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Supplementary Material Available: Crystal data, fractional coordinates, anisotropic thermal parameters, bond distances, bond angles, and isotropic thermal parameters for **19** (6 pages). Ordering information is given on any current masthead page.

Stereoselective Reduction of Bicyclic Ketals. A New, Enantioselective Synthesis of Isolaurepinnacin and Lauthisan Skeletons[1]

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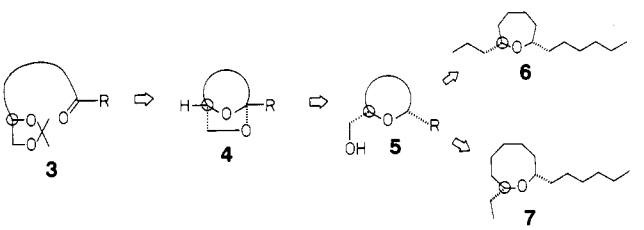
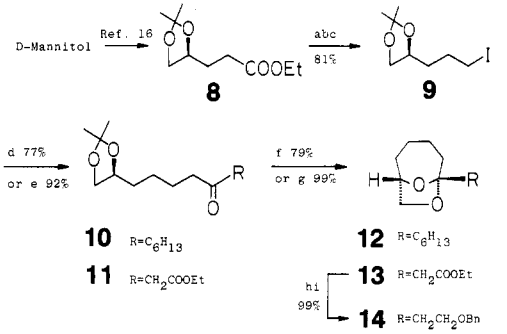
A general synthetic strategy for constructing seven- and eight-membered cyclic ether derivatives is described. The important feature of this work is a highly stereoselective reduction of bicyclic ketals, i.e., cis-selective reduction with triethylsilane/$TiCl_4$ and trans-selective reduction with diisobutylaluminum hydride (DIBAL). The procedure completed a new and efficient synthesis of isolaurepinnacin and lauthisan skeletons in optically active forms.

In view of the increasing number of biologically active marine natural products containing medium- and large-sized cyclic ether derivatives,[2] much attention has recently been focused on efficient approaches toward these systems. In particular, the lauthisan family,[3] having an eight-membered cyclic ether, which was mainly isolated from the genus *Laurencia*, has been a major synthetic challenge within the past decade.[4-11] The pioneering work in this field has been established by Masamune and co-workers, i.e., the total synthesis of *dl*-laurencin.[4] However, their

Scheme I



Scheme II[a]



[a] Conditions: (a) $LiAlH_4$, Et_2O, 0 °C; (b) *p*-TsCl, Et_3N, CH_2Cl_2; (c) KI, K_2CO_3, acetone, reflux; (d) $CH_3C(=NNMe_2)C_6H_{13}$, *n*-BuLi, THF, -78 °C → room temperature, then SiO_2, CH_2Cl_2; (e) CH_3COCH_2COOEt, LDA, THF, 0 °C; (f) *p*-TsOH·H_2O, CH_2Cl_2, reflux, 24 h; (g) *p*-TsOH·H_2O, CH_2Cl_2, reflux, 3 h; (h) $LiAlH_4$, Et_2O, 0 °C; (i) NaH, THF, 0 °C, then benzyl bromide.

(1) The preliminary work was presented at the 16th International Symposium on the Chemistry of Natural Products (IUPAC), Kyoto, Japan, May 29-June 3, 1988 (Abstract PB 90).

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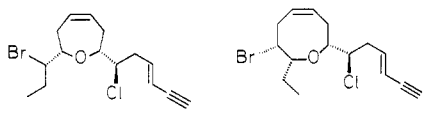
0022-3263/89/1954-5153$01.50/0

work suffers from the defects of lengthy and impractical procedures. More recently, some other groups have succeeded in producing considerably revised approaches to reach the lauthisan skeleton. For example, Overman and Thompson reported an enantioselective synthesis of laurenyne by using the Sharpless catalytic asymmetric epoxidation to introduce the asymmetric center.[6a] Clark and Holmes discovered that the Enders asymmetric alkylation followed by the Baeyer–Villiger oxidation serves as a useful tactic to afford the lauthisan skeleton in an optically active form.[7a] In spite of these efforts, most of the work lacks a general flexibility in constructing the ring stereochemistry in a desired fashion, and also, the studies are restricted mostly to racemic compounds.

Our interest in these molecules arises from our recent success with the highly stereoselective reduction of bicyclic ketals as applied to the total synthesis of (−)-(*R*,*R*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid.[12] In this paper we will describe the extension of this methodology to seven- and eight-membered cyclic ethers **6** and **7**, skeletons of isolaurepinnacin (**1**) and laurepinnacin (**2**), respectively,[13]



ISOLAUREPINNACIN(1) LAUREPINNACIN(2)

as outlined in the strategy in Scheme I. Our results disclosed here provide a remarkably efficient entry into the target system with either cis or trans stereochemistry in an enantiomerically well-defined form. In addition, through this work we have succeeded in identifying the absolute configuration of isolaurepinnacin.

Results and Discussion

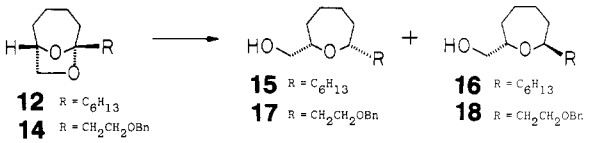
Synthesis of Isolaurepinnacin Skeleton. According to our synthetic strategy, the necessary key intermediates of bicyclic ketals **12** and **13** would be derived from the intramolecular transketalization of acetonides **10** and **11**. To construct these systems, we chose to investigate two approaches based on the alkylation of dimethylhydrazones[14] and of acetoacetic esters (Scheme II).[15]

The first approach started with an enantiomerically well recognized iodide, **9**, which is readily available from D-mannitol as a chiral source.[16] Alkylation of **9** with the lithium salt of 2-octanone dimethylhydrazone proceeded smoothly. The next step for regeneration of the carbonyl group from dimethylhydrazone derivatives is usually performed under weakly acidic or oxidative cleavage conditions.[14,17] Fortunately, we found that the silica gel mediated hydrolytic procedure gave, very cleanly, the desired ketone **10** without affecting the acid-sensitive acetonide function.[18] The reaction of **10** with a catalytic amount of *p*-toluenesulfonic acid in refluxing dichlromethane was rather slow but gave bicyclic ketal **12** in 60.8% overall yield from **9**.

On the other hand, the intramoecular transketalization of β-keto ester **11**, which was simply prepared from iodide **9** and the dianion of ethyl acetoacetate, occurred much faster to give **13**, which was further converted to benzyl ether **14** in excellent overall yield.

With two kinds of bicyclic ketals, **12** and **14**, in hand, we then proceeded with the stereoselective reduction of these compounds. The results are summarized in Table I. In accordance with our previous observations,[12] reduction of **12** with Et_3SiH in the presence of $TiCl_4$ afforded an 86.0:14.0 ratio of cis/trans isomers **15** and **16** as determined by capillary GC analyses, whereas the use of diisobutylaluminum hydride (DIBAL) showed a high trans selectivity (**15**:**16** = 4.7:95.3). The stereochemistry of each

Table I. Stereoselective Reduction of Bicyclic Ketals 12 and 14



12 R = C_6H_{13}; **14** R = CH_2CH_2OBn

15 R = C_6H_{13}; **17** R = CH_2CH_2OBn

16 R = C_6H_{13}; **18** R = CH_2CH_2OBn

substrate	reagent[a]/ Lewis acid[b]	temp, °C	time, h	yield,[c] %	ratio,[d] 15:16 or 17:18
12	$Et_3SiH/TiCl_4$	−78	0.5	91	86.0:14.0
12	DIBAL/−	rt[e]	12	96	4.7:95.3
14	$Et_3SiH/TiCl_4$	−78	0.33	86	91.1:8.9
14	DIBAL/−	rt[e]	15	88	1.9:98.1

[a] We used 4 equiv. [b] We used 1.2 equiv. [c] Isolated yield. [d] Determined by capillary GC. [e] Room temperature.

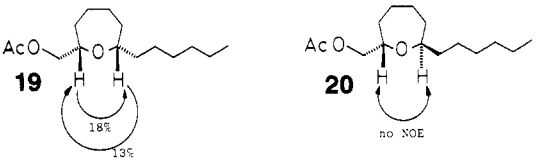


Figure 1. Configuration of **19** and **20** as deduced by ^1H NMR nuclear Overhauser effect (NOE) experiments. Diagnostic enhancements are indicated.

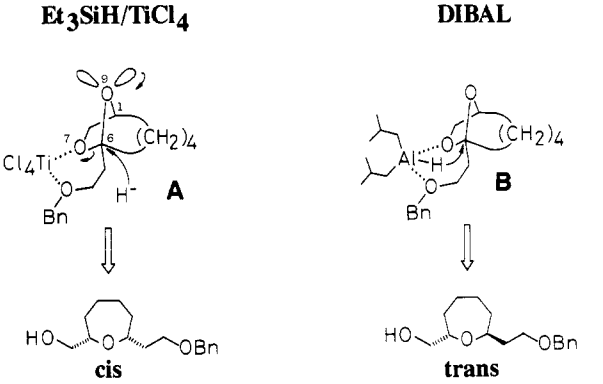


Figure 2. Plausible reactive intermediates for reduction of bicyclic ketals with $Et_3SiH/TiCl_4$ or DIBAL.

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(16) Takano, S.; Kurotaki, A.; Takahashi, M.; Ogasawara, K. *Synthesis* **1986**, 403. For a general review, see: Hanessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach*; Pergamon: Oxford, 1983.

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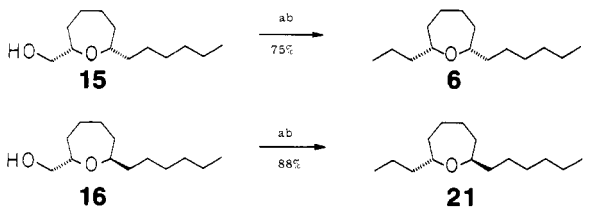
Scheme III[a]



[a] Conditions: (a) Tf_2O, pyridine, −15 °C; (b) EtMgBr, CuBr, THF, 0 °C.

isomer was ascertained by NOE experiments with the corresponding acetates **19** and **20** (Figure 1); cis-isomer **19** showed a strong NOE between the two methine hydrogens at C-2 and C-7, but no enhancement with the methine hydrogens of trans-isomer **20** could be observed. Interestingly, an increased selectivity could be realized by using benzyl ether **14**: 91.1:8.9 with $Et_3SiH/TiCl_4$; 1.9:98.1 with DIBAL.

