatography (3:1 hexane/ethyl acetate) afforded pure hexol **43** (139 mg, 71%) as a colorless oil. The same compound was obtained from the reduction of **41b**. For the continuation of the synthesis a mixture of **41a/b** (3.00 g, 3.6 mmol) was reduced to give 1.52 g, (78%) of pure **43**: $[\alpha]^{20}_D$ = +19.5° (*c* 3); ^{1}H NMR δ 0.05 (s, 3 H, SiCH_3), 0.08 (s, 3 H, SiCH_3), 0.78 (d, *J* = 8.0 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.97 (d, *J* = 6.5 Hz, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H, 2-CH_3, 4-CH_3, 10-CH_3, 12-CH_3), 0.84 (t, *J* = 8.8 Hz, 3 H, 15-H), 0.86 (s, 9 H, SiC(CH_3)$_3$), 1.08 (s, 3 H, 6-CH_3), 1.36 (s, 3 H, isopropylidene CH_3), 1.40 (s, 3 H, isopropylidene CH_3), 1.49 (mc, 2 H, 14-H), 1.66 (s, 1 H, OH), 1.71 (s, 3 H, 8-CH_3), 1.72–1.88 (m, 3 H, 2-H, 4-H, 12-H), AB system (δ$_A$ = 2.06, δ$_B$ = 2.26, *J*$_{AB}$ = 13.5 Hz, 2 H, 7-H), 2.28 (s, 1 H, OH), 2.45 (mc, 1 H, 10-H), 3.45–3.54 (m, 4 H), 3.57 (dd, *J* = 9.0, 2 Hz, 1 H, 1-H, 3-H, 5-H, 11-H), 3.70 (mc, 1 H, 13-H), 4.03 (d, *J* = 2.5 Hz, 1 H, OH), 5.28 (d, *J* = 8.5 Hz, 1 H, 9-H); ^{13}C NMR δ −4.61, −4.50, 6.66, 10.87, 12.22, 13.20, 13.94, 17.74, 18.17, 19.37, 25.00, 25.17, 25.64, 29.68, 31.02, 34.80, 35.91, 38.56, 46.31, 63.31, 74.10, 76.43, 77.13, 78.01, 78.73, 99.10, 130.29, 133.33; IR (film) 3420 vs, 3000–2850 vs, 1660 w, 1460 vs, 1380 vs, 1250 vs, 1200 vs, 1160 vs, 1070 vs, 1040 vs, 1010 vs, 940 s, 910 s, 870 vs, 835 vs, 780 vs, 760 s, 735 w, 690 w, 670 m; MS (CI, isobutane, 160 eV, 120 °C) *m*/*e* (relative intensity) 544.9 (16, (M + H)$^+$), 526.9 (23, ((M + H) − H_2O)$^+$), 487 (58, ((M + H) − C_4H_{10})$^+$), 469 (49, ((M + H) − H_2O − C_4H_{10})$^+$), 231 (31), 173 (100, (C_3H_6O-TBDMS)$^+$).

(2*S*,3*R*,4*S*,5*R*,6*S*,10*S*,11*R*,12*R*,13*R*)-1,11-Di-*O*-acetyl-13-*O*-(*tert*-butyldimethylsilyl)-2,4,6,8,10,12-hexamethyl-3,5-*O*-isopropylidene-8(*E*)-pentadecene-1,3,5,6,11,13-hexol (44). Hexol **43** (5.50 g, 10.1 mmol) in pyridine (10 mL) was treated with acetic anhydride (2.20 g, 21.5 mmol) and DMAP (50 mg) for 16 h at 22 °C. Saturated aqueous $NaHCO_3$ was added, and the mixture was concentrated in vacuo and then diluted with dichloromethane. The phases were separated and the organic phase was washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. Flash chromatography (5:1 hexane/ethyl acetate) furnished the diacetate **44** (6.22 g, 98%) as a colorless oil: $[\alpha]^{20}_D$ = +0.6 (*c* 10); ^{1}H NMR δ 0.01 (s, 3 H, SiCH_3), 0.03 (s, 3 H, SiCH_3), 0.80 (t, *J* = 7.5 Hz, 3 H, 15-H), 0.87 (s, 9 H, SiC(CH_3)$_3$), 0.87 (hidden, 3 H), 0.94 (d, *J* = 7.0 hz, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 1.05 (d, *J* = 7.4 Hz, 3 H, 2-CH_3, 4-CH_3, 10-CH_3, 12-CH_3), 1.10 (s, 3 H, 6-CH_3), 1.38 (s, 3 H, isopropylidene CH_3), 1.43 (s, 3 H, isopropylidene CH_3), 1.48 (mc, 2 H, 14-H), 1.76 (s, 3 H, 8-CH_3), 1.68–1.80 (m, 1 H), 1.88–2.04 (m, 2 H, 2-H, 4-H, 12-H), AB system (δ$_A$ = 1.93, δ$_B$ = 2.25, *J*$_{AB}$ = 12.8 Hz, 2 H, 7-H), 2.04 (s, 6 H, acetate CH_3), 2.48 (s, 1 H, OH), 2.72 (mc, 1 H, 10-H), 3.44–3.61 (m, 3 H, 3-H, 5-H, 13-H), AB part of an ABX system (δ$_A$ = 3.83, δ$_B$ = 4.05, *J*$_{AB}$ = 11.7 Hz, *J*$_{AX}$ = 7.0 Hz, *J*$_{BX}$ = 4.5 Hz, 2 H, 1-H), 4.92 (dd, *J* = 8, 4.5 Hz, 1 H, 11-H), 5.01 (d, *J* = 8.8 Hz, 1 H, 9-H); ^{13}C NMR δ −5.11, −4.23, 6.44, 9.40, 9.54, 13.99, 14.39, 17.84, 18.36, 19.10, 20.40, 20.72, 24.18, 25.66, 28.02, 29.51, 31.14, 33.40, 37.95, 46.83, 65.04, 72.29, 73.76, 75.86, 78.38, 78.79, 98.90, 131.33, 131.89, 170.33, 170.44; IR (film) 3540 m, 2960 vs, 2940 vs, 2880 s, 2860 s, 2260 w, 1735 vs, 1460 s, 1380 vs, 1370 vs, 1245 vs, 1200 vs, 1160 s, 1150 s, 1095 vs, 1075 vs, 1060 s, 1015 vs, 985 s, 970 m, 940 m, 910 s, 875 s, 835 vs, 775 s, 735 vs, 695 w, 670 w, 650 w; MS (EI, 80 eV, 80 °C) *m*/*e* (relative intensity) 628.3 (2, M$^+$), 613.3 (2, (M − CH$_3$)$^+$), 356.1 (9), 273 (15), 271 (20), 215.1 (98), 173 (100, (C_3H_6O-TBDMS)$^+$), 165.1 (27), 155 (35), 117 (75), 95 (25), 83 (36), 72.9 (49), 43 (92, (CH_3CO)$^+$). Anal. Calcd for $C_{34}H_{64}O_8Si$: C, 64.93; H, 10.26. Found: C, 64.54; H, 9.97.

