Tandem Intramolecular Michael Addition/Aldol Condensation or Acylation Applied to D-Glucose-Derived Substrates: Preparation of Enantiomeric Octahydronaphthalenone Derivatives Equipped with C- and O-Functionalities

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An enantiomerically pure (1,2-isopropylidenedioxy)tetrahydrofuran derivative, **9**, bearing acetonyl and propionaldehyde side chains smoothly underwent aldol cyclization under basic conditions. The major product was the *cis*-aldol **21S**, accompanied by the trans-diastereomer **21R** in a ratio of 4 to 1. Further functionalized substrates **10** and **11**, with either a (4-acetyl)- or a (4-ethoxycarbonyl)-3(*E*)-butenyl group, smoothly underwent a tandem Michael addition/aldol condensation or acylation by treatment with sodium hydride (NaH). In the case of **10**, two cis-fused octahydronaphthalenones, **23** and **25**, and a trans-fused diasteromer, **24**, were isolated in 20%, 33%, and 11% yields, respectively. The substrate **11** provided a cis-substituted perhydrobenzofuran derivative, **26**, and cis- and trans-fused octahydronaphthalenediones, **27** and **28**, in 52%, 17%, and 9% yields, respectively. An intramolecular S_N2' type cyclization of the corresponding 5-chloro-3(*E*)-pentenyl derivative, **14**, provided exclusively (96%) the perhydrobenzofuran derivative, **29**, in which the two newly introduced substituents are disposed in a cis relationship. The stereochemical assignments for each cyclization product were achieved by ^1H NMR analysis of the cyclization products or their chemically modified compounds. Preferential formation of the cis-fused carbocycles in the present studies is rationalized from a stereoelectronic viewpoint. Furthermore, the effect of substituents on the cyclization was investigated using two tetrahydrofuran derivatives, **20S** and **20R**. Base treatment of **20S** gave the cis-fused tandem cyclization product **30** and the trans diastereomer **31** in a ratio of 3.8 to 1. In contrast, **20R** gave two cyclization products, **32** and **33**, in a ratio of 5 to 1, as a result of a preferential trans cyclization mode.

Introduction

Development of a novel and efficient methodology for enantioselective or enantiospecific carbocyclization is a major objective in current organic synthesis. A variety of useful approaches is found in the literature, especially in the context of natural product synthesis.[1] The representative approaches are classified as follows: (1) Diels-Alder approaches in an intramolecular fashion,[2] (2) anionic intramolecular carbon-carbon bond formations such as the double Michael cyclization,[3] (3) 1,3-dipolar cycloaddition for five-membered carbocycle formation,[4] and (4) free-radical-induced carbon-carbon bond formation for both five- and six-membered carbocyclizations.[5] For access to enantiomerically pure carbocycles, the substrates prepared from carbohydrates are frequently used. Significant developments have been achieved recently in the field of synthetic carbohydrate chemistry by means of radical-mediated carbocyclization.[6] In regard to polycarbocycles formation, Deslongchamps and co-workers have amply demonstrated the promising features of both intramolecular and transannular cyclizations.[7]

We recently reported the base-catalyzed carbocyclization of D-glucose-derived substrates such as **3** and **5** (Scheme I). These reactions provided enantiomerically pure 5- or 3-C-alkylated 4-hydroxycyclohex-2-enones, i.e. **4**[8] and **6**.[9]

(1) Recent leading reviews in these fields: (a) Ho, T.-L. *Carbocycle Construction in Terpene Synthesis*; VCH Publishers: New York and Weinheim, 1988. (b) Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron* **1990**, *46*, 1385.

(2) Reviews: (a) Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. *Natural Products Synthesis Through Pericyclic Reactions*; ACS Monograph 180; American Chemical Society: Washington, D.C., 1983; pp 119-254. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876. (b) Ciganek, E. *Org. React.* **1984**, *32*, 1. (c) Taber, D. F. *Intramolecular Diels-Alder and Alder Ene Reactions*; Springler-Verlag: Berlin, 1983. (d) Taber, D. F. In *Reactivity and Structure Concepts in Organic Chemistry*; Springer-Verlag: Berlin, 1984; Vol. 18, p 1. (e) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (f) Craig, D. *Chem. Soc. Rev.* **1987**, *26*, 2379. (g) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*: In *Tetrahedron Organic Chemistry Series*; Baldwin, J. E., Magnus, P. D., Eds.; Pergamin Press: Oxford, 1990; Vol. 8, pp 1-208.