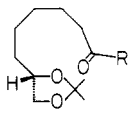
This remarkable difference in the stereoselectivity of these reactions can be explained in terms of the reactive intermediates A and B as depicted in Figure 2.[12,19] Thus, the cis-selective reduction with $Et_3SiH/TiCl_4$ is probably due to a complex formation of titanium(IV) chloride with both the O-7 and the benzyl ether oxygen atoms;[20] the hydride attacks from the rear face of the ketal oxygen via transition state A. The specific migrating aptitude of O-7 seems to be ascribed to the anomeric effects[21] of O-9 as similarly pointed out by Mundy et al.[22] The reduction with DIBAL proceeds via transition state B, wherein the hydride transfer occurs intramolecularly from the syn face of the reagent itself, leading to trans products. From the fact that in both reagent systems **14** showed better selectivity than **12**, we believe **14** functions as a bidenate ligand in forming more favorable complexes.

Since the obtained cis/trans isomeric mixture was readily separable by flash chromatography,[23] further advances to the final synthetic target have been carried out (Scheme III). The most straightforward approach toward this end would be direct nucleophilic alkylation on the alcoholic carbon atom. This could be achieved by taking advantage of the powerful copper(I)-catalyzed C–C bond formations using alkyl triflates, which we have recently discovered in this laboratory.[24] Namely, treatment of **15** with triflic anhydride followed by alkylation with ethylmagnesium bromide in the presence of 0.2 equiv of CuBr afforded the desired compound **6**, $[\alpha]_D$ +1.5°. The overall yield for the six-step sequence from iodide **9** was 35.7%. The application of the same technology to **16** produced trans-isomer **21**; $[\alpha]_D$ +20.5°.

Alternatively, the synthesis of **6** from **17** was completed as illustrated in Scheme IV by the following sequential treatment: (1) triflation followed by CuBr-catalyzed alkylation with ethylmagnesium bromide; (2) reductive debenzylation (H_2, 10% Pd/C, ethanol); and (3) tosylation followed by alkylation with n-Bu_2CuLi. The optical activity of **6** obtained by this procedure was determined as $[\alpha]_D$ +1.6°, and the overall yield for the 10-step sequence from iodide **9** was 46.6%. The intermediate **17** was highly labile, to provide an enantiomer of **6** by similar elaboration of the side chain: (1) triflation followed by CuBr-catalyzed alkylation with pentylmagnesium bromide; (2) reductive debenzylation; and (3) tosylation followed by alkylation with Me_2CuLi. The optical activity of **26** exhibited a completely opposite sign of rotation: $[\alpha]_D$ −1.3°.

The products **6** and **26** prepared from this experiment were found to be identical (IR, ^1H NMR) with an authentic sample kindly provided by Dr. Fukuzawa.[25] The only difference is the optical rotation: the reported value for **6** is $[\alpha]_D$ −2.5°.[13] According to a private communication from Dr. Fukuzawa, however, the reported optical rotation should be corrected to $[\alpha]_D$ +3.3°, and in addition, this value was rather large due to contamination.[25] Consequently, we could demonstrate unambiguously that the synthetic product **6** possesses the same absolute configuration as the natural substance.

Synthesis of Laurepinnacin Skeleton (Lauthisan). As the above discussion indicates, the stereoselective reduction of bicyclic ketals provides an extremely efficient route to the cyclic ether derivatives. It now becomes of interest to apply the technique to the lauthisan skeleton (**7**). A compound homologous to **10** or **11** is ketone **27** (R



27

= C_6H_{13} or CH_2COOEt).[26] Not surprisingly, however, all attempts at the intramolecular trans ketalization of **27** proved unsuccessful.[28] We expected that this difficulty could be overcome simply by introduction of the cis double bond within the molecule, thereby facilitating the ring-closure.[29] Therefore, we turned our attention to the preparation of **32** or **33**.

As outlined in Schemes V and VI, we adopted two routes for this purpose. The first one relies on a stereoselective synthesis of a *Z* olefin by using Still's reagent.[30] Thus, condensation of **28**, which is readily accessible from L-malic acid,[31] with methyl [bis(2,2,2-trifluoroethoxy)phosphi-

(19) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron Lett.* **1987**, *28*, 6613. Mori, A.; Ishihara, K.; Arai, I.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 755. Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Organomet. Chem.* **1985**, *285*, 83.

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(21) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: Berlin, 1983. Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983.

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(24) Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett.* **1989**, *30*, 1281, 3999.

(25) We are grateful to Dr. Akio Fukuzawa, Hokkaido University, for providing the ^1H and ^{13}C NMR and mass spectra of **6** and **7** and also informing us on the optical rotation of **6**.

(26) In analogy to the Scheme II procedure, ketone **27** was derived from i, which is accessible from ii.[27]

i ii

(27) Gerth, D. B.; Giese, B. *J. Org. Chem.* **1986**, *51*, 3726.

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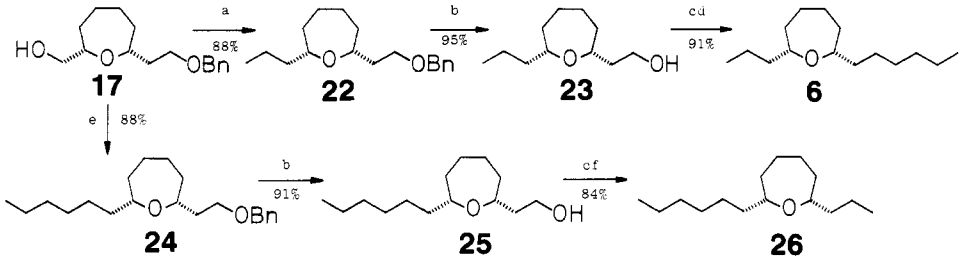
(29) It is known that the compounds containing a cis double bond have a high tendency to form medium- or large-sized rings. See, for example: Itoh, A.; Saito, T.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1456. Hashimoto, S.; Itoh, A.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 4192.

(30) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

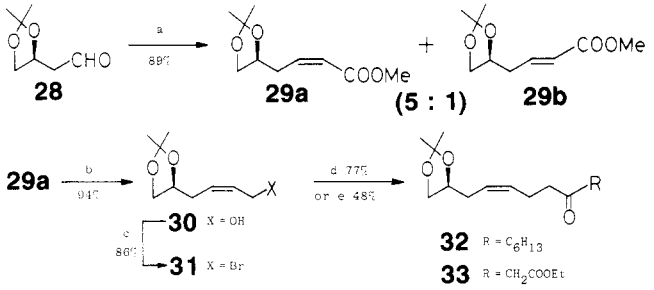
(31) Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 1389. See also: Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1982**, *23*, 4883.

Scheme IV[a]



[a] Conditions: (a) Tf_2O, pyridine, then EtMgBr, CuBr; (b) H_2, 10% Pd/C, EtOH; (c) *p*-TsCl, Et_3N, CH_2Cl_2; (d) *n*-Bu_2CuLi, Et_2O, 0 °C; (e) Tf_2O, pyridine, then $C_5H_{11}MgBr$, CuBr; (f) Me_2CuLi, Et_2O, 0 °C.

Scheme V[a]



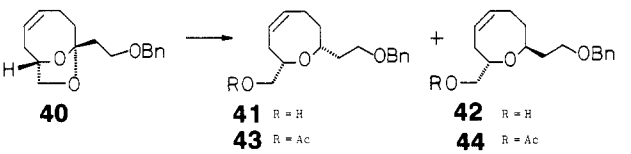
[a] Conditions: (a) NaH, $(CF_3CH_2O)_2P(O)CH_2COOMe$, Et_2O, −78 °C; (b) $LiAlH_4$, Et_2O; (c) CBr_4, K_2CO_3, PPh_3, Et_2O; (d) $CH_3C(=NNMe_2)C_6H_{13}$, *n*-BuLi, THF, room temperature, then SiO_2, CH_2Cl_2; (e) CH_3COCH_2COOEt, LDA, THF, HMPA, 0 °C.

nyl]acetate gave a mixture of *Z* and *E* olefins in a 5:1 ratio. Conversion of **29a** to bromide **31** was accomplished by a two-step procedure: reduction with $LiAlH_4$ followed by treatment with CBr_4/PPh_3. Subsequent alkylation of bromide **31** with 2-octanone dimethylhydrazone or ethyl acetoacetate gave desired products **32** and **33** in 77% and 48% yields, respectively. A major disadvantage of this route is not only a tedious separation at the stage of condensation with Still's reagent but also the difficulty of scaling up the whole reaction sequence. These problems forced us to search for a more practical solution.

The successful synthesis of **33** via the partial reduction of an alkyne derivative is presented in Scheme VI. Reaction of epoxide **34**[32] with the lithium salt of propargyl alcohol tetrahydropyranyl ether (3.8 equiv) and $BF_3{\cdot}OEt_2$ (3.8 equiv)[33] afforded **35**,[34] which was converted to acetonide **36** via hydrolysis to triol and acetonide protection in 73% yield. This product was transformed into bromide **37** and then conveniently alkylated with the dianion of ethyl acetoacetate to give **38** in large quantities. Carefully controlled catalytic hydrogenation of **38** using 5% Pd/$BaSO_4$ and quinoline[35] yielded quantitatively the desired compound **33**.

The intramolecular transketalization of **33** was next examined under a variety of conditions. Fortunately, we found that the reaction was best performed in refluxing 1,2-dichloroethane (0.032 M solution) in the presence of 0.5 equiv of *p*-TsOH·H_2O to afford **39** in 32% yield.[36] Treatment of **32** under similar conditions, however, produced the bicyclic ketal derivative only in low yield. Therefore, we decided to employ the β-keto ester route instead of the dimethylhydrazone route and proceeded with the final stage of this study. After transformation of **39** to benzyl ether **40**, the stereoselective reduction was performed.

Table II. Stereoselective Reduction of Bicyclic Ketal 40



reagent[a]/ Lewis acid[b]	temp, °C	time, h	yield,[c] %	ratio,[d] 41:42
$Et_3SiH/TiCl_4$	−78	1	71	98.5:1.5
DIBAL/−	rt[e]	34	89 (10)	3.0:97.0

[a] We used 4 equiv. [b] We used 1.2 equiv. [c] Isolated yield; value in parentheses is recovery. [d] Determined by capillary GC. [e] Room temperature.

As shown in Table II, the use of two kinds of reducing agents also afforded two different stereoisomers, **41** and **42**, with almost complete selectivity.[37] The structure of these stereoisomers was confirmed analogously as before: the NOE experiments on the corresponding acetates **43** and **44** clarified the cis orientation of **43**.