(2*S*,3*R*,4*S*,5*R*,6*S*,10*S*,11*R*,12*R*,13*R*)-11-*O*-Acetyl-13-*O*-(*tert*-butyldimethylsilyl)-2,4,6,8,10,12-hexamethyl-3,5-*O*-isopropylidene-8(*E*)-pentadecene-1,3,5,6,11,13-hexol (45). To a solution of potassium (400 mg, 10 mmol) in *tert*-butyl alcohol (20 mL) and THF (5 mL) was added diacetate **45** (6.00 g, 9.54 mmol) in THF (10 mL). After being stirred overnight at 22 °C, the mixture was concentrated in vacuo at 70 °C. The residue was diluted with dichloromethane and water. The phases were separated and the organic phase was washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. Flash chromatography (3:1 hexane/ethyl acetate) afforded primary alcohol **45** (5.10 g, 91%) as a colorless oil: $[\alpha]^{20}_D$ = +3.5° (*c* 2.5); ^{1}H NMR δ −0.04 (s, 3 H, SiCH_3), −0.02 (s, 3 H, SiCH_3), 0.74 (t, *J* = 7.8 Hz, 3 H, 15-H), 0.82 (s, 9 H,

$SiC(CH_3)_3$), 0.81 (d, J = 7 Hz, 3 H), 0.88 (d, J = 7,3 Hz, 3 H), 0.97 (d, J = 7.4 Hz, 3 H), 0.99 (d, J = 6.9 Hz, 3 H, 2-CH_3, 4-CH_3, 10-CH_3, 12-CH_3), 1.04 (s, 3 H, 6-CH_3), 1.33 (s, 3 H, isopropylidene CH_3), 1.37 (s, 3 H, isopropylidene CH_3), 1.44 (mc, 2 H, 14-H), 1,65–1.80 (m, 3 H, 2-H, 4-H, 12-H), 1.70 (s, 3 H, 8-CH_3), AB system (δ_A = 1.90, δ_B = 2.42, J_{AB} = 13 Hz, 2 H, 7-H), 1.99 (s, 3 H, acetate CH_3), 2.43 (s, 2 H, OH), 2.68 (mc, 1 H, 10-H), 3.40–3.57 (m, 5 H, 1-H, 3-H, 5-H, 13-H), 4.84 (dd, J = 8.9 hz, 1 H, 11-H), 4.93 (d, J = 10.3 Hz, 1 H, 9-H); ^{13}C NMR δ −4.84, −3.98, 6.85, 9.72, 9.79, 13.96, 14.69, 18.09, 18.57, 19.42, 21.02, 24.56, 25.89, 28.22, 29.78, 31.17, 33.64, 36.18, 38.19, 46.90, 63.66, 72.55, 74.16, 76.44, 77.21, 78.61, 78.98, 99.18, 131.63, 132.02, 170.97; IR (film) 3500 s, 2960 vs, 2920 vs, 2880 s, 2855 s, 2240 w, 1720 vs, 1460 s, 1380 vs, 1250 vs, 1200 s, 1160 s, 1095 s, 1070 s, 1015 vs, 985 s, 965 m, 910 s, 870 m, 835 s, 770 s, 730 vs, 670 w, 650 w; MS (EI, 80 eV, 180 °C) m/e (relative intensity) 586.3 (0.1, M^+), 571.2 (0.4, $(M - CH_3)^+$), 319.2 (3), 271.1 (10), 173.1 (100, $(C_3H_6O$-TBDMS$)^+$), 165.1 (14), 155.1 (17), 117 (39), 99 (17), 83 (17), 75 (19), 73 (25), 43.1 (47, $(CH_3CO)^+$).