(3) Intramolecular double Michael reaction for natural product synthesis: Ihara, M.; Suzuki, M.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1990**, *112*, 1164 and the previous works from their group cited therein. A leading review of the stereochemical aspects on Michael reactions has appeared recently: Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *19*, 227.

(4) Some leading reviews of several types of 1,3-dipolar cycloadditions: (a) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, p 1. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (c) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. See also, ref 1a, pp 89-117. (d) Trost, B. M. *Pure Appl. Chem.* **1988**, *60*, 1615 and the precedent papers cited therein.

(5) Some leading references on free-radical cyclizations: (a) Beckwith, A. L. *Tetrahedron* **1981**, *37*, 3073. (b) Hart, D. J. *Science* **1984**, *223*, 883. (c) Geise, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986. (d) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (e) Curran, D. P. *Synthesis* **1988**, 417 and 489. (f) Curran, D. P. In *Advances in Free Radical Chemistry*; Tanner, D. D., Ed.; JAI Press: Greenwich, 1990; Vol. 1, pp 121-157. (g) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1990**, *55*, 5442.

(6) Some recent papers on this subject: (a) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116. (b) Pak, H.; Canalda, I. I.; Fraser-Reid, B. *J. Org. Chem.* **1990**, *55*, 3009. (c) Gaudino, J. J.; Wilcox, C. S. *Carbohydr. Res.* **1990**, *206*, 233. (d) Gaudino, J. J.; Wilcox, C. S. *J. Am. Chem. Soc.* **1990**, *112*, 4374. (e) Rajan Babu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1759. (f) Andersson, F. O.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1990**, *55*, 4699. (g) Marco-Contelles, J.; Martinez-Grau, A. *Tetrahedron* **1991**, *47*, 7663.

(7) (a) Lavallee, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 3457. (b) Berube, G.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 5255. (c) Lamothe, S.; Ndibwami, A.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 1641. (d) Lavallee, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 5117. (e) Lavallee, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 6033. (f) Ruel, R.; Deslongchamps, P. *Tetrahedron Lett.* **1990**, *31*, 3961.

(8) (a) Suami, T.; Tadano, K.; Ueno, Y.; Fukabori, C. *Chem. Lett.* **1985**, 1557. (b) Tadano, K.; Ueno, Y.; Fukabori, C.; Hotta, Y.; Suami, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1727.

(9) Tadano, K.; Miyazaki, M.; Ogawa, S.; Suami, T. *J. Org. Chem.* **1988**, *53*, 1574.