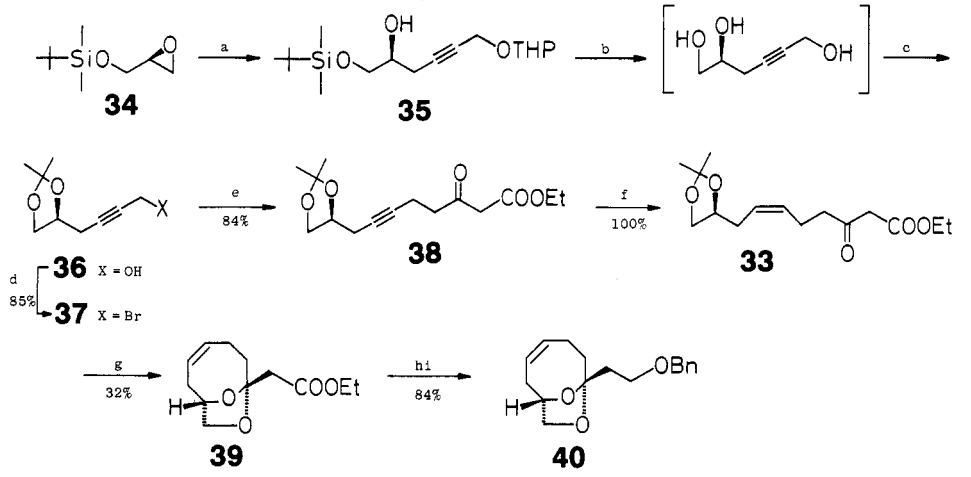
The final stage of this study was the elaboration on the side chain as outlined in Scheme VII. The left chain was built up by sequential treatment of alcohol **41** with triflic anhydride and Me_2CuLi in 83.4% yield. Reductive debenzylation of **45** was accompanied by hydrogenation of the double bond to produce alcohol **46**, which was further converted to the target molecule **7** by treatment with *p*-toluenesulfonyl chloride followed by Lipshutz's reagent (*n*-$Bu_2Cu(CN)Li_2$).[38] The optical rotation of **7** was $[\alpha]_D$ +13.9°, while the reported value is $[\alpha]_D$ +5.3°. The other spectral data including IR, ^1H and ^{13}C NMR, and MS were in good agreement with those of the authentic sample.[25] Thus the procedures described here completed the total synthesis of the lauthisan skeleton. The overall yield for the 11-step sequence from bromide **37** was 12.5%.

Conclusion

A general methodology for highly stereoselective synthesis of seven- and eight-membered cyclic ethers was developed. The method relies on a stereoselective reduction of bicyclic ketals; that is, the reduction with $Et_3SiH/TiCl_4$ gave cis products, whereas the reduction

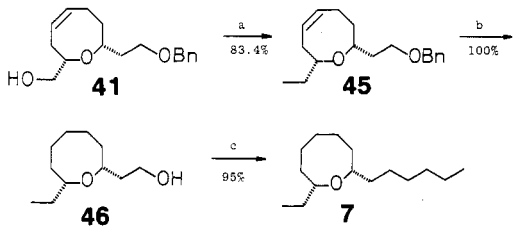
(32) Baldwin, J. J.; Raab, A. W.; Mensler, K.; Arison, B. H.; McClure, D. E. *J. Org. Chem.* **1978**, *43*, 4876.
(33) Yamaguchi, M.; Hirao, I. *J. Chem. Soc., Chem. Commun.* **1984**, 202.
(34) Although a small amount of regioisomer was also formed by this reaction, the impurity was cleanly removed at the stage of **36**. We found that the use of the methoxymethyl derivative of **34** was less satisfactory.
(35) Cram, D. J.; Allinger, N. L. *J. Am. Chem. Soc.* **1956**, *78*, 2518.
(36) The yield was highly dependent on the concentration of the reactant: at 0.156 M, 14%, and at 0.04 M, 27%.
(37) A rather decreased yield when $Et_3SiH/TiCl_4$ was used was due to the concomitant debenzylation of the product. Cf.: Kon, K.; Isoe, S. *Tetrahedron Lett.* **1984**, *25*, 3739.
(38) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. Lipshutz, B. H. *Synthesis* **1987**, 325.

Scheme VI[a]



[a] Conditions: (a) $HC{\equiv}CCH_2OTHP$, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C; (b) *p*-TsOH·H_2O, MeOH, reflux; (c) $(CH_3)_2C(OMe)_2$, PPTS, MeOH, reflux; (d) CBr_4, K_2CO_3, PPh_3, Et_2O; (e) CH_3COCH_2COOEt, LDA, THF, 0 °C; (f) H_2, 5% Pd/$BaSO_4$, quinoline, MeOH; (g) *p*-TsOH·H_2O, $ClCH_2CH_2Cl$, reflux, 11 h; (h) $LiAlH_4$, Et_2O; (i) NaH, THF, 0 °C, then benzyl bromide.

Scheme VII[a]



[a] Conditions: (a) Tf_2O, pyridine, then Me_2CuLi, Et_2O, 0 °C; (b) H_2, 10% Pd/C, EtOH; (c) *p*-TsCl, Et_3N, then *n*-$Bu_2Cu(CN)Li_2$, THF, room temperature.

with DIBAL gave trans products. Particularly noteworthy is their excellence in both stereoselectivity and total yield. Because of the ready availability of bicyclic ketal intermediates in optically active forms, the whole sequence should prove extremely valuable for the enantioselective synthesis of cyclic ether derivatives. Indeed, in the present paper we have explored this feature in the synthesis of **6**, **7**, **21**, and **26**. We believe that the presently developed stereochemically well-defined transformations will have considerable synthetic utility.

Experimental Section[39]

General Methods. All boiling points are uncorrected. Kugelrohr distillation boiling points refer to the bath temperature. The NMR spectra were recorded on a Hitachi R-90H spectrometer (90 MHz for ^1H NMR analysis and 22.6 MHz for ^{13}C NMR analysis) or on a JEOL GX-400 spectrometer (400 MHz for ^1H NMR analysis). All NMR spectra were taken in $CDCl_3$ solution and are reported in parts per million (δ) downfield from TMS as an internal standard with *J* values given in hertz. The IR spectra (cm^{-1}) were measured on neat compounds with a JASCO Model A-302 infrared spectrophotometer. High-resolution mass spectra were obtained with a JEOL HX-100 spectrometer. Optical rotations were measured on a Union PM-101 polarimeter. Capillary GC analyses were performed on a Hitachi G-3000 flame-ionization instrument with an Ulbon HR-54 column (50 m × 0.25 mm). Thin-layer chromatography (TLC) was conducted by using Merck precoated Kieselgel 60F-254 plates (0.25 mm), and for reverse-phase TLC, Merck HPTLC RP-8F-254s plates were employed. Preparative TLC was carried out on 2-mm-thick Merck Kieselgel 60PF-254. Column chromatography was done on Wakogel C-300, and for flash chromatography, Merck Kieselgel (230–400 mesh) was employed.

All solvents were dried immediately before use. Et_2O and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl; dichloromethane, 1,2-dichloroethane, triethylamine, pyridine, dimethylformamide (DMF), and hexamethylphosphoramide (HMPA) were distilled from CaH_2; acetone was distilled from K_2CO_3; $TiCl_4$ was purified according to literature procedure[40] and used as a dichloromethane solution. All reactions were carried out in a nitrogen or argon atmosphere. On workup, all extracts were washed with brine and dried over sodium sulfate.

(*S*)-4-(3-Iodopropyl)-2,2-dimethyl-1,3-dioxolane (9). To a suspension of $LiAlH_4$ (120 mg, 4.3 mmol) in Et_2O (30 mL) at 0 °C was added dropwise **8** (1.2 g, 6.38 mmol)[16] in Et_2O (20 mL), and the reaction mixture was stirred for 2 h. The mixture was quenched with a minimum amount of water, dried, filtered, and concentrated. The obtained alcohol (1 g) was dissolved in CH_2Cl_2 (10 mL) and treated with *p*-TsCl (1.4 g, 7.5 mmol) and triethylamine (1.5 mL). Stirring was continued at room temperature for 1.5 h, and the mixture was extracted with CH_2Cl_2. The extract was dried and evaporated. This material was treated with KI (1.3 g, 7.6 mmol) and K_2CO_3 (130 mg) in refluxing acetone (50 mL) for 15 h. After evaporation of the solvent, the residue was extracted with Et_2O. Following solvent removal, the crude iodide was purified by distillation to give 1.4 g (81% from **8**) of **9** as a colorless oil: R_f 0.48 (hexane/Et_2O, 2:1); bp 78–80 °C (1.5 mmHg); $[\alpha]^{15}_D$ +7.09° (*c* 1.1, $CHCl_3$); IR 3000, 2950, 2880, 1385, 1370, 1250, 1235, 1215, 1065, 860; ^1H NMR (90 MHz) 1.34 (3 H, s), 1.40 (3 H, s), 1.5–2.2 (4 H, m), 3.23 (2 H, t, J = 6.6), 3.4–3.7 (1 H, m), 3.9–4.2 (2 H, m).

1,2-Di-*O*-isopropylidene-(*S*)-1,2-dihydroxytridecan-7-one (10). To a solution of 2-octanone dimethylhydrazone (3.3 mL, 18 mmol)[41] in THF (30 mL) at −78 °C was added *n*-BuLi (1.40 M in hexane, 12.8 mL, 18 mmol). The mixture was stirred for 0.5 h, and then iodide **9** (3.0 mL, 16.5 mmol) in THF (20 mL) was added at the same temperature. The reaction mixture was allowed to warm to room temperature. After 2 h, the mixture was quenched with water, concentrated, and extracted with Et_2O. The extract was dried and evaporated. This material was hydrolyzed by stirring with 20 g of silica gel in CH_2Cl_2 (100 mL) at room temperature for 12 h. Filtration followed by evaporation of the solvent provided a crude ketone, which was purified by chromatography (hexane/Et_2O, 2:1) to give 3.43 g (77%) of **10** as a colorless oil: R_f 0.37 (hexane/Et_2O, 2:1); $[\alpha]^{16}_D$ +5.25° (*c* 1.22, MeOH); IR 2950, 2920, 2850, 1710 1380, 1370, 1060; ^1H NMR (90 MHz) 0.88 (3 H, *t*, J = 6.0), 1.2–1.7 (14 H, m), 1.34 (3 H, s), 1.40

(39) For convenience, we use the nomenclature of cyclic ether derivatives as oxacycloalkanes.