(2*R*,3*S*,4*S*,5*R*,6*S*,10*S*,11*R*,12*R*,13*R*)-11-Acetoxy-13-[(*tert*-butyldimethylsilyl)oxy]-6-hydroxy-2,4,6,8,10,12-hexamethyl-3,5-(isopropylidenedioxy)-8(*E*)-pentadecenoic Acid (46). Alcohol **45** (4.00 g, 6.8 mmol) in DMF (40 mL) was treated with PDC (15.4 g, 41 mmol) and water (1 mL) for 5 h at 22 °C. Water (200 mL) was added and the mixture was extracted with five portions of ethyl acetate (400 mL each). The combined organic phases were washed with water, dried over $MgSO_4$, and concentrated in vacuo at 50 °C. Flash chromatography (2:1 hexane/ethyl acetate) afforded acid **46** (3.30 g, 81%) as colorless crystals: mp 151–153 °C; $[\alpha]^{20}_D$ = −1.5° (c 1.5); ^{1}H NMR ($CDCl_3/D_2O$) δ −0.01 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$), 0.78 (t, J = 7.8 Hz, 3 H, 15-H), 0.84 (d, J = 7.4 Hz, 3 H), 0.91 (d, J = 7.3 Hz, 3 H), 1.05 (d, J = 7.5 Hz, 3 H, 4-CH_3, 10-CH_3, 12-CH_3), 0.86 (s, 9 H, $SiC(CH_3)_3$), 1.08 (s, 3 H, 6-CH_3), 1.22 (d, J = 7.8 Hz, 3 H, 2-CH_3), 1.39 (s, 3 H, isopropylidene CH_3), 1.42 (s, 3 H, isopropylidene CH_3), 1.47 (mc, 2 H, 14-H), 1.74 (s, 3 H, 8-CH_3), 1.76 (mc, 1 H), 1.83 (mc, 1 H, 4-H, 12-H), AB system (δ_A = 1.97, δ_B = 2.25, J_{AB} = 13.5 Hz, 2 H, 7-H), 2.04 (s, 3 H, acetate CH_3), 2.65 (dd, J = 10.5, 7 Hz, 1 H, 2-H), 2.72 (mc, 1 H, 10-H), 3.52 (mc, 1 H, 13-H), 3.56 (d, J = 2.5 Hz, 1 H, 5-H), 3.84 (dd, J = 10.3, 2 Hz, 1 H, 3-H), 4.89 (dd, J = 8, 4.5 Hz, 1 H, 11-H), 5.00 (d, J = 9.5 Hz, 1 H, 9-H); ^{13}C NMR δ −4.81, −3.09, 6.89, 9.72, 9.90, 14.60, 14.97, 18.15, 18.75, 19.45, 21.01, 24.40, 25.95, 28.30, 29.70, 31.60, 33.70, 38.17, 41.56, 46.98, 72.60, 74.37, 75.72, 78.72, 99.60, 131.45, 132.41, 171.21, 179.15; IR (KBr) 3480 m, 3960 vs, 3940 vs, 3880 s, 3860 s, 1730 vs, 1710 vs, 1460 s, 1380 s, 1250 vs, 1200 s, 1170 s, 1155 s, 1145 s, 1130 s, 1095 s, 1080 s, 1060 s, 1020 vs, 990 m, 970 m, 940 m, 910 m, 890 m, 840 vs, 790 s, 685 m, 550 w, 530 w, 470 w; MS (EI, 80 eV, 230 °C) m/e (relative intensity) 600.2 (0.4, M^+), 585.2 (1, $(M - CH_3)^+$), 356.1 (6), 271.1 (19), 245.1 (14), 187 (100), 173.1 (81, $(C_3H_6O$-TBDMS$)^+$), 169.1 (23), 165.1 (29), 117.1 (73), 73 (40), 43 (43, $(CH_3CO)^+$). Anal. Calcd for $C_{32}H_{60}O_8Si$: C, 63.96; H, 10.06. Found: C, 64.10; H, 9.94.

(2*R*,3*S*,4*S*,5*R*,6*S*,10*S*,11*R*,12*R*,13*R*)-6,11,13-Trihydroxy-2,4,6,8,10,12-hexamethyl-3,5-(isopropylidenedioxy)-8(*E*)-pentadecenoic Acid (47). For desilylation, seco acid **46** (3.00 g, 5.0 mmol) was dissolved in 15 mL of a 1 M solution of tetra-*n*-butylammonium fluoride in THF and the resultant mixture refluxed for 15 h. The solvent was evaporated in vacuo and the residue was purified by flash chromatography (4:4:1 hexane/ethyl acetate/methanol) to give seco acid **47** (1.62 g, 76%) as a colorless viscous oil: $[\alpha]^{20}_D$ = +1.2 (c 1); ^{1}H NMR δ 0.84 (t, J = 7.5 Hz, 3 H, 15-H), 0.86 (d, J = 7.5 Hz, 3 H), 0.95 (d, J = 7.5 Hz, 3 H), 1.00 (d, J = 7.0 Hz, 3 H, 4-CH_3, 10-CH_3, 12-CH_3), 1.04 (s, 3 H, 6-CH_3), 1.16 (d, J = 7.5 Hz, 3 H, 2-CH_3), 1.36 (s, 3 H, isopropylidene CH_3), 1.37 (s, 3 H, isopropylidene CH_3), 1.36–1.50 (m, 2 H, 14-H), 1.54–1.84 (m, 2 H, 4-H, 12-H), 1.70 (s, 3 H, 8-CH_3), 1.91 (d, J = 13.5 Hz, 1 H, 7-H), 2.22 (d, J = 13.5 Hz, 1 H, 7-H), 2.46–2.67 (m, 2 H, 2-H, 10-H), 3.33 (t, J = 5.5 Hz, 1 H), 3.49 (s, 1 H), 3.66–3.85 (m, 2 H, 3-H, 5-H, 11-H, 13-H), 4.97 (d, J = 10.0 Hz, 1 H, 9-H), 4.60–6.80 (s, wide, 4 H, 6-OH, 11-OH, 13-OH, -COOH); ^{13}C NMR δ 6.63, 10.61, 10.93, 15.07, 15.81, 18.45, 19.48, 25.51, 27.06, 29.64, 31.58, 35.99, 37.79, 41.77, 46.10, 73.83, 74.28, 75.87, 78.33, 79.91, 99.60, 131.05, 132.52, 177.73.

(2*S*,3*R*,4*S*,5*R*,6*R*,10*S*,11*R*,12*R*,13*R*)-2,4,6,8,10,12-Hexamethyl-3,5-*O*-isopropylidene-8(*E*)-pentadecene-1,3,5,6,11,13-hexol (48). A mixture of the thiophenoxides **41a/b** (3.00 g, 3.6 mmol) was reduced with lithium as described for **40a/b** to furnish, after flash chromatography (1:1 hexane/ethyl acetate), the tetrol (1.10 g, 71%) as a colorless oil: $[\alpha]^{20}_D$ = +13.7° (c 3); ^{1}H NMR δ 0.91 (t, J = 7.5 Hz, 3 H, 15-H), 0.96–1.05 (m, 12 H, 2-CH_3, 4-CH_3, 10-CH_3, 12-CH_3), 1.08 (s, 3 H, 6-CH_3), 1.40 (s, 3 H, isopropylidene CH_3), 1.42 (mc, 2 H, 14-H), 1.44 (s, 3 H, isopropylidene CH_3), 1.64–1.84 (m, 3 H, 2-H, 4-H, 12-H), 1.76 (s, 3 H, 8-CH_3), 2.02 (s, 1 H, OH), AB system (δ_A = 2.05, δ_B = 2.28, J_{AB} = 13.5 Hz, 2 H, 7-H), 2.50 (br, 1 H, O*H*), 2.63 (mc, 1 H, 10-H), 3.60 (br, 2 H, O*H*), 3.44–3.60 (m, 5 H, 1-H, 3-H, 5-H, 11-H), 3.84 (mc, 1 H, 13-H), 4.94 (d, J = 10.0 Hz, 1 H, 9-H); ^{13}C NMR δ 6,71, 10.65, 11.23, 13.96, 16.63, 18.66, 19.81, 21.03, 27.40, 29.76, 31.39, 36.10, 37.74, 76.36, 77.42, 80.88, 99.36, 131.81, 132.58; MS (CI, 160 eV, 250 °C) m/e (relative intensity) 430.9 (20, $(M + H)^+$), 336.9 (48), 173 (100), 99 (57). Anal. Calcd for $C_{24}H_{46}O_6$: C, 66.94; H, 10.77. Found: C, 66.82; H, 10.60.