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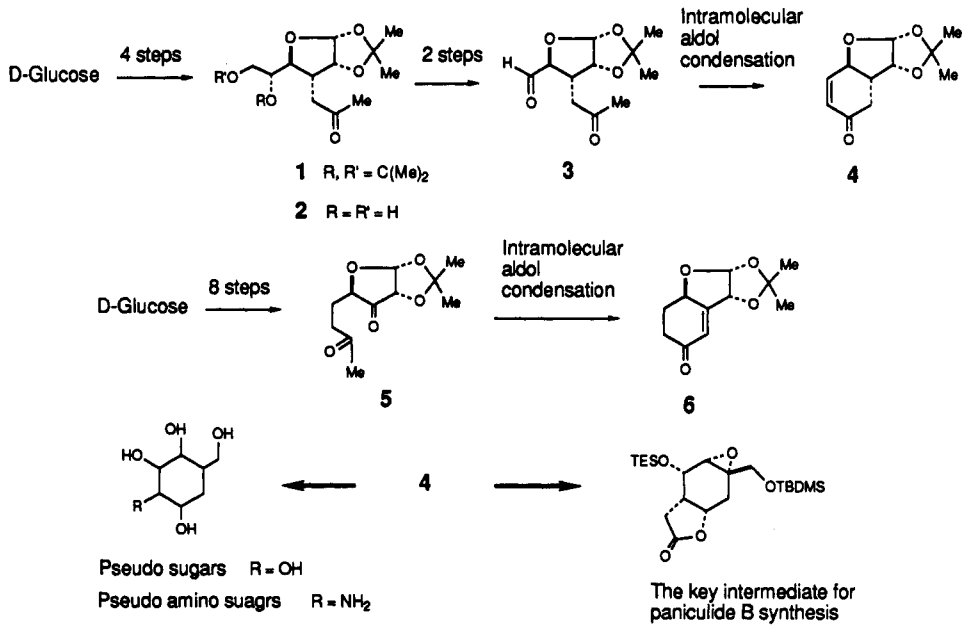
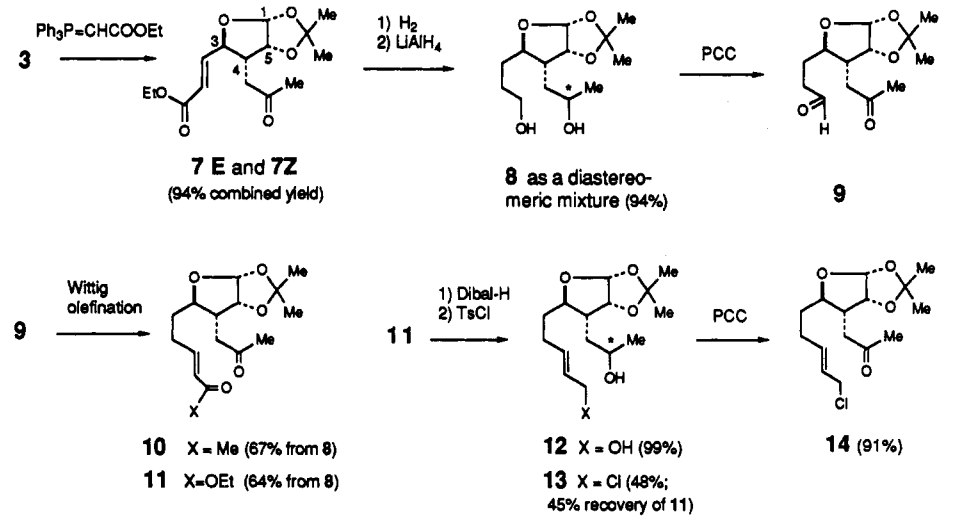
Scheme I



Scheme II



The synthetic approaches to **4** and **6** have some antecedents in the literature such as the Ferrier reaction.[10-12] The versatility of **4** has been demonstrated through (1) the stereoselective synthesis of pseudo-sugars (carbocyclic analogues of hexopyranoses) and pseudo-amino sugars[8,13] and (2) the formal total synthesis of sesquiterpene (+)-paniculide B.[14]

As part of our ongoing efforts directed at the transformation of carbohydrates to carbocycles[15] and its application to natural product synthesis,[16] we describe herein a preparation of enantiomerically pure and densely functionalized octahydronaphthalene derivatives. The present approach features a tandem intramolecular Michael addition/aldol condensation or acylation applied to D-glucose-derived substrates.[17]

(10) (a) Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455. (b) Blattner, R.; Ferrier, R.; Haines, S. R. *J. Chem. Soc., Perkin Trans. 1* **1983**, *55*, 565. (c) Ferrier, R. J.; Haines, S. R. *Carbohydr. Res.* **1984**, *130*, 135.

(11) Reviews on relevant carbocyclizations based on the carbohydrate–substrate approaches: (a) Fraser-Reid, B.; Tsang, R. In *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic Press: New York, 1989; Vol. 2, pp 123–162. (b) Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K.; Reissig, H.-U. *Organic Synthesis Highlights*; VCH Publishers: Weinheim, 1991; pp 255–259.

(12) Other enantiomeric cyclohexenone derivatives have been used for natural product synthesis: (a) Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. *J. Org. Chem.* **1989**, *54*, 3738. (b) Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, *111*, 2599. (c) Asaoka, M.; Shima, K.; Fujii, N.; Takei, H. *Tetrahedron* **1988**, *44*, 4757. (d) Asaoka, M.; Sukurai, M.; Takei, H. *Tetrahedron Lett.* **1991**, *32*, 7567,

(13) Tadano, K.; Fukabori, C.; Miyazaki, M.; Kimura, H.; Suami, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2189.