(40) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, 1988; p 357.

(41) Prepared from 2-octanone and 1,1-dimethylhydrazine via the well-known procedure;[14] bp 64–66 °C (7 mmHg).

(3 H, s), 2.39 (4 H, m), 3.3–3.6 (1 H, m), 3.9–4.1 (2 H, m); MS, m/e 270 (M^+, 0.4) 255 (36), 212 (3), 195 (62), 177 (6), 142 (8), 127 (11), 113 (100), 101 (14), 95 (7), 85 (23), 81 (18), 72 (33), 67 (16), 55 (14), 43 (40), 41 (21); HRMS calcd for $C_{16}H_{30}O_3$ 270.2195, found 270.2172.

(1*S*,6*R*)-6-Hexyl-7,9-dioxabicyclo[4.2.1]nonane (12). A solution of **10** (132 mg, 0.49 mmol) containing a catalytic amount of *p*-TsOH·H_2O in CH_2Cl_2 (10 mL) was refluxed for 24 h. After dilution with CH_2Cl_2, the organic layer was treated conventionally. The crude product was purified by chromatography (hexane/Et_2O, 20:1) to afford 82 mg (79%) of **12** as a colorless oil: R_f 0.41 (hexane/Et_2O, 20:1); $[\alpha]^{14}_D$ −51.5° (*c* 1.10, MeOH); IR 2930, 2860, 1450, 1180, 1030, 780; ^{1}H NMR (90 MHz) 0.88 (3 H, t, J = 6.0), 1.28 (6 H, m), 1.65 (12 H, m), 3.73 (1 H, dd, J = 7.5, 2.0), 3.87 (1 H, d, J = 7.5), 4.51 (1 H, m); ^{13}C NMR 14.04, 22.58, 22.82, 23.37, 24.22, 29.53, 31.87, 35.50, 38.52, 40.75, 69.19, 76.24, 112.83; MS, m/e 212 (M^+, 5), 169 (3), 155 (9), 142 (9), 127 (13), 113 (100), 95 (5), 85 (28), 81 (9), 67 (15), 55 (17), 43 (33), 41 (18); HRMS calcd for $C_{13}H_{24}O_2$ 212.1776, found 212.1773.

Ethyl (*S*)-8,9-Di-*O*-isopropylidene-8,9-dihydroxy-3-oxononanoate (11). To a solution of lithium diisopropylamide (1.2 mmol from 210 μL of *i*-Pr_2NH and 0.72 mL of 1.67 M *n*-BuLi) in THF (1 mL) at −25 °C was added ethyl acetoacetate (70 μL, 0.54 mmol), and the reaction mixture was stirred at 0 °C for 20 min. Then iodide **9** (122 mg, 0.45 mmol) was introduced, and stirring was continued at 0 °C for 0.5 h. The mixture was quenched with water, concentrated, and extracted with Et_2O. Following solvent removal, the crude product was purified by chromatography (hexane/Et_2O, 1:1) to give 113 mg (92%) of **11** as a colorless oil: R_f 0.37 (hexane/Et_2O, 1:1); $[\alpha]^{25}_D$ +5.60° (*c* 1.14, EtOH); IR 3000, 2940, 2860, 1740, 1715, 1370, 1240, 1050, 850; ^{1}H NMR (90 MHz) 1.20 (3 H, t, J = 7.3), 1.34 (3 H, s), 1.39 (3 H, s), 1.2–1.8 (6 H, m), 2.55 (2 H, t, J = 6.6), 3.41 (2 H, s), 3.3–3.6 (1 H, m), 3.9–4.2 (2 H, m), 4.19 (2 H, q, J = 7.3); MS, m/e 272 (M^+, 2), 257 (100), 211 (9), 197 (28), 185 (5), 169 (22), 151 (32), 143 (17), 127 (23), 115 (16), 109 (53), 105 (13), 101 (15), 81 (21), 72 (41), 67 (7), 58 (8), 43 (26); HRMS calcd for $C_{14}H_{24}O_5$ 272.1624, found 272.1633.

Ethyl [(1*S*,6*S*)-7,9-Dioxabicyclo[4.2.1]nonan-6-yl]acetate (13). A solution of **11** (1.2 g, 4.4 mmol) containing a catalytic amount of *p*-TsOH·H_2O in CH_2Cl_2 (50 mL) was refluxed for 3 h. The usual workup followed by purification by chromatography (hexane/AcOEt, 4:1) gave 934 mg (99%) of **13** as a colorless oil: R_f 0.29 (hexane/AcOEt, 4:1); $[\alpha]^{25}_D$ −59.9° (*c* 1.42, EtOH); IR 2950, 1740, 1190, 1120, 1040; ^{1}H NMR (90 MHz) 1.26 (3 H, t, J = 7.3), 1.5–2.1 (8 H, m), 2.69 (2 H, s), 3.6–4.0 (2 H, m), 4.15 (2 H, q, J = 7.3), 4.54 (1 H, m); MS, m/e 214 (M^+, 4), 196 (7), 172 (26), 144 (3), 133 (8), 127 (36), 115 (100), 109 (4), 100 (13), 87 (8), 82 (15), 67 (17), 58 (13), 54 (12), 43 (10); HRMS calcd for $C_{11}H_{18}O_4$ 214.1205, found 214.1164.

(1*S*,6*S*)-6-[2-(Benzyloxy)ethyl]-7,9-dioxabicyclo[4.2.1]nonane (14). To a suspension of $LiAlH_4$ (250 mg, 6.5 mmol) in Et_2O (20 mL) at 0 °C was added dropwise **13** (1.4 g, 6.54 mmol) in Et_2O (30 mL), and the reaction mixture was stirred for 1 h. The mixture was quenched with a minimum amount of water, dried, filtered, and concentrated.

To a suspension of NaH (310 mg, 60% dispersion, 7.8 mmol) in THF (15 mL) at 0 °C was added (cannula) the above-obtained alcohol (1.2 g) in THF (30 mL). After 20 min at room temperature, benzyl bromide (0.93 mL, 7.8 mmol) was added and the solution refluxed for 18 h. The mixture was quenched with water, concentrated, and extracted with Et_2O. Following solvent removal, the crude product was purified by chromatography (hexane/AcOEt, 10:1) to give 1.7 g (99%) of **14** as a colorless oil: R_f 0.30 (hexane/AcOEt, 10:1); $[\alpha]^{25}_D$ −42.5° (*c* 1.38, EtOH); IR 2930, 2860, 1455, 1370, 1180, 1120, 785, 740, 700; ^{1}H NMR (90 MHz) 1.5–1.9 (8 H, m), 2.03 (2 H, t, J = 7.2), 3.61 (2 H, t, J = 7.2), 3.73 (2 H, m), 4.4–4.6 (1 H, m), 4.49 (2 H, s), 7.31 (5 H, s); MS, m/e 262 (M^+, 2), 244 (1), 190 (2), 179 (11), 162 (18), 156 (37), 148 (3), 134 (5), 127 (9), 108 (38), 107 (47), 97 (7), 91 (100), 85 (33), 79 (23), 67 (10), 55 (38), 43 (2); HRMS calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1562.

General Procedure for the Reductive Cleavage of Bicyclic Ketals 12, 14, and 40. With $Et_3SiH/TiCl_4$. To a solution of bicyclic ketal (0.47 mmol) in CH_2Cl_2 (2 mL) at −78 °C were added Et_3SiH (1.88 mmol) and $TiCl_4$ (1 M in CH_2Cl_2, 0.57 mmol), and the reaction mixture was stirred at this temperature for the period of time indicated in Tables I and II. The mixture was quenched with water and extracted with CH_2Cl_2. The extract was dried and evaporated. Capillary GC analysis showed two peaks, and the major peak was assigned as a cis isomer.

With DIBAL. To a solution of bicyclic ketal (3.8 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added DIBAL (1 M in hexane, 15.2 mmol), and the reaction mixture was stirred at this temperature for the period of time indicated in Tables I and II. The mixture was quenched with water, filtered, and extracted with CH_2Cl_2. The extract was dried and evaporated. Capillary GC analysis showed two peaks, and the major peak was assigned as a trans isomer.

Each cis or trans stereoisomer obtained was cleanly separated by flash chromatography (solvent system indicated in TLC data), and the physical and spectral data are as follows.

(2*S*,7*S*)-7-Hexyl-2-(hydroxymethyl)-1-oxacycloheptane (15): R_f 0.40 (benzene/Et_2O, 4:1); $[\alpha]^{21}_D$ −6.47° (*c* 1.70, MeOH); IR 3430, 2920, 2850, 1450, 1110, 1040; ^{1}H NMR (90 MHz) 0.88 (3 H, t, J = 6.0), 1.1–1.9 (18 H, m), 2.13 (1 H, br), 3.49 (4 H, m); ^{13}C NMR 14.07, 22.64, 25.11, 25.47, 26.33, 29.34, 31.84, 32.06, 36.66, 37.21, 66.42, 80.29, 81.02; MS, m/e 215 (M^+ + 1, 0.5), 183 (100), 165 (72), 149 (5), 129 (18), 123 (24), 109 (76), 97 (48), 95 (83), 83 (47), 81 (34), 67 (35), 57 (30), 55 (38), 43 (10); HRMS calcd for $C_{13}H_{26}O_2$ 214.1933, found 214.1951.

(2*S*,7*R*)-7-Hexyl-2-(hydroxymethyl)-1-oxacycloheptane (16): R_f 0.32 (benzene/Et_2O, 4:1); $[\alpha]^{14}_D$ +24.5° (*c* 0.62, MeOH); IR 3400, 2920, 2850, 1450, 1115, 1080, 1040, 730; ^{1}H NMR (90 MHz) 0.88 (3 H, t, J = 6.0), 1.1–2.0 (18 H, m), 2.03 (1 H, br), 3.40 (2 H, m), 3.66 (2 H, m); ^{13}C NMR 14.07, 22.64, 26.45, 26.78, 27.61, 29.37, 31.81, 32.03, 35.93, 36.30, 65.72, 74.47, 75.69; MS, m/e 215 (M^+ + 1, 0.6), 183 (97), 165 (60), 129 (96), 123 (25), 111 (74), 109 (85), 95 (100), 93 (84), 83 (73), 81 (56), 67 (58), 55 (50), 43 (15); HRMS calcd for $C_{13}H_{26}O_2$ 214.1933, found 214.1936.