(2*S*,3*R*,4*S*,5*R*,6*R*,10*S*,11*R*,12*R*,13*R*)-1,11,13-Tri-*O*-acetyl-2,4,6,8,10,12-hexamethyl-3,5-*O*-isopropylidene-8(*E*)-pentadecene-1,3,5,6,11,13-hexol (48). A mixture of the thiophenoxides **41a/b** (3.00 g, 3.6 mmol) was reduced with lithium as described for **40a/b** to furnish, after flash chromatography (1:1 hexane/ethyl acetate), the tetrol (1.10 g, 71%) as a colorless oil; which was dissolved in pyridine (3 mL) and treated with acetic anhydride (1.4 g, 13.5 mmol) and DMAP (50 mg) for 16 h at 22 °C. Workup as described for **44** delivered **48** (1.32 g, 93%) as a colorless oil: $[\alpha]^{20}_D$ = +26.0° (c 1.5); ^{1}H NMR δ 0.88 (t, J = 7.5 Hz, 3 H, 15-H), 0.89 (d, J = 7.0 Hz, 3 H), 0.97 (d, J = 7.0 Hz, 3-H), 0.99 (d, J = 7.0 Hz, 3 H), 1.03 (d, J = 7.0 Hz, 3 H, 2-CH_3, 4-CH_3, 10-CH_3, 12-CH_3), 1.08 (s, 3 H, 6-CH_3), 1.36–1.48 (m, 2 H, 14-H), 1.39 (s, 3 H, isopropylidene CH_3), 1.44 (s, 3 H, isopropylidene CH_3), 1.58–1.86 (m, 2 H), 1.94 (mc, 1 H, 2-H, 4-H, 12-H), 1.78 (s, 3 H, 8-CH_3), 2.01 (s, 3 H, acetate CH_3), 2,03 (s, 3 H, acetate CH_3), 2.06 (s, 3 H, acetate CH_3), AB system (δ_A = 1.98, δ_B = 2.38, J_{AB} = 12.5 Hz, 2 H, 7-H), 2.81 (mc, 1 H, 10-H), 3.47–3.53 (m, 2 H, 3-H, 5-H), AB part of an ABX system (δ_A = 3.83, δ_B = 4.03, J_{AB} = 9.8 Hz, J_{AX} = 6.2 Hz, J_{BX} = 4.4 Hz, 2 H, 1-H), 4.79 (t, J = 6.4 Hz, 1 H, 11-H), 4.92 (d, J = 9.2 Hz, 1 H, 9-H), 5.00 (dt, J = 7.2, 3.0 Hz, 1 H, 13-H); ^{13}C NMR δ 6.61, 10.17, 10.54, 14.33, 15.70, 18.82, 19.76, 20.86, 20.96, 21.20, 25.57, 29.78, 31.68, 33.57, 34.16, 37.08, 50.57, 65.43, 72.96, 74.21, 77.71, 78.07, 99.41, 131.38, 132.74, 170.57, 170.70, 171.13; IR (film) 3500 m, 2980 vs, 2940 vs, 2880 s, 1730 vs, 1660 s, 1450 s, 1370 vs, 1130–1200 s, 1130 vs, 980 s, 940 s, 870 s, 830 s, 600 m; HRMS (EI, 80 eV, 90 °C) mass calcd for $C_{30}H_{50}O_8$ ($M^+ - H_2O$) 538.350 57, found 538.350 656.

(2*R*,3*S*,4*S*,5*R*,6*R*,10*S*,11*R*,12*R*,13*R*)-6,11,13-Trihydroxy-3,5-(isopropylidenedioxy)-8(*E*)-2,4,6,8,10,12-hexamethylpentadecenoic Acid (49). Triacetate **48** (900 mg, 16.2 mmol) was selectively deacetylated at the primary position as described for the conversion of **44** into **45** to give, after flash chromatography (3:1 hexane/ethyl acetate), the primary alcohol (766 mg, 92%). Oxidation as described for **45** furnished the 11,13-diacetoxy seco acid (590 mg, 80%), which was stirred with 100 mL of a 10% solution of KOH in methanol for 2 days at 22 °C. The mixture was neutralized with 1 M aqueous hydrochloric acid, concentrated in vacuo, and purified by flash chromatography to furnish the seco acid **49** (423 mg, 89%) as a clear viscous oil: $[\alpha]^{20}_D$ = +2.3° (c 0.5); ^{1}H NMR δ 0.83 (t, J = 7.5 Hz, 3 H, 15-H), 0.90 (d, J = 7.2 Hz, 3 H), 0.94 (d, J = 7.2 Hz, 3 H), 0.96 (d, J = 7.0 Hz, 3 H, 4-CH_3, 10-CH_3, 12-CH_3), 1.01 (s, 3 H, 6-CH_3), 1.17 (d, J = 7.0 Hz, 3 H, 2-CH_3), 1.36 (s, 3 H, isopropylidene CH_3), 1.38 (s, 3 H, isopropylidene CH_3), 1.31–1.84 (m, 4 H, 4-H, 12-H, 14-H), 1.67 (s, 3 H, 8-CH_3), 2.01 (d, J = 13.5 Hz, 1 H, 7-H), 2.22 (d, J = 13.5 Hz, 1 H, 7-H), 2.48–2.65 (m, 2 H, 2-H, 10-H), 3.34 (dd, J = 7.5, 5.0 Hz, 1 H), 3.56 (s, 1 H), 3.73 (d, J = 9.5 Hz, 1 H), 3.82 (t, J = 7.0 Hz, 1 H, 3 H, 5 H, 11-H, 13-H), 4.90 (d, J = 10.0 Hz, 1 H, 9-H), 6.20–6.80 (s, br, 4 H, 6-OH, 11-OH, 13-OH, COOH); ^{13}C NMR δ 6.69, 10.64, 11.09, 14.98, 18.58, 19.78, 20.85, 27.31, 29.60, 29.68, 31.73, 36.19, 38.03, 41.84, 50.48, 73.71, 74.38, 75.86, 99.78, 131.83, 132.63, *C*OOH cannot be found.