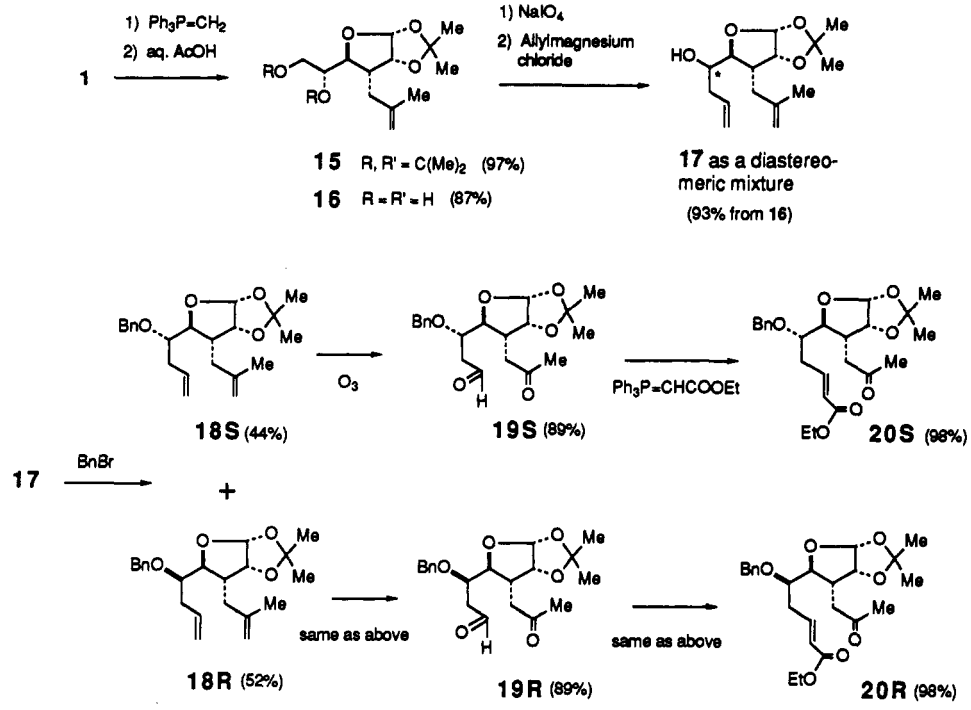
(14) Tadano, K.; Miyake, A.; Ogawa, S. *Tetrahedron* **1991**, *47*, 7259.

(15) Other carbocyclization approaches from our laboratories: (a) Suami, T.; Tadano, K.; Kameda, Y.; Iimura, Y. *Chem. Lett.* **1984**, 1919; *J. Carbohydr. Chem.* **1987**, *6*, 231. (b) Suami, T.; Tadano, K.; Ueno, Y.; Iimura, Y. *Chem. Lett.* **1985**, 37; *J. Carbohydr. Chem.* **1987**, *6*, 245. (c) Tadano, K.; Maeda, H.; Hoshino, M.; Iimura, Y.; Suami, T. *Chem. Lett.* **1986**, 1081; *J. Org. Chem.* **1987**, *52*, 1946. (d) Tadano, K.; Kimura, H.; Hoshino, M.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Jpn*, **1987**, *60*, 3673. (e) Tadano, K.; Hakuba, K.; Kimura, H.; Ogawa, S. *J. Org. Chem.* **1989**, *54*, 276.

(16) (a) Tadano, K.; Hoshino, M.; Ogawa, S.; Suami, T. *Tetrahedron Lett.* **1987**, *24*, 2741. (b) Tadano, K.; Hoshino, M.; Ogawa, S.; Suami, T. *J. Org. Chem.* **1988**, *53*, 1427. (c) Tadano, K.; Kimura, H.; Ogawa, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1355.

(17) A synthesis of aryl mono-*C*-glycosyl derivatives based on a Michael addition/aldol condensation based on the carbohydrate template appeared recently: Kraus, G. A.; Shi, J. *J. Org. Chem.* **1990**, *55*, 4922.

Scheme III



Results and Discussion

Preparation of the Substrates for the Tandem Cyclization. We chose enantiomerically pure tetrasubstituted tetrahydrofurans, **10**, **11**, and **14**, as substrates for the present work (Scheme II). Each substrate bears two side chains, namely, an acetonyl group and a 3(*E*)-butenyl group which is activated by a terminal functionality such as C(=O)Me for **10**, COOEt for **11**, or CH_2Cl for **14**. Both side chains are vicinally disposed in a trans relationship in all substrates.