(2*S*,7*R*)-7-[2-(Benzyloxy)ethyl]-2-(hydroxymethyl)-1-oxacycloheptane (17): R_f 0.41 (hexane/Et_2O, 1:2); $[\alpha]^{25}_D$ −31.6° (*c* 0.50, EtOH); IR 3430, 2900, 2850, 1450, 1360, 1100, 730, 690; ^{1}H NMR (90 MHz) 1.3–2.0 (10 H, m), 2.70 (1 H, br), 3.3–3.8 (6 H, m), 4.51 (2 H, s), 7.32 (5 H, s); ^{13}C NMR 24.86, 25.41, 31.78, 36.75, 37.06, 66.21, 67.58, 72.88, 78.95, 80.93, 127.40, 127.61, 128.13, 138.10; MS, m/e 264 (M^+, 2), 246 (1), 233 (3), 228 (0.5), 215 (0.6), 197 (2), 173 (4), 158 (12), 127 (22), 107 (18), 91 (100), 81 (7), 79 (8), 73 (3), 67 (10), 65 (7), 57 (7), 55 (7), 41 (6); HRMS calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1743.

(2*S*,7*S*)-7-[2-(Benzyloxy)ethyl]-2-(hydroxymethyl)-1-oxacycloheptane (18): R_f 0.33 (hexane/Et_2O, 1:2); $[\alpha]^{25}_D$ +35.7° (*c* 0.28, EtOH); IR 3440, 2920, 2850, 1455, 1370, 1120, 1100, 1030, 740, 700; ^{1}H NMR (90 MHz) 1.2–2.0 (10 H, m), 3.3–4.1 (7 H, m), 4.53 (2 H, s), 7.33 (5 H, s); ^{13}C NMR 27.03, 31.57, 35.63, 36.63, 65.75, 68.16, 72.91, 73.40, 75.20, 127.43, 127.64, 128.13, 137.77; MS, m/e 264 (M^+, 2), 246 (2), 233 (8), 197 (3), 169 (2), 158 (8), 141 (3), 127 (11), 107 (10), 91 (100), 81 (5), 79 (5), 67 (8), 65 (6), 55 (7), 41 (6); HRMS calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1746.

(2*S*,8*R*)-8-[2-(Benzyloxy)ethyl]-2-(hydroxymethyl)-1-oxacyclooct-4-ene (41): R_f 0.24 (hexane/AcOEt, 2:1); $[\alpha]^{24}_D$ −13.23° (*c* 0.62, MeOH); IR 3440, 2930, 2870, 1455, 1100, 1055, 725, 695; ^{1}H NMR (90 MHz), 1.3–2.7 (9 H, m), 3.2–3.8 (6 H, m), 4.50 (2 H, s), 5.73 (2 H, m), 7.32 (5 H, s); ^{13}C NMR 23.52, 30.66, 36.05, 36.91, 66.24, 67.18, 72.98, 76.45, 81.73, 127.16, 127.55, 127.83, 128.28, 131.58, 138.22; MS, m/e 276 (M^+, 0.4), 257 (0.2), 245 (2), 227 (0.3), 209 (0.4), 199 (0.4), 170 (6), 161 (5), 139 (4), 107 (12), 91 (100), 79 (16), 71 (13), 67 (7), 65 (8), 55 (7), 54 (6), 41 (8); HRMS calcd for $C_{17}H_{24}O_3$ 276.1725, found 276.1725.

(2*S*,8*S*)-8-[2-(Benzyloxy)ethyl]-2-(hydroxymethyl)-1-oxacyclooct-4-ene (42): R_f 0.16 (hexane/AcOEt, 2:1); $[\alpha]^{22}_D$ +22.0° (*c* 0.1, MeOH); IR 3400, 2920, 2870, 1455, 1100, 1045, 725, 695; ^{1}H NMR (90 MHz) 1.2–2.7 (9 H, m), 3.3–4.2 (6 H, m), 4.53 (2 H, s), 5.5–6.1 (2 H, m), 7.53 (5 H, s); ^{13}C NMR 25.38, 28.52, 37.49, 37.58, 65.02, 67.06, 70.08, 72.91, 77.52, 126.73, 127.74, 127.86, 128.38, 132.16, 137.71; MS, m/e 278 (M^+, 0.2), 259 (0.6), 245 (9), 183 (2), 161 (5), 159 (9), 142 (6), 139 (6), 131 (6), 117 (5), 107 (15), 91 (100), 81 (9), 79 (18), 71 (17), 67 (6), 55 (5), 43 (2); HRMS calcd for $C_{17}H_{24}O_3$ 276.1725, found 276.1746.

Spectral data of acetates **19**, **20**, **43**, and **44** are as follows.

19: IR 2910, 2860, 1740, 1450, 1365, 1240, 1130, 1040; ^{1}H NMR (400 MHz) 0.88 (3 H, t, J = 6.6), 1.2–1.4 (8 H, m), 1.4–1.6 (6 H,

m), 1.6–1.8 (4 H, m), 2.07 (3 H, s), 3.38 (1 H, m), 3.70 (1 H, dddd, J = 8.9, 7.0, 4.6, 3.9), 4.00 (1 H, dd, J = 11.2, 4.6), 4.03 (1 H, dd, J = 11.2, 7.0).

20: IR 2920, 2860, 1740, 1450, 1365, 1240, 1130, 1040; ^{1}H NMR (400 MHz) 0.88 (3 H, t, J = 6.6), 1.2–1.5 (14 H, m), 1.7–1.9 (4 H, m), 2.07 (3 H, s), 3.61 (1 H, m), 3.85 (1 H, m), 3.96 (1 H, dd, J = 11.2, 3.9), 4.00 (1 H, dd, J = 11.2, 7.3).

43: IR 2920, 2850, 1740, 1450, 1360, 1235, 1105, 1040; ^{1}H NMR (400 MHz) 1.47–1.76 (4 H, m), 2.05 (3 H, s), 2.10 (2 H, m), 2.28 (1 H, m), 2.48 (1 H, m), 3.49 (1 H, ddt, J = 7.3, 4.4, 3.0), 3.54 (1 H, ddd, J = 9.3, 5.4, 3.9), 3.67 (1 H, dt, J = 9.3, 4.9), 3.73 (1 H, m), 3.95 (1 H, dd, J = 11.4, 4.4), 4.03 (1 H, dd, J = 11.7, 7.3), 4.47 (1 H, d, J = 12.2), 4.51 (1 H, d, J = 12.2), 5.75 (2 H, m), 7.31–7.38 (5 H, m).

44: IR 2920, 2850, 1740, 1450, 1365, 1240, 1110, 1040; ^{1}H NMR (400 MHz) 1.49 (1 H, m), 1.65 (2 H, m), 1.75 (1 H, m), 2.07 (3 H, s), 2.10 (2 H, m), 2.17 (1 H, m), 2.35 (1 H, m), 3.49 (1 H, dt, J = 9.2, 5.7), 3.64 (1 H, dt, J = 9.2, 6.8), 3.89 (2 H, m), 4.16 (1 H, dd, J = 11.2, 6.9), 4.17 (1 H, dd, J = 11.2, 5.6), 4.43 (1 H, d, J = 12.0), 4.52 (1 H, dd, J = 12.0), 5.66 (1 H, q, J = 9.0), 5.91 (1 H, q, J = 9.0), 7.32–7.34 (5 H, m).

(2*S*,7*R*)-2-Hexyl-7-propyl-1-oxacycloheptane (6). To a mixture of alcohol **15** (145 mg, 0.68 mmol) and pyridine (160 μL) in CH_2Cl_2 (2 mL) at −15 °C was added dropwise triflic anhydride (170 μL, 1.0 mmol) in CH_2Cl_2 (0.5 mL), and the reaction mixture was stirred for 0.5 h. The mixture was diluted with CH_2Cl_2, washed, and dried. Evaporation of the solvent provided a crude triflate, which was azeotropically dried with toluene and used for the next reaction.

In a 25-mL two-necked round-bottom flask were placed CuBr (20 mg, 0.15 mmol) and THF (1 mL), and EtMgBr (0.74 M in Et_2O, 1.4 mL, 1.0 mmol) was added at 0 °C. To this mixture was transferred (cannula) the above-obtained triflate in THF (3 mL), and the reaction mixture was stirred at the same temperature for 20 min. The mixture was quenched with saturated aqueous NH_4Cl, filtered, concentrated, and extracted with Et_2O. Following solvent removal, the crude product was purified by chromatography (hexane/Et_2O, 50:1) to give 115 mg (75%) of **6** as a colorless oil: R_f 0.36 (hexane/Et_2O, 50:1); $[\alpha]^{24}_D$ +1.5° (c 0.97, $CHCl_3$); bp 94–96 °C (2.0 mmHg); IR 2950, 2920, 2850, 1465, 1455, 1375, 1340, 1140, 1100; ^{1}H NMR (400 MHz) 0.88 (3 H, t, J = 6.8), 0.90 (3 H, t, J = 7.0), 1.2–1.4 (6 H, m), 1.4–1.6 (4 H, m), 1.6–1.75 (2 H, m), 3.35–3.45 (2 H, m); ^{13}C NMR 14.16, 19.56, 22.73, 25.41, 26.36, 29.41, 31.97, 36.94, 37.52, 39.71, 80.02, 80.32; MS, m/e 226 (M^+, 0.6), 183 (30), 165 (20), 141 (55), 123 (67), 109 (22), 97 (67), 84 (47), 83 (56), 73 (20), 70 (44), 67 (29), 56 (56), 55 (100), 43 (39), 41 (40); HRMS calcd for $C_{15}H_{30}O$ 226.2297, found 226.2306.

(2*R*,7*R*)-2-Hexyl-7-propyl-1-oxacycloheptane (21) was prepared from **16** in an 88% yield similarly as described for **6**: R_f 0.39 (hexane/Et_2O, 20:1); $[\alpha]^{23}_D$ +20.5° (c 3.20, $CHCl_3$); IR 2950, 2910, 2850, 1460, 1450, 1370, 1130, 1105, 1090; ^{1}H NMR (400 MHz) 0.88 (3 H, t, J = 7.0), 0.90 (3 H, t, J = 7.1), 1.2–1.4 (8 H, m), 1.4–1.55 (2 H, m), 1.7–1.85 (2 H, m), 3.57 (2 H, br s); ^{13}C NMR 14.13, 14.25, 19.65, 22.70, 26.42, 27.45, 29.50, 31.94, 36.45, 36.72, 38.95, 74.07, 74.29; MS, m/e 226 (M^+, 0.6), 210 (0.4), 183 (37), 177 (5), 165 (23), 149 (8), 141 (70), 123 (100), 109 (31), 97 (44), 95 (43), 83 (50), 81 (53), 69 (45), 67 (38), 55 (77), 43 (36), 41 (35); HRMS calcd for $C_{15}H_{30}O$ 226.2298, found 226.2318.