(2*R*,3*S*,4*S*,5*R*,6*S*,10*S*,11*R*,12*R*,13*R*)-13-Ethyl-6,11-dihydroxy-3,5-*O*-(isopropylidenedioxy)-2,4,6,8,10,12-hexamethyl-8(*E*)-tredecenolide (50). For macrolactonization, seco acid **47** (249 mg, 0.56 mmol) in THF (6 mL) was treated with triethylamine (92 μL, 0.60 mmol) for 10 min at 22 °C. 2,4,6-Trichlorobenzoyl chloride (142 mg, 0.58 mmol) was added and the mixture was stirred at 22 °C for 2 h. The mixture was filtered under an argon atmosphere and the filtrate was diluted with toluene (500 mL). This solution was added dropwise over a period of 4 h to a refluxing solution of DMAP (1.84 g, 15 mmol) in toluene (200 mL). To achieve high dilution conditions, the dropping funnel was arranged on the head of a 30-cm Vigreux column, half of which was rinsed by the refluxing toluene. The mixture was refluxed for an additional hour and then concentrated in vacuo. The residue was triturated with five 10-mL portions of ether. The ether extract was evaporated and the residue was purified by flash chromatography (3:1 hexane/ethyl acetate) to give lactone **50** (193 mg, 81%) as colorless crystals: mp 144–146 °C; $[\alpha]^{20}_D$ = +72.7° (c 1); ^{1}H NMR (major conformer) δ 0.78 (d, J = 7.5 Hz, 3 H), 0.86 (d, J = 7.5 Hz, 3 H), 0.94 (d, J = 7.3 Hz, 3 H, 4-CH_3, 10-CH_3, 12-CH_3), 0.88 (t, J = 7.5 Hz, 3 H, 13-CH_2CH_3), 1.14 (s, 3 H, 6-CH_3), 1.17 (d, J = 7.0 Hz, 3 H, 2-CH_3), 1.36 (s, 6 H, isopropylidene CH_3), 1.52–1.80 (m, 3 H, 4-H, 13-CH_2CH_3), 1.84 (s, 3 H, 8-CH_3), 2.07–2.16 (m, 1 H, 12-H), 2.18 (d, J = 13.5 Hz, 1 H, 7-H), 2.19 (s, 1 H, 6-OH), 2.52 (d, J = 13.5 Hz, 1 H, 7-H), 2.53–2.68 (m, 2 H, 2-H, 10-H), 2.80 (dd, J = 10.8, 5.4 Hz, 1 H, 11-H), 3.54 (s, 1 H, 11-OH), 3.63 (d, J = 2.2 Hz, 1 H, 5-H), 3.82 (dd, J = 10.2, 2.0 Hz, 1 H, 3-H),

5.21 (ddd, J = 10.8, 5.4, 2.0 Hz, 1 H, 13-H), 5.38 (d, J = 10.3 Hz, 1 H, 9-H); ^{1}H NMR (minor conformer) δ 3.54 (d, J = 2.0 Hz, 1 H, 5-H), 3.73 (dd, J = 10.0, 2.2 Hz, 1 H, 3-H), 4.50 (dt, J = 10.8, 3.0 Hz, 1 H, 13-H), 5.09 (d, J = 10.8 Hz, 1 H, 9-H); ^{13}C NMR (major conformer) δ 6.63, 8.94, 10.47, 10.79, 15.40, 17.86, 19.58, 24.82, 29.84, 31.64, 32.22, 34.33, 39.54, 42.17, 49.67, 72.59, 75.70, 76.46, 77.17, 78.32, 99.73, 131.42, 134.53, 177.78; MS (EI, 80 eV, 60 °C) m/e (relative intensity) 426 (6, M^+), 411 (4, $(M - CH_3)^+$), 326 (16), 285 (28), 187 (38), 169 (25), 99 (40), 85 (31), 69 (29), 43 (100). Anal. Calcd for $C_{24}H_{42}O_6$: C, 67.57; H, 9.92. Found: C, 67.75; H, 10.04.

(2*R*,3*S*,4*S*,5*R*,6*R*,10*S*,11*R*,12*R*,13*R*)-13-Ethyl-6,11-dihydroxy-3,5-*O*-(isopropylidenedioxy)-2,4,6,8,10,12-hexamethyl-8(*E*)-tredecenolide (51). Seco acid **49** (100 mg, 0.225 mmol) was lactonized as described for seco acid **47** to furnish analytically pure lactone **51** (79 mg, 82%) as a colorless oil. **51**; $[\alpha]^{20}_D$ = +41.2° (c 2); ^{1}H NMR (major conformer) δ 0.78–1.08 (m, 12 H, 4-CH_3, 10-CH_3, 12-CH_3, 13-CH$_2$CH_3), 1.17 (d, J = 7.0 Hz, 3 H, 2-CH_3), 1.34 (s, 3 H, 2-CH_3), 1.40 (s, 3 H, isopropylidene CH_3), 1.44 (s, 3 H, isopropylidene CH_3), 1.40–1.92 (m, 4 H, 4-H, 7-H, 13-CH_2CH$_3$), 1.72 (s, 3 H, 8-CH_3), 2.00–2.20 (m, 2 H, 7-H, 12-H), 2.50–2.92 (m, 2 H, 2-H, 10-H), 2.86 (s, 1 H, OH), 3.14 (s, 1 H, OH), 3.48–3.64 (m, 1 H), 3.76–3.92 (m, 2 H, 3-H, 5-H, 11-H), 5.24 (mc, 1 H, 13-H), 5.46 (d, J = 10.0 Hz, 1 H, 9-H); ^{1}H NMR (minor conformer) δ 4.56 (mc, 1 H, 13-H), 5.24 (hidden, 1 H, 9-H); ^{13}C NMR (major conformer) δ 7.05, 9.08, 10.51, 10.99, 15.20, 17.88, 18.38, 19.70, 24.64, 24.95, 29.81, 32.60, 33.53, 39.70, 42.19, 51.55, 72.73, 75.02, 75.98, 91.48, 100.23, 128.14, 136.88, 177.90; MS (EI, 80 eV, 60 °C) m/e (relative intensity) 426 (6, M^+), 411 (4, $(M - CH_3)^+$), 326 (16), 285 (28), 187 (38), 169 (25), 99 (40), 85 (31), 69 (29), 43 (100). Anal. Calcd for $C_{24}H_{42}O_6$: C, 67.57; H, 9.92. Found: C, 67.13; H, 10.06.