Preparation of these substrates was achieved starting with our previously described compound **3**.[8] Wittig olefination of **3** with $Ph_3P=CHCOOEt$ gave a mixture of *E* and *Z* α,β-unsaturated esters **7-E** and **7-Z** in a combined yield of 94%. It should be emphasized that the Wittig reagent reacted with the aldehyde function exclusively, indicating a highly chemoselective reaction, although we cannot account for this selectivity. Hydrogenation of the *E*/*Z* mixture of **7** followed by lithium aluminum hydride ($LiAlH_4$) reduction of the resulting saturated ester[18] gave an inseparable diastereomeric mixture of diols **8** in a combined yield of 94%. Simultaneous oxidation of the primary and secondary hydroxyl groups of **8** with pyridinium chlorochromate (PCC)[19] gave keto-aldehyde **9**.[20] Wittig olefination of **9** with $Ph_3P=CHC(=O)Me$ or with $Ph_3P=CHCOOEt$ provided the substrate **10** or **11** in an overall yield of 67% or 64% from **8**, respectively. These reactions proceeded chemoselectively and stereoselectively to provide the *E*-isomers exclusively. Diisobutylaluminum hydride (Dibal-H) reduction of **11** followed by treatment of the resulting allylic alcohol **12** with an excess of *p*-toluenesulfonyl chloride (TsCl) in CH_2Cl_2 provided the allylic chloride **13** in 45% yield (48% of **12** was recovered).[23] Oxidation of **13** using PCC gave another substrate, **14**.

We considered it important to investigate the effect of a substituent on the cyclization. In order to learn more about this effect, two substrates, **20R** and **20S**, both of which bear a benzyloxy group in one side chain, were prepared as shown in Scheme III. The reported compound **1**[8] was subjected to Wittig methylenation. Acid hydrolysis of the adduct **15** gave diol **16**. Glycol cleavage of **16** by sodium periodate ($NaIO_4$) mediated oxidation followed by Grignard reaction using allylmagnesium chloride provided a nearly 4:5 mixture of the diastereomeric homoallylic alcohols **17** in a combined yield of 93%. The hydroxyl groups of the mixture of **17** were protected as benzyl ethers. The mixture of benzyl ethers was cleanly separated by column chromatography on silica gel, providing **18S** (44%) and **18R** (52%). Although determination of the configuration of the carbon bearing the benzyloxy group in **18S** or **18R** was difficult by means of spectral analysis, these configurations were established as depicted in a later stage. Ozonolysis of the vinyl group in **18S** or **18R** provided keto-aldehyde **19S** or **19R**, respectively. Finally, Wittig olefination of **19S** or **19R** provided exclusively *E*-isomer **20S** or **20R** in good overall yield.

Tandem Cyclization of the Substrates. The Reaction Conditions. We first investigated the intramolecular aldol reaction of the intermediate **9**. Refluxing in benzene in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.8 molar equiv), compound **9** smoothly underwent intramolecular reaction to provide a diastereomeric mixture of aldols **21S** and **21R** (Scheme IV). The mixture was easily separated by column chromatography on silica gel to provide **21S** and **21R** in 53% and 13% yields from **8**, respectively. The structure of each diastereomer was determined by ^1H NMR analysis of the corresponding

(18) Hydrogenation of the mixture **7** (Raney Ni T-4 catalyst in EtOH) was accompanied by reduction of the carbonyl function in the acetonyl group.

(19) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

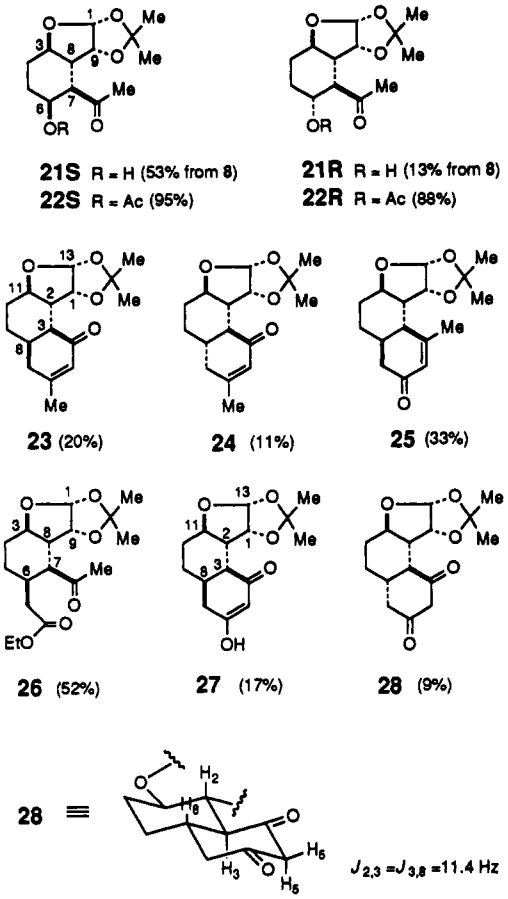
(20) Other oxidation conditions such as the Corey-Kim procedure[21] or Swern oxidation[22] gave either a complex mixture or a low yield of **9**.