(2*R*,7*R*)-2-[2-(Benzyloxy)ethyl]-7-propyl-1-oxacycloheptane (22). Via the procedure described for **6**, **17** (220 mg, 0.83 mmol) was treated with 1.5 equiv of triflic anhydride followed by reaction with 1.5 equiv of EtMgBr in the presence of 0.2 equiv of CuBr to afford 188 mg (82%) of **22** as a colorless oil: R_f 0.33 (hexane/Et_2O, 10:1); $[\alpha]^{24}_D$ −26.0° (c 0.90, MeOH); IR 2930, 2860, 1500, 1450, 1360, 1140, 1100, 735, 700; ^{1}H NMR (90 MHz) 0.88 (3 H, t, J = 6.0), 1.2–1.9 (14 H, m), 3.3–3.7 (4 H, m), 4.49 (2 H, s), 7.32 (5 H, s); MS, m/e 276 (M^+, 6), 258 (12), 233 (3), 203 (3), 185 (23), 177 (5), 170 (13), 159 (16), 149 (7), 141 (47), 127 (28), 123 (20), 107 (45), 91 (100), 81 (12), 73 (10), 55 (8), 43 (2); HRMS calcd for $C_{18}H_{28}O_2$ 276.2089, found 276.2104.

(2*R*,7*R*)-2-(2-Hydroxyethyl)-7-propyl-1-oxacycloheptane (23). Benzyl ether **22** (185 mg, 0.67 mmol) was hydrogenated in EtOH (15 mL) with 10% Pd/C (20 mg) as catalyst. The reaction mixture was filtered through Celite and rinsed thoroughly with AcOEt. Following solvent removal, the crude product was purified by chromatography (hexane/AcOEt, 1:1) to give 118 mg (95%) of **23** as a colorless oil: R_f 0.46 (hexane/AcOEt, 1:1); $[\alpha]^{23}_D$ −15.0° (c 0.68, MeOH); IR 3400, 2950, 2920, 2850, 1450, 1135, 1100, 1060, 1030, 1000, 780, 760; ^{1}H NMR (90 MHz) 0.91 (3 H, t, J = 6.0), 1.2–1.9 (14 H, m), 2.48 (1 H, br s), 3.3–3.7 (2 H, m), 3.78 (2 H, t, J = 5.5); MS, m/e 186 (M^+, 16), 157 (2), 143 (100), 141 (36), 125 (27), 123 (35), 107 (11), 101 (11), 97 (13), 88 (12), 81 (45), 75 (41), 68 (87), 55 (48), 43 (15); HRMS calcd for $C_{11}H_{22}O_2$ 186.1620, found 186.1599.

Preparation of 6 from 23. To a mixture of **23** (115 mg, 0.62 mmol) and triethylamine (300 μL) in CH_2Cl_2 (5 mL) at 0 °C was added p-TsCl (140 mg, 0.73 mmol), and the reaction mixture was stirred at room temperature overnight. The usual workup followed by purification by chromatography (hexane/Et_2O, 4:1) gave 196 mg (93%) of tosylate. This material was azeotropically dried with toluene and used for the next reaction.

To a solution of n-Bu_2CuLi (0.87 mmol from 1.1 mL of 1.58 M n-BuLi and 175 mg of CuI) in Et_2O (3 mL) at 0 °C was added (cannula) the above-obtained tosylate in Et_2O (5 mL), and the reaction mixture was stirred at this temperature for 1.5 h. The mixture was quenched with saturated aqueous NH_4Cl, filtered, and extracted with Et_2O. Following solvent removal, the crude product was purified by chromatography, to afford 118 mg (91%) of **6**: $[\alpha]^{24}_D$ +1.6° (c 1.2, $CHCl_3$).

(2*R*,7*R*)-2-[2-(Benzyloxy)ethyl]-7-hexyl-1-oxacycloheptane (24). Via the procedure described for **6**, **17** (200 mg, 0.76 mmol) was treated with 1.5 equiv of triflic anhydride followed by reaction with 1.5 equiv of $C_5H_{11}MgBr$ in the presence of 0.2 equiv of CuBr, to afford 213 mg (88%) of **24** as a colorless oil: R_f 0.42 (hexane/Et_2O, 10:1); $[\alpha]^{24}_D$ −22.1° (c 1.32, MeOH); IR 2920, 2850, 1450, 1360, 1100, 730, 695; ^{1}H NMR (90 MHz) 0.88 (3 H, t, J = 6.0), 1.1–1.9 (20 H, m) 3.2–3.5 (2 H, m), 3.58 (2 H, m), 4.49 (2 H, s), 7.32 (5 H, s); MS, m/e 318 (M^+, 8), 300 (10), 245 (3), 233 (6), 227 (25), 212 (8), 183 (51), 177 (7), 165 (14), 159 (22), 152 (3), 138 (5), 127 (33), 107 (42), 95 (26), 91 (100), 81 (10), 73 (9), 55 (8), 43 (3); HRMS calcd for $C_{21}H_{34}O_2$ 318.2559, found 318.2560.

(2*R*,7*R*)-7-Hexyl-2-(2-hydroxyethyl)-1-oxacycloheptane (25) was prepared from **24** in 91% yield similarly as described for **23**: R_f 0.39 (hexane/Et_2O, 1:1); $[\alpha]^{24}_D$ −12.4° (c 0.84, MeOH); IR 3400, 2930, 2860, 1460, 1135, 1100, 1055, 1000, 785, 760; ^{1}H NMR (90 MHz) 0.88 (3 H, t, J = 6.3), 1.2–1.9 (20 H, m), 2.40 (1 H, br s), 3.3–3.6 (2 H, m), 3.78 (2 H, t, J = 5.5); MS, m/e 228 (M^+, 10), 183 (21), 165 (15) 143 (100), 138 (3), 125 (22), 115 (12), 109 (10), 107 (8), 101 (6), 97 (35), 88 (9), 83 (16), 81 (21), 75 (23), 68 (52), 55 (23), 43 (5); HRMS calcd for $C_{14}H_{28}O_2$ 228.2089, found 228.2081.

(2*R*,7*S*)-2-Hexyl-7-propyl-1-oxacycloheptane (26): An Enantiomer of 6. Via the similar procedure described for **6** from **23**, **25** (95 mg, 0.42 mmol) was treated with p-TsCl (95 mg, 0.5 mmol) and triethylamine (200 μL) to afford 147 mg (92%) of tosylate. To a solution of Me_2CuLi (0.57 mmol from 0.87 mL of 1.31 M MeLi and 114 mg of CuI) in Et_2O (2 mL) at −15 °C was added the above-obtained tosylate in Et_2O (3 mL), and the reaction mixture was stirred at this temperature for 2 h. The usual workup followed by purification by chromatography (hexane/Et_2O, 50:1) yielded 79 mg (92%) of **26** as a colorless oil: $[\alpha]^{23}_D$ −1.3° (c 0.96, $CHCl_3$); spectral data were superimposable with those of **6**.

Methyl (*S*)-5,6-Di-*O*-isopropylidene-5,6-dihydroxy-2-hexenoate (29a,b). To a suspension of NaH (42 mg, 60% dispersion, 1.05 mmol) in Et_2O (2 mL) at −78 °C was added $(CF_3CH_2O)_2P(O)CH_2COOMe$ (334 mg, 1.05 mmol) in Et_2O (2 mL), and the reaction mixture was stirred for 10 min. Then **28** (135 mg, 0.94 mmol)[31] in Et_2O (2 mL) was introduced (cannula) and the reaction mixture stirred at the same temperature for 1 h. The mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. Following solvent removal, the crude product was purified by flash chromatography (hexane/Et_2O, 4:1 to 1:1) to give 140 mg (74%) of **29a** and 28 mg (15%) of **29b**. **29a**: R_f 0.57 (hexane/Et_2O, 1:1); $[\alpha]^{16}_D$ −10.0° (c 0.5, $CHCl_3$); IR 2980, 2940, 2860, 1720, 1645, 1435, 1375, 1365, 1225, 1205, 1170, 1060; ^{1}H NMR (90 MHz) 1.35 (3 H, s), 1.42 (3 H, s), 2.95 (2 H, m), 3.71 (3 H, s), 3.6–4.3 (3 H, m), 5.89 (1 H, dt, J = 11.4, 1.5), 6.34 (1 H, dt, J = 11.4, 7.0); MS; m/e 185 (M^+ − 15, 100), 169 (10), 142 (4), 125 (68), 111 (27), 101 (78), 97 (11), 93 (24), 83 (12), 72 (23), 59 (6), 55 (4), 43 (21); HRMS calcd for $C_{10}H_{16}O_4 - CH_3$ 185.0814, found 185.0836. **29b**: R_f 0.45 (hexane/Et_2O, 1:1); $[\alpha]^{16}_D$ +16.0° (c 0.6,

$CHCl_3$); IR (neat) 2980, 2940, 2860, 1720, 1645, 1435, 1375, 1370, 1270, 1170, 1065; ^1H NMR (90 MHz) 1.35 (3 H, s), 1.42 (3 H, s), 2.48 (2 H, br t, J = 6.0), 3.73 (3 H, s), 3.4–4.4 (3 H, m), 5.91 (1 H, dt, J = 15.6, 1.3), 6.94 (1 H, dt, J = 15.6, 8.1); MS, m/e 185 (M^+ – 15, 100), 169 (8), 143 (4), 125 (11), 111 (18), 101 (83), 97 (6), 93 (19), 83 (9), 72 (16), 59 (4), 43 (13); HRMS found for $C_{10}H_{16}O_4 - CH_3$ 185.0822.