(2*R*,3*S*,4*S*,5*R*,6*S*,8*R*,9*R*,10*S*,11*R*,12*R*,13*R*)- and (2*R*,3*S*,4*S*,5*R*,6*S*,8*S*,9*S*,11*R*,12*R*,13*R*)-13-Ethyl-6,9,11-trihydroxy-3,5-*O*-(isopropylidenedioxy)-2,4,6,8,10,12-hexamethyltredecanolide (52 and 53). For hydroboration, lactone **50** (160 mg, 0.38 mmol) in THF (100 μL) was treated with borane–dimethyl sulfide complex (200 μL, 2.00 mmol) at 22 °C for 16 h. NaOH (3 N, 700 μL) and H_2O_2 (30%, 700 μL) were added at 0 °C and the mixture was stirred at 0 °C for 20 min and then neutralized with hydrochloric acid (2 N). Extraction with several 20-mL portions of ether, washing of the combined extracts with water, drying over $MgSO_4$, and evaporation of the solvent in vacuo furnished the crude product (140 mg), which was separated by HPLC (1:10 2-propanol/hexane) to give **52** (120 mg, 72%) as colorless crystals (mp 223 °C) and **53** (15 mg, 9%) as a colorless oil. Additionally, 22 mg (13%) of the hydroborated seco acid **56** was isolated.

52: $[\alpha]^{20}_D$ = +22.3° (c 1); ^{1}H NMR δ 0.89 (t, J = 7.5 Hz, 3 H, 13-CH$_2$CH_3), 0.82 (d, J = 7.2 Hz, 3 H), 0.98 (d, J = 7.2 Hz, 3 H), 1.15 (d, J = 7.0 Hz, 3 H), 1.17 (d, J = 7.0 Hz, 3 H), 1.18 (d, J = 7.0 Hz, 3 H, 2-CH_3, 4-CH_3, 8-CH_3, 10-CH_3, 12-CH_3), 1.30 (s, 3 H, 6-CH_3), 1.44 (s, 3 H, isopropylidene CH_3), 1.46 (s, 3 H, isopropylidene CH_3), 1.42–1.88 (m, 9 H, 4-H, 7-H, 8-H, 10-H, 12-H, 13-CH_2, OH), 2.06 (s, 1 H, OH), 2.79 (dq, J = 10.5, 7.2 Hz, 1 H, 2-H), 2.89 (d, J = 5.0 Hz, 1 H, O*H*), 3.34 (d, J = 9.2 Hz, 1 H, 9-H), 3.50 (d, J = 9.7 Hz, 1 H), 3.74 (d, J = 10.2 Hz, 1 H, 3-H, 11-H), 3.55 (s, 1 H, 5-H), 5.28 (ddd, J = 9.0, 5.0, 1 Hz, 1 H, 13-H); ^{13}C NMR δ 6.89, 8.72, 8.89, 10.57, 13.73, 19.89, 20.31, 25.55, 29.14, 29.55, 29.66, 32.73, 36.49, 36.80, 41.22, 42.14, 70.04, 74.38, 76.27, 77.58, 77.68, 81.24, 101.21, 177.42.

53: $[\alpha]^{20}_D$ = +9.1° (c 0.7); ^{1}H NMR δ 0.93 (t, J = 7.5 Hz, 3 H, 13-CH$_2$CH_3), 0.80 (d, J = 7.5 Hz, 3 H), 1.00 (d, J = 7.2 Hz, 3 H), 1.19 (d, J = 7.5 Hz, 3 H), 1.27 (d, J = 7.0 Hz, 3 H), 1.30 (d, J = 7.0 Hz, 3 H, 2-CH_3, 4-CH_3, 8-CH_3, 10-CH_3, 12-CH_3), 1.23 (s, 3 H, 6-CH_3), 1.38 (s, 3 H, isopropylidene CH_3), 1.44 (s, 3 H, isopropylidene CH_3), 1.40–1.91 (m, 8 H, 4-H, 7-H, 8-H, 10-H, 12-H, 13-CH_2-), 2.36 (s, 1 H, O*H*), 2.94–3.06 (m, 2 H, 2-H, 9-H), 3.48 (s, 1 H, O*H*), 3.52 (d, J = 8.0 Hz, 1 H), 3.74 (dd, J = 10.0, 2.5 Hz, 1 H, 3-H, 11-H), 3.60 (s, 1 H, 5-H), 3.72 (s, 1 H, OH), 5.10 (ddd, J = 9.0, 5.0, 1 Hz, 1 H, 13-H); ^{13}C NMR δ 6.46, 8.66, 8.91, 10.64, 15.61, 19.63, 21.09, 23.21, 25.29, 29.19, 29.64, 36.32, 36.47, 37.18, 40.69, 44.55, 69.65, 72.96, 76.84, 78.85, 80.63, 83.79, 178.0.

56: ^{1}H NMR δ 0.77 (d, J = 7.2 Hz, 3 H), 0.89 (d, J = 7.2 Hz, 3 H), 1.01 (d, J = 7.0 Hz, 3 H), 1.02 (d, J = 7.2 Hz, 3 H, 4-CH_3, 8-CH_3, 10-CH_3, 12-CH_3), 0.95 (t, J = 7.5 Hz, 3 H, 15-H), 1.21 (d, 3 H, 2-CH_3), 1.22 (s, 3 H, 6-CH_3), 1.40 (s, 3 H, isopropylidene CH_3), 1.43 (s, 3 H, isopropylidene CH_3), 1.37–1.99 (m, 9 H, 2-H, 4-H, 7-H, 8-H, 10-H, 12-H, 14-H), 2.92 (s, 2 H, OH), 3.51 (d, J = 10.0 Hz, 1 H), 3.55–3.65 (m, 2 H), 3.62 (s, 1 H), 3.81 (d, J = 9.5 Hz, 1 H, 3-H, 5-H, 9-H, 11-H, 13-H), 4.60 (s, 3 H, OH); ^{13}C NMR δ 4.01, 7.17, 11.12, 11.95, 14.04, 18.78, 19.63, 25.22, 26.58, 29.88, 31.12, 32.63, 34.83, 36.21, 39.69, 42.31, 63.85, 75.99, 78.67, 79.41, 82.31, 99.51, COOH cannot be found.