(21) Corey, E. J.; Kim, C. K. *J. Am. Chem. Soc.* **1972**, *94*, 7586.

(22) Huang, S. L.; Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(23) For introduction of a leaving group to the primary hydroxyl group of **12**, the following conditions were examined: (a) CCl_4, Ph_3P in THF (formation of a complex mixture); (b) NBS, Ph_3P in DMF (22% yield of the corresponding allylic bromide); (c) NCS, Ph_3P in DMF (54% yield of **13** but no recovery of **12**).

Scheme IV

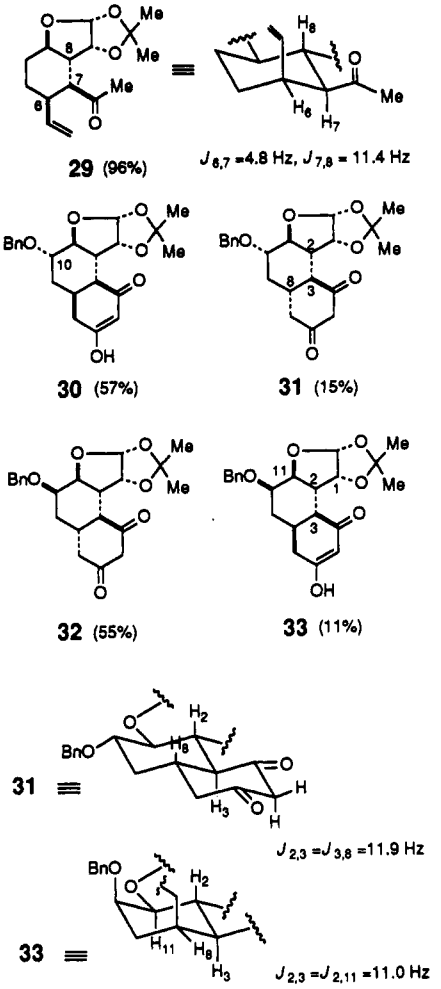


acetate, i.e. **22S** or **22R**. In the ^{1}H NMR spectrum of **22S**, the methine proton at C-7 appears at δ 2.82 as a doublet of doublets with $J_{6,7}$ = 2.9 and $J_{7,8}$ = 11.7 Hz. On the other hand, that of **22R** appears at δ 3.01 as a triplet with $J_{6,7}$ = $J_{7,8}$ = 11.0 Hz. The acetyl group at C-7 of **21S** and **21R** is oriented equatorially in both compounds. The hydroxyl group at C-6 assumes an axial orientation in **21S** and an equatorial orientation in **21R**.

The intramolecular Michael reaction of the substrate **10** was investigated next. Use of DBU as the base caused significant decomposition of the substrate in this case. When methanolic sodium methoxide was used, a 1,4-conjugated addition of the methoxide was the sole result. Treatment of **10** with cesium carbonate (Cs_2CO_3), the Deslongchamps's base,[7] gave a complex mixture in our case. We eventually found that brief treatment of **10** with 0.4 molar equiv of NaH in DMF at 0 °C provided the best and most reproducible results. Three tandem cyclization products, **23**, **24**, and **25**, were isolated in 20%, 11%, and 33% yields, respectively, by column chromatography on silica gel. Under similar conditions (1.0 molar equiv of NaH), the substrate **11** cyclized smoothly, providing the Michael adduct **26** in 52% yield along with the tandem acylation products **27** and **28** in 17% and 9% yields, respectively. When **11** was treated with 4.5 molar equiv of NaH, the tandem cyclization occurred almost exclusively, resulting in the formation of **27** and **28** in 56% and 13% yields, respectively. Cesium carbonate was effective for the initial Michael addition, providing an inseparable mixture (8:1) of **26** and the presumed trans-substituted derivative in a combined yield of 74%. The structure determinations of the cyclization products, **23**–**28**, are described below.