(*S*)-(*Z*)-1,2-Di-*O*-isopropylidene-1,2,6-trihydroxy-4-hexene (30). To a suspension of $LiAlH_4$ (38 mg, 1.0 mmol) in Et_2O (2 mL) at 0 °C was added dropwise **29a** (200 mg, 1.0 mmol) in Et_2O (2 mL), and the reaction mixture was stirred at room temperature for 2 h. The mixture was quenched with a minimum amount of water, dried, filtered, and concentrated. The alcohol obtained was purified by chromatography (hexane/AcOEt, 1:1) to give 162 mg (94%) of **30** as a colorless oil: R_f 0.13 (hexane/Et_2O, 1:1); $[\alpha]^{21}_D$ +10.28° (*c* 4.24, MeOH); IR 3400, 2960, 2910, 2850, 1370, 1360, 1240, 1205, 1150, 1050; ^1H NMR (90 MHz) 1.35 (3 H, s), 1.42 (3 H, s), 2.03 (1 H, br), 2.38 (2 H, br t, J = 6.0), 3.4–3.7 (1 H, m), 3.9–4.3 (4 H, m), 5.58 (1 H, dt, J = 11.0, 7.3), 5.84 (1 H, dt, J = 11.0, 6.6); MS, m/e 157 (M^+ – 15, 28), 101 (100), 97 (10), 79 (14), 73 (15), 67 (10), 59 (9), 43 (34); HRMS calcd for $C_9H_{16}O_3 - CH_3$ 157.0865, found 157.0848.

(*S*)-(*Z*)-6-Bromo-1,2-di-*O*-isopropylidene-1,2-dihydroxy-4-hexene (31). To a mixture of **30** (250 mg, 1.45 mmol) and PPh_3 (760 mg, 2.9 mmol) containing a small amount of K_2CO_3 (30 mg) in Et_2O (12 mL) at 0 °C was added portionwise CBr_4 (962 mg, 2.9 mmol), and the reaction mixture was stirred at room temperature for 2 h and finally refluxed for 15 min. The mixture was diluted with pentane, filtered, and concentrated. The crude bromide was purified by chromatography (hexane/Et_2O, 2:1) to give 293 mg (86%) of **31** as a colorless oil: R_f 0.51 (hexane/Et_2O, 1:1); $[\alpha]^{22}_D$ +16.0° (*c* 1.5, $CHCl_3$); IR 3000, 2940, 2880, 1380, 1370, 1200, 1160, 1060, 780, 755, 660; ^1H NMR (90 MHz) 1.35 (3 H, s), 1.43 (3 H, s), 2.43 (2 H, br t, J = 6.0), 3.4–3.7 (1 H, m), 3.8–4.3 (4 H, m), 5.56 (1 H, dt, J = 11.0, 6.8), 6.90 (1 H, dt, J = 11.0, 7.5).

(*S*)-(*Z*)-1,2-Di-*O*-isopropylidene-1,2-dihydroxy-4-tetradecen-8-one (32). To a solution of 2-octanone dimethylhydrazone (50 mg, 0.31 mmol) in THF (0.7 mL) at –78 °C was added *n*-BuLi (0.2 mL, 0.33 mmol), and the reaction mixture was stirred for 0.5 h. Then **31** (54 mg, 0.23 mmol) (which was azeotropically dried with toluene) in THF (1 mL) was introduced (cannula), and the reaction mixture was stirred at room temperature overnight. The mixture was quenched with water and extracted with Et_2O. The extract was dried and evaporated. This material was treated as described for **10**, to afford 50 mg (77%) of **32** as a colorless oil: R_f 0.44 (hexane/Et_2O, 1:1); $[\alpha]^{23}_D$ +11.4° (*c* 1.14, $CHCl_3$); IR 2980, 2950, 2920, 2860, 1710, 1375, 1365, 1245, 1210, 1155, 1065, 850; ^1H NMR (90 MHz) 0.88 (3 H, t, J = 6.0), 1.1–1.8 (8 H, m), 1.34 (3 H, s), 1.41 (3 H, s), 2.1–2.6 (8 H, m), 3.4–3.7 (1 H, m), 3.9–4.2 (2 H, m), 5.42 (2 H, m); MS, m/e 282 (M^+, 0.4), 267 (13), 224 (6), 165 (6), 113 (20), 101 (100), 85 (4), 79 (8), 72 (6), 55 (4), 43 (16), 41 (6); HRMS calcd for $C_{17}H_{30}O_3$ 282.2195, found 282.2214.

Ethyl (*S*)-(*Z*)-9,10-Di-*O*-isopropylidene-9,10-dihydroxy-3-oxo-6-decenoate (33). To a solution of lithium diisopropylamide (1.91 mmol) in THF (3 mL) at –20 °C was added ethyl acetoacetate (0.12 mL, 0.91 mmol), and the reaction mixture was stirred at 0 °C for 0.5 h. Then HMPA (1.5 mL) followed by **31** (194 mg, 0.83 mmol) (which was azeotropically dried with toluene) in THF (3 mL) was introduced, and stirring was continued at 0 °C for 3 h. The mixture was quenched with saturated aqueous NH_4Cl, concentrated, and extracted with AcOEt. Following solvent removal, the crude product was purified by chromatography (elution first with 49:1 CH_2Cl_2/MeOH, second with 1:1 hexane/Et_2O) to afford 113 mg (48%) of **33** as a colorless oil: R_f 0.27 (hexane/Et_2O, 1:1); $[\alpha]^{24}_D$ +12.8° (*c* 1.0, $CHCl_3$); IR 3000, 2950, 1745, 1720, 1370, 1320, 1245, 1160, 1065, 850; ^1H NMR (90 MHz) 1.28 (3 H, t, J = 7.0), 1.35 (3 H, s), 1.41 (3 H, s), 2.2–2.7 (6 H, m), 3.42 (2 H, s), 3.4–3.7 (1 H, m), 4.11 (2 H, q, J = 7.0), 3.9–4.2 (2 H, m), 5.44 (2 H, m); MS, m/e 284 (M^+, 0.4), 269 (17), 223 (4), 209 (3), 191 (3), 181 (11), 163 (5), 155 (4), 139 (4), 121 (9), 115 (3), 101 (100), 93 (5), 83 (4), 79 (6), 73 (13), 59 (2), 43 (8); HRMS calcd for $C_{15}H_{24}O_5$ 284.1624, found 284.1617.

(*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1,2-epoxypropane (34). A mixture of (*R*)-3-(tosyloxy)-1,2-propanediol (4.92 g, 20 mmol),[32] *tert*-butyldimethylchlorosilane (3.12 g, 21 mmol), imidazole (3.40 g, 50 mmol), KI (20 mg), and 4-(dimethylamino)-pyridine (20 mg) in DMF (20 mL) was stirred at room temperature overnight. The mixture was quenched with water and extracted with Et_2O. The extract was dried and evaporated.

To an ice-cooled solution of the above-obtained product in MeOH (20 mL) and Et_2O (10 mL) was added sodium (460 mg, 20 mg-atom) in small portions over approximately 1 h. Stirring was continued with ice cooling for 1 h, and the mixture was concentrated. The residue was diluted with Et_2O, and the organic layer was treated conventionally. The crude product obtained was purified by chromatography (hexane/Et_2O, 9:1 to 1:1) to afford 3.18 g (85%) of **34** as a colorless oil: R_f 0.61 (hexane/Et_2O, 1:1); bp 60–63 °C (2 mmHg); $[\alpha]^{19}_D$ +4.95° (*c* 1.94, benzene); IR 2890, 2860, 2810, 2800, 1480, 1440, 1240, 1085, 820, 760; ^1H NMR (90 MHz) 0.08 (6 H, s), 0.90 (9 H, s), 2.62 (1 H, dd, J = 5.1, 2.6), 2.76 (1 H, dd, J = 5.1, 4.0), 3.07 (1 H, m), 3.66 (1 H, dd, J = 12.3, 4.6), 3.84 (1 H, dd, J = 12.3, 3.5); MS, m/e 131 (M^+ – 57, 27), 117 (4), 101 (100), 89 (3), 75 (21), 73 (11), 59 (31), 57 (4), 45 (4), 41 (5); HRMS calcd for $C_9H_{20}O_2Si - C_4H_9$ 131.0528, found 131.0536.

(*S*)-5,6-Di-*O*-isopropylidene-5,6-dihydroxy-2-hexyn-1-ol (36). To a solution of 1-[(tetrahydropyranyl)oxy]-2-propyne (2.02 mL, 14.1 mmol) in THF (20 mL) at –78 °C was added *n*-BuLi (8.5 mL, 14.1 mmol), and the reaction mixture was stirred for 0.5 h. Then **34** (880 mg, 4.7 mmol) in THF (3 mL) followed by BF_3·OEt_2 (1.73 mL, 14.1 mmol) was added at the same temperature, and stirring was continued for 1 h. The mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. Following solvent removal, the crude product was purified by chromatography (hexane/Et_2O, 9:1 to 1:2) to give 1.235 g of **35** as a colorless oil: R_f 0.40 (hexane/Et_2O, 1:1).

A solution of **35** (1.235 g, 3.75 mmol) containing a small amount of *p*-TsOH·H_2O in MeOH (5 mL) was refluxed overnight. The mixture was neutralized with $NaHCO_3$, filtered, and concentrated. The crude triol obtained was treated with 2,2-dimethoxypropane (2 mL) and pyridinium *p*-toluenesulfonate (20 mg) in MeOH (2 mL) under refluxing overnight. The solution was neutralized with $NaHCO_3$, filtered, and concentrated. The crude acetonide was purified by chromatography (hexane/AcOEt, 4:1, to AcOEt only) to give 582 mg (73% from **34**) of **36** as a colorless oil: R_f 0.57 (AcOEt); $[\alpha]^{20}_D$ +11.67° (*c* 0.6, MeOH); IR 3400, 3000, 2950, 2880, 1380, 1370, 1255, 1220, 1155, 1065, 1020; ^1H NMR (90 MHz) 1.35 (3 H, s), 1.43 (3 H, s), 2.10 (1 H, br s), 2.4–2.6 (2 H, m), 3.6–3.9 (2 H, m), 4.0–4.3 (3 H, m); MS, m/e 155 (M^+ – 15, 100), 101 (90), 95 (13), 83 (4), 73 (11), 67 (26), 65 (7), 59 (7), 55 (3), 43 (37); HRMS calcd for $C_9H_{14}O_3 - CH_3$ 155.0708, found 155.0700.

(*S*)-1,2-Di-*O*-isopropylidene-1,2-dihydroxy-6-bromo-4-hexyne (37) was prepared from **36** in 85% yield similarly as described for **31**: R_f 0.70 (Et_2O); $[\alpha]^{24}_D$ +23.09° (*c* 4.14, $CHCl_3$); IR 2980, 2930, 2860, 2220, 1380, 1370, 1250, 1210, 1150, 1110, 1070; ^1H NMR (90 MHz) 1.35 (3 H, s), 1.43 (3 H, s), 2.4–2.7 (2 H, m), 3.6–3.9 (1 H, m), 3.90 (2 H, t, J = 2.3), 4.0–4.4 (2 H, m).