Table III. Crystal Data[41] and Experimental Details for Structure Determinations of **46** and **52**

	46	**52**
formula	$C_{32}H_{60}O_8Si$	$C_{24}H_{44}O_7$
formula wt	600.9	444.6
crystal system	triclinic	orthorhombic
a, Å	7.751 (2)	9.206 (3)
b, Å	15.200 (3)	14.754 (10)
c, Å	9.197 (2)	18.720 (6)
α, deg	103.73 (2)	90
β, deg	114.17 (2)	90
γ, deg	88.69 (2)	90
V, Å^3	951.8	2543
space group	$P\bar{1}$	$P2_12_12_1$
Z	1	4
d_{calcd}, g/cm^3	1.047	1.161
crystal size, mm	0.6 × 0.15 × 0.05	0.2 × 0.025 × 0.7
radiation	Cu Kα	Cu Kα
λ, Å	1.5418	1.5418
μ, cm^{-1}	8.61	5.8
temp, °C	21	21
data collection instrument	STOE four circle	STOE four circle
orientatn reflctns, no., range (2θ, deg)	34, 46–58	32, 21.5–48
scan method	ω–2θ, 0.02–0.04°/step	
scan width	$\Delta\omega$ = 0.94° + 0.23° tan ω	$\Delta\omega$ = 1.5° + 0.23° tan ω
measuring time, s/step	0.6–1.8	0.5–2.0
data collection range (2θ, deg)	5–120	5–120
no. of reflctns collected	5825	1529
no. of unique reflctns	2849	1529
unique reflections with $F_o > 2\sigma(F_o)$	2084	1095
no. of parameters refined	315	280
largest Δ/σ, final cycle	0.084	0.0073
largest residual peak, e/Å^3	0.318	0.585
R^a	0.089	0.077
R_w^b	0.094	0.047
goodness of fit indicator^c	1.01	2.27

$^a R = \sum||F_o| - |F_c||/\sum|F_o|$. $^b R_w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$; $w = 1/\sigma^2(|F_o|)$. ^{c}Goodness of fit = $[\sum w(|F_o| - |F_c|)^2/(N_{obs} - N_{parameters})]^{1/2}$.

(2*R*,3*S*,4*S*,5*R*,6*R*,8*R*,9*R*,10*S*,11*R*,12*R*,13*R*)-(2*R*,3*S*,4*S*,5*R*,-6*R*,8*S*,9*S*,10*S*,11*R*,12*R*,13*R*)-13-Ethyl-6,9,11-trihydroxy-3,5-*O*-(isopropylidenedioxy)-2,4,6,8,10,12-hexamethyltredecanolide (54 and 55). Analogously to **50** lactone, **51** (80 mg, 0.195 mmol) was hydroborated to furnish after HPLC (conditions as above) **54** (60 mg, 69%) and **55** (7 mg, 8%) as colorless oils.

54: $[\alpha]^{20}_D$ = +13.1° (c 0.5); ^{1}H NMR δ 0.91 (t, J = 7.5 Hz, 3 H, 13-CH$_2$CH_3), 0.80 (d, J = 7.2 Hz, 3 H), 0.97 (d, J = 7.2 Hz, 3 H), 0.99 (d, J = 7.0 Hz, 3 H), 1.18 (d, J = 7.0 Hz, 3 H), 1.26 (d, J = 7.0 Hz, 3 H, 2-CH_3, 4-CH_3, 8-CH_3, 10-CH_3, 12-CH_3), 1.21 (s, 3 H, 6-CH_3), 1.46 (s, 3 H, isopropylidene CH_3), 1.48 (s, 3 H, isopropylidene CH_3), 1.48–1.88 (m, 8 H, 4-H, 7-H, 8-H, 10-H, 12-H, 13-CH_2), 2.21 (s, 1 H, O*H*), 2.78 (dq, J = 10.5, 6.5 Hz, 1 H, 2-H), 2.90 (d, J = 8 Hz, 1 H, O*H*), 3.34 (d, J = 10.5 Hz, 1 H, 9-H), 3.50 (d, J = 10.0 Hz, 1 H), 3.78 (d, J = 11.0 Hz, 1 H, 3-H, 11-H), 3.94 (s, 1 H, 5-H), 5.28 (ddd, J = 8,5, 5.5, 1 Hz, 1 H, 13-H); ^{13}C NMR δ 6.74, 8.76, 10.59, 13.54, 19,52, 19.86, 25.52, 26.73, 29.61, 29.85, 32.20, 35.58, 36.34, 41.03, 42,06, 69.89, 74.38, 76.34, 78.07, 79.64, 80.38, 101.34, 177.39; HRMS (EI, 80 eV, 100 °C) mass calcd for $C_{23}H_{41}O_7$ ($M^+ - CH_3$) 429.285 23, found 429.285 065.

55: $[\alpha]^{20}_D$ = +2° (c 0.1); ^{1}H NMR δ 0.94 (t, J = 7.5 Hz, 3 H, 13-CH$_2$CH_3), 0.78 (d, J = 7.2 Hz, 3 H), 1.02 (d, J = 7.0 Hz, 3 H), 1.04 (d, J = 7.5 Hz, 3 H), 1.21–1.32 (m, 15 H, 2-CH_3, 4-CH_3, 6-CH_3, 8-CH_3, 10-CH_3, 12-CH_3, isopropylidene CH_3), 1.42–1.87 (m, 8 H, 4-H, 7-H, 8-H, 10-H, 12-H, 13-CH_2, 2.88–2.98 (m, 2 H, 2-H, 9-H), 2.92 (s, 1 H, O*H*), 3.51 (dd, J = 9.5, 1.5 Hz, 1 H), 3.73 (dd, J = 9.5, 2.0 Hz, 1 H, 3-H, 11-H), 3.76 (s, 1 H, O*H*), 3.90 (s, 1 H, 5-H), 5.13 (ddd, J = 8.5, 5.5, 1 Hz, 1 H, 13-H).