It is likely that the formation of the trans-fused octahydronaphthalenones **24** or **28** from **10** or **11** was a consequence of the retro-Michael reaction/recyclization of the initially formed Michael adducts. This assumption suggests that compounds **24** and **28** are thermodynamically controlled products. If this interpretation is correct, the major cyclization products **23**, **25**, **26**, and **27** can be regarded as kinetically controlled products.

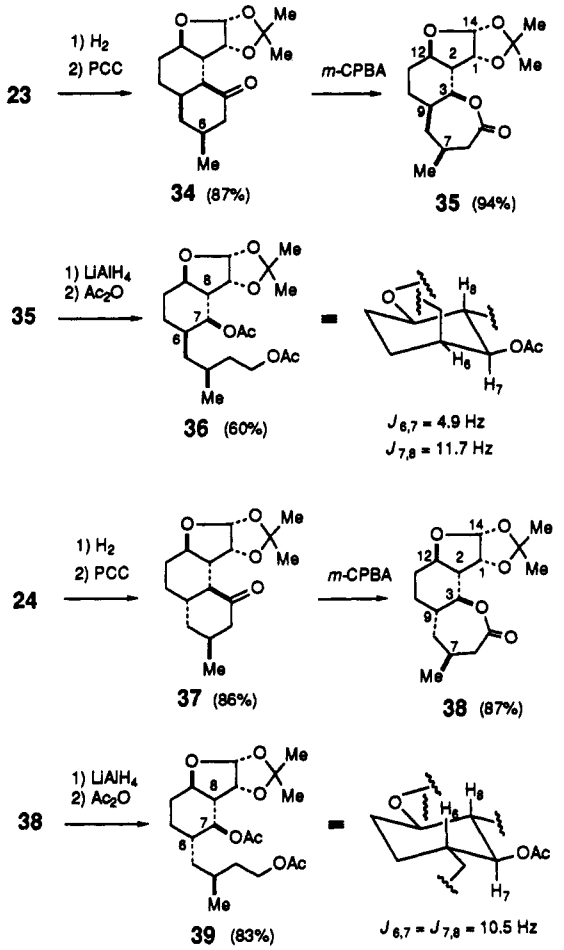
Scheme V



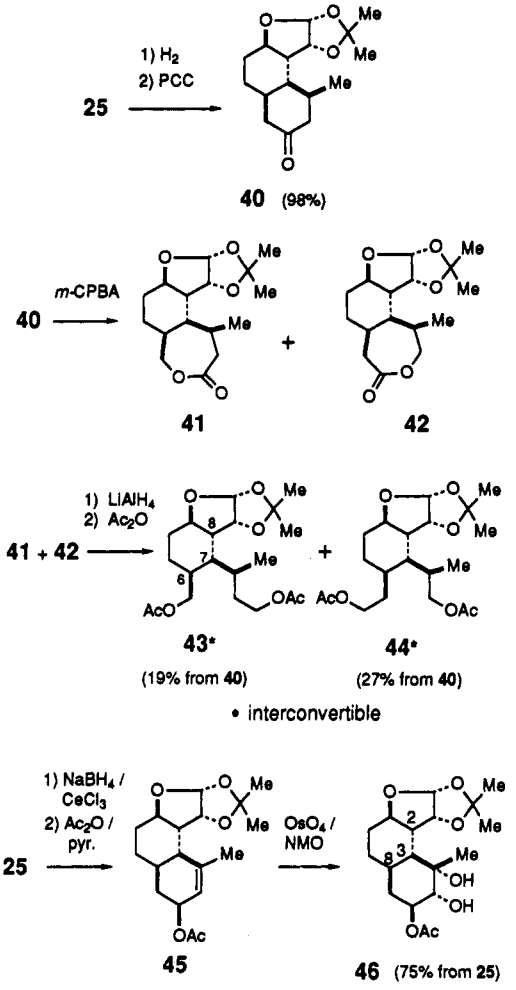
We next investigated the cyclization of the allylic chloride **14**. In the case of **14**, the expected S_N2' type cyclization is irreversible and the reaction should give a kinetically controlled product. When compared **14** was treated with an excess of NaH (5 molar equiv) in DMF at 0 °C, a cis-substituted cyclization product **29** was obtained in 96% yield (Scheme V); none of the trans-substituted product was detected in the reaction mixture. The structure of **29** was confirmed by ^{1}H NMR analysis, in which H-7 appeared at δ 2.83 as a doublet of doublets with $J_{6,7}$ = 4.8 and $J_{7,8}$ = 11.4 Hz. From these results, we believe that the initial Michael additions of **10** and **11** proceed under kinetic control to provide cis-substituted adducts preferentially.