Ethyl (*S*)-9,10-Di-*O*-isopropylidene-9,10-dihydroxy-3-oxo-6-decyne-1-carboxylate (38). To a solution of lithium diisopropylamide (12 mmol) in THF (10 mL) at –20 °C was added ethyl acetoacetate (0.75 mL, 5.88 mmol), and the reaction mixture was stirred at 0 °C for 0.5 h. Then **37** (1.05 g, 4.51 mmol) (which was azeotropically dried with toluene) in THF (10 mL) was introduced at the same temperature, and stirring was continued for 3 h. The mixture was quenched with saturated aqueous NH_4Cl, concentrated, and extracted with AcOEt. Following solvent removal, the crude product was purified by chromatography (elution first with 49:1 CH_2Cl_2/MeOH, second with 2:1 hexane/Et_2O) to afford 1.07 g (84%) of **38** as a colorless oil: R_f 0.18 (hexane/Et_2O, 2:1); $[\alpha]^{24}_D$ +30.8° (*c* 1.0, $CHCl_3$); IR 3000, 2950, 1745, 1725, 1370, 1320, 1250, 1230, 1215, 1160, 1070, 1040, 745; ^1H NMR (90 MHz) 1.28 (3 H, t, J = 7.3), 1.35 (3 H, s), 1.41 (3 H, s), 2.3–2.6 (4 H, m), 2.6–2.9 (2 H, m), 3.45 (2 H, s), 3.6–3.9 (1 H, m), 3.9–4.2 (2 H, m), 4.20 (2 H, q, J = 7.3); MS, m/e 267 (M^+ – 15, 28), 221 (5), 207 (4), 195 (3), 179 (18), 151 (3), 137 (9), 133 (8), 119 (6), 101 (100), 91 (8), 83 (4), 73 (13), 59 (5), 43 (34); HRMS calcd for $C_{15}H_{22}O_5 - CH_3$ 267.1233, found 267.1204.

Preparation of 33 from 38. A mixture of **38** (1.07 g, 3.79 mmol), 5% Pd/$BaSO_4$ (70 mg), and quinoline (70 mg) in MeOH (20 mL) was stirred at room temperature under a hydrogen atmosphere. After absorption of the theoretical amount of hydrogen, the catalyst was removed by filtration through Celite. Following solvent removal, the crude product was purified by chromatog-

raphy (hexane/AcOEt, 3:1) to give 1.08 g (100%) of **33**: R_f 0.58 ($MeOH/H_2O$, 4:1; reverse-phase silica gel TLC; **38**: R_f 0.63).

Ethyl [(1*S*,7*S*)-8,10-Dioxabicyclo[5.2.1]-3-decen-7-yl]-acetate (39). A solution of **33** (450 mg, 1.58 mmol) and *p*-$TsOH\cdot H_2O$ (160 mg, 0.85 mmol) in 1,2-dichloroethane (50 mL) was refluxed for 11 h. The mixture was neutralized with $NaHCO_3$, filtered, and concentrated. This material was purified by flash chromatography (hexane/AcOEt, 4:1) to give 114 mg (32%) of **39** as a colorless oil: R_f 0.31 (hexane/AcOEt, 4:1); $[\alpha]^{25}_D$ −44.7° (*c* 0.51, $CHCl_3$); IR 3020, 2980, 2930, 2870, 1735, 1370, 1225, 1120, 720; ^1H NMR (90 MHz) 1.26 (3 H, t, J = 7.3), 1.8–2.6 (6 H, m), 2.61 (2 H, s) 3.6–4.0 (2 H, m), 4.14 (2 H, q, J = 7.3), 4.50 (1 H, m), 5.5–6.1 (2 H, m); ^{13}C NMR 14.25, 22.36, 32.06, 37.64, 45.99, 60.41, 68.16, 77.40, 109.65, 125.02, 133.77, 169.45; MS, *m/e* 226 (M^+, 12), 208 (2), 195 (5), 183 (3), 172 (2), 166 (12), 144 (17), 139 (100), 130 (20), 115 (31), 111 (18), 101 (9), 94 (38), 88 (33), 85 (30), 79 (55), 72 (27), 67 (26), 59 (29), 55 (15), 43 (35), 41 (30); HRMS calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1226.

(1*S*,7*S*)-7-[2-(Benzyloxy)ethyl]-8,10-dioxabicyclo[5.2.1]-3-decene (40). To a solution of **39** (75 mg, 0.33 mmol) in Et_2O (4 mL) at 0 °C was added $LiAlH_4$ (10 mg, 0.26 mmol), and the reaction mixture was stirred at room temperature for 1 h. Then the mixture was quenched with a minimum amount of water, diluted with AcOEt, dried, and filtered through Celite. Evaporation of the solvent gave a crude alcohol (65 mg).

To a suspension of NaH (20 mg, 60% dispersion, 0.5 mmol) in THF (1.5 mL) at 0 °C was added the above-obtained alcohol in THF (3 mL), and the reaction mixture was stirred for 10 min. Then benzyl bromide (50 μL, 0.42 mmol) was introduced and the mixture stirred at room temperature overnight and finally refluxed for 5 h. The mixture was quenched with water and extracted with AcOEt. Following solvent removal, the crude product was purified by preparative TLC (hexane/AcOEt, 4:1) to give 76 mg (84%) of **40** as a colorless oil: R_f 0.35 (hexane/AcOEt, 4:1); $[\alpha]^{25}_D$ −52.5° (*c* 1.04, $CHCl_3$); IR 3020, 2930, 2860, 1495, 1450, 1365, 1110, 1100, 1070, 1015, 920, 730, 725, 700; ^1H NMR (90 MHz) 1.7–2.6 (8 H, m), 3.59 (2 H, t, J = 7.2), 3.6–3.9 (2 H, m), 4.46 (1 H, m), 4.48 (2 H, s), 5.6–6.0 (2 H, m), 7.31 (5 H, s); MS, *m/e* 274 (M^+, 3), 184 (5), 179 (18), 168 (20), 139 (52), 111 (30), 107 (16), 91 (100), 85 (15), 79 (16), 71 (13), 55 (6), 43 (9), 41 (7); HRMS calcd for $C_{17}H_{22}O_3$ 274.1569, found 274.1576.

(2*R*,8*R*)-2-[2-(Benzyloxy)ethyl]-8-ethyl-1-oxacyclo-5-octene (45). To a mixture of **41** (29 mg, 0.105 mmol) and pyridine (26 μL) in CH_2Cl_2 (1 mL) at −15 °C was added dropwise triflic anhydride (44 mg, 0.16 mmol) in CH_2Cl_2 (1 mL), and the reaction mixture was stirred for 15 min. The mixture was diluted with CH_2Cl_2 and treated conventionally. This material was azeotropically dried with toluene and used for the next reaction.

To a solution of Me_2CuLi (0.16 mmol from 0.22 mL of 1.43 M MeLi and 33 mg of CuBr) in Et_2O (1 mL) at −15 °C was added (cannula) the above-obtained triflate in Et_2O (1 mL), and the reaction mixture was stirred at this temperature for 1 h. The usual workup followed by purification by chromatography (hexane/Et_2O, 9:1) yielded 24 mg (83.4%) of **45** as a colorless oil: R_f 0.37 (hexane/Et_2O, 9:1); $[\alpha]^{23}_D$ −9.44° (*c* 0.36, MeOH); IR 3000, 2920, 2850, 1455, 1360, 1110, 1095, 1065, 730, 715, 695; ^1H NMR (90 MHz) 0.90 (3 h, t, J = 7.0), 1.2–2.6 (10 H, m), 3.16 (1 H, br quintet, J = 5.5), 3.4–3.8 (3 H, m), 4.48 (2 H, s), 5.73 (2 H, m), 7.32 (5 H, s); MS, *m/e* 274 (M^+, 0.4), 216 (1), 207 (3), 191 (1), 183 (2), 173 (3), 161 (9), 144 (2), 131 (4), 125 (4), 107 (14), 91 (100), 81 (8), 79 (15), 71 (16), 67 (6), 65 (6), 55 (6), 54 (6), 41 (7); HRMS calcd for $C_{18}H_{26}O_2$ 274.1933, found 274.1952.

(2*R*,8*R*)-8-Ethyl-2-(2-hydroxyethyl)-1-oxacyclooctane (46) was prepared from **45** in 100% yield similarly as described for **23**: R_f 0.34 (hexane/Et_2O, 1:1); $[\alpha]^{24}_D$ −11.8° (*c* 0.56, MeOH); IR 3400, 2930, 2850, 1460, 1350, 1100, 1055; ^1H NMR (90 MHz) 0.94 (3 H, t, J = 7.0), 1.1–2.1 (15 H, m), 3.2–3.7 (2 H, m), 3.80 (2 H, t, J = 5.4); MS, *m/e* 186 (M^+, 4), 157 (27), 141 (19), 139 (18), 129 (5), 123 (17), 121 (11), 112 (15), 110 (15), 95 (30), 83 (42), 82 (76), 81 (62), 75 (62), 69 (67), 68 (55), 67 (99), 59 (43), 57 (56), 56 (60), 55 (100), 54 (47), 41 (82); HRMS calcd for $C_{11}H_{22}O_2$ 186.1620, found 186.1621.

(2*S*,8*R*)-8-Ethyl-2-hexyl-1-oxacyclooctane (7). Via the procedure described for **6** from **23**, alcohol **46** (19 mg, 0.102 mmol) was treated with 1.5 equiv of *p*-TsCl followed by reaction with 2.3 equiv of $n\text{-}Bu_2Cu(CN)Li_2$ in THF (at room temperature overnight) to afford 22 mg (95%) of **7**: R_f 0.83 (hexane/Et_2O, 2:1); $[\alpha]^{18}_D$ +13.9° (*c* 0.15, $CHCl_3$); IR 2910, 2860, 1460, 1090; ^1H NMR (400 MHz) 0.88 (3 H, t, J = 7.5), 0.93 (3 H, t, J = 7.5), 1.2–1.8 (12 H, m), 3.34 (1 H, m), 3.40 (1 H, m); ^{13}C NMR 10.93, 14.16, 22.70, 24.19, 26.36, 27.24, 29.56, 29.86, 31.97, 33.46, 33.73, 37.12, 79.65, 81.12; MS, *m/e* 226 (M^+, 0.5), 225 (0.6), 197 (20), 179 (8), 168 (9), 141 (31), 123 (38), 112 (26), 97 (76), 84 (49), 83 (68), 70 (58), 69 (70), 56 (61), 55 (100), 43 (44), 41 (56); HRMS calcd for $C_{15}H_{30}O$ 226.2297, found 226.2315.

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