Erythronolide B (5). Lactone **54** (65 mg, 0.146 mmol) was oxidized with PCC (110 mg, 0.51 mmol) in dichloromethane (2 mL) as described[3c] to give the crude 9-ketone (42 mg, 65%), which was hydrolyzed with 80% acetic acid (2 mL) as described[3e] to give erythronolide B (**5**; 23 mg, 50%) as colorless crystals, in all respects identical with an au-

thentic sample. As the NMR data in the literature are incomplete, we recorded ^1H and ^{13}C NMR spectra in $CDCl_3$ and DMSO-d_6 at 270 MHz. The signals were assigned by ^1H-^1H and ^1H-^{13}C-COSY measurements.

5; mp 223 °C; $[\alpha]^{20}_D = -64.9°$ (*c* 1, MeOH);[8e,40] ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7.0 Hz, 3 H, 12-CH_3), 0.93 (t, J = 7.3 Hz, 3 H, 13-CH_2CH_3), 1.02 (d, J = 7.0 Hz, 3 H, 10-CH_3), 1.07 (d, J = 7.1 Hz, 3 H, 4-CH_3), 1.22 (d, J = 6.7 Hz, 3 H, 8-CH_3), 1.30 (d, J = 6.8 Hz, 3 H, 2-CH_3), 1.31 (s, 3 H, 6-CH_3), 1.44 (dd, J_{AB} = 14.7 Hz, $J_{A7,8}$ = 10.5 Hz, 1 H, 7-H), 1.44-1.58 (m, 1 H, 13-CH_2), 1.68-1.82 (m, 2 H, 12-H, 13-CH_2CH$_3$), 1.90 (dd, J_{AB} = 14.7 Hz, $J_{B7,8}$ = 4.8 Hz, 1 H, 7-H), 1.99 (mc, 1 H, 4-H), 2.67 (s, 1 H, OH), 2.72-2.86 (m, 3 H, 2-H, 8-H, 10-H), 3.07 (s, 1 H, OH), 3.68 (mc, 1 H, 11-H), 3.72 (s, 2 H, OH), 3.88 (d, J = 9.5 Hz, 1 H, 3-H), 3.92 (s, 1 H, 3-H), 5.22 (dq, J = 9.5, 3.8 Hz, 1 H, 13-H); ^{13}C NMR ($CDCl_3$) δ 6.14, 7.17, 9,14, 10,50, 25.52, 26.44, 36.42, 40.28, 40.92, 42.33, 43.89, 70.57, 75.83, 75.99, 79.71, 80.48, carbonyl C's cannot be found; ^1H NMR (DMSO-d_6) δ 0.80 (t, J = 7.6 Hz, 3 H, 13-CH_2CH_3), 0.85 (d, J = 7.5 Hz, 6 H, 10-CH_3, 12-CH_3), 0.88 (d, J = 7.3 Hz, 3 H, 4-CH_3), 1.04 (d, J = 6.9 Hz, 3 H, 8-CH_3), 1.09 (d, J = 7.0 Hz, 3 H, 2-CH_3), 1.18 (s, 3 H, 6-CH_3), 1.19 (mc, 1 H, 7-H), 1.36-1.71 (m, 3 H, 12-H, 13-CH_2), 1.85 (dd, J = 15, 7.0 Hz, 1 H, 7-H), 2.01 (mc, 1 H, 4-H), 2.50 (mc, 1 H, 2-H), 2.66 (mc, 1 H, 8-H), 2.84 (mc, 1 H, 10-H), 3.36-3.44 (m, 2 H, 5-H, 11-OH), 3.51 (dd, J = 10.0, 5.2 Hz, 1 H, 3-H), 3.85 (dd, J = 10.5, 4.5 Hz, 1 H, 11-H), 4.19 (s, 1 H, 6-OH), 4.48 (d, J = 5.2 Hz, 1 H, 5-OH), 4,57 (d, J = 5.8 Hz, 1 H, 3-OH), 5.34 (dq, J = 9.5, 5.0 Hz, 1 H, 13-H); ^{13}C NMR (DMSO-d_6) δ 7.60 (4-CH_3), 8.21, 9.00 (10-CH_3, 12-CH_3), 10.24 (CH_2CH_3), 15.04 (2-CH_3), 17.30 (8-CH_3), 25.42 (CH_2CH_3), 26.31 (6-CH_3), 35.71 (4-C), 37.65 (7-C), 39.81 (12-C), 40.51 (10-C), 42.00 (8-C), 43.31 (2-C), 69.49 (11-C), 73.61 (13-C), 74.13 (6-C), 77.49 (3-C), 79.85 (5-C), 174.86 (1-C), 216.28 (9-C).

X-ray Analyses. See Table III and supplementary material.

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Supplementary Material Available: Tables of analytical data (^1H and ^{13}C NMR, IR, and MS spectra and optical rotations) of intermediates and results of the single-crystal X-ray analysis of compounds **46** and **52** including positional parameters, U values, intramolecular distances, bond angles, and torsional angles (27 pages); listing of observed and calculated structure factors (43 pages). Ordering information is given on any current masthead page.

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Synthesis of Optically Active Cyclobutanones by the Photolysis of Chromium-Alkoxycarbene Complexes in the Presence of Optically Active Ene-Carbamates

Louis S. Hegedus,* Roderick W. Bates, and Björn C. Söderberg

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. *Received July 16, 1990*

Abstract: Optically active ene-carbamates derived from (*S*)-phenylglycine were allowed to photochemically react with a variety of (alkoxy)(alkyl)chromium-carbene complexes. Cyclobutanones were formed in fair to good yield with generally excellent control of stereochemistry.

Introduction

Cyclobutanones are important intermediates in the synthesis of a wide range of natural products and other complex organic molecules.[1] They are most often made by the [2 + 2] cycloaddition reaction between ketenes and olefins,[2] a process that has been the subject of several recent studies.[3] In contrast, asymmetric induction into the ketene-olefin cycloaddition process has been little studied. With the chiral auxiliary on the ketene fragment, induction was high (80-97%) with use of optically active ketene iminium salts of symmetrical ketenes,[4] but somewhat lower (~50%) in the cycloaddition of optically active (menthyloxy)(methyl)ketene to ethyl propenyl ether.[5] Similarly, cycloaddition of dichloroketene to optically active enol ethers proceeded with diastereomeric excesses ranging from 50 to >95%.[6]

Recent research in our laboratory has centered on the ketene-like reactivity of heteroatom-stabilized (Fischer) carbenes when photolyzed with visible light[7] and the use of this process to synthesize β-lactams,[8] α-amino acid esters,[9] and cyclobutanones.[10]

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