We also examined the cyclization of the benzyl ether **20S** or **20R**. When **20S** was treated with 1.0 molar equiv of NaH, two tandem cyclization products, **30** and **31**, were obtained in 57% and 15% yields, respectively (Scheme V). The structure determinations of **30** and **31** are described below. The cyclization of **20S** also proceeded preferentially in a cis cyclization mode. On the other hand, treatment of **20R** with NaH provided two tandem cyclization products, **32** and **33**, in 55% and 11% yields, respectively. In this case, the trans-fused perhydronaphthalenedione **32** was the major product. From these results, we concluded that the benzyloxy group participated significantly to bias

Scheme VI



Scheme VII



the stereochemical course of the Michael addition.

Structure Determination of the Cyclization Products. In many cases, the ^1H NMR peak patterns of the methylene and methine protons of the cyclization products were overlapping and complicated. We therefore decided to transform the cyclization products into derivatives suitable for accurate structure determination by ^1H NMR analysis.

The tandem cyclization product **23** was hydrogenated, and the product was oxidized with PCC to provide a decalone derivative **34** (Scheme VI). The configuration of the methyl group at C-6 was tentatively assigned as depicted, by rationalizing that the hydrogenation should occur from the less hindered convex site of **23**. Baeyer–Villiger oxidation of **34** with *m*-chloroperbenzoic acid (*m*-CPBA) provided ϵ-lactone **35** exclusively. Reduction of **35** with $LiAlH_4$ followed by acetylation of the product gave a perhydrobenzofuran derivative **36**. The ^1H NMR spectrum of **36** revealed the H-7 signal as a doublet of doublets at δ 4.90 with $J_{6,7}$ = 4.9 and $J_{7,8}$ = 11.7 Hz. As migration of a C–C bond to a C–O bond in the Baeyer–Villiger rearrangement proceeds with retention of configuration, the structures of **35** and of the precursor **23** were established as depicted.

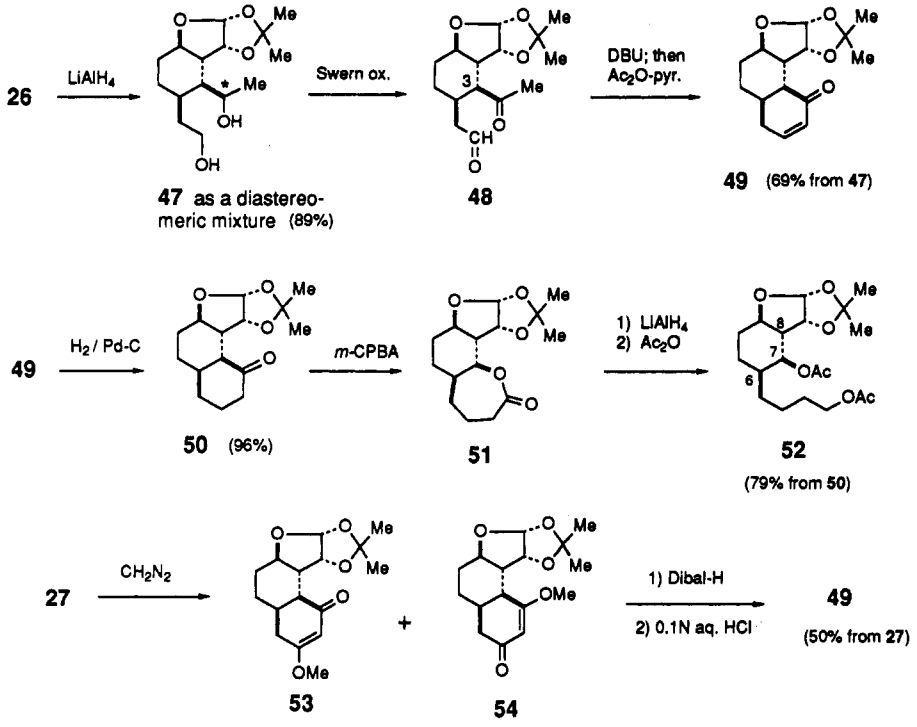
Hydrogenation of **24** followed by PCC oxidation of the product provided a decalone derivative **37**. The configuration of the methyl group in **37** was tentatively assigned as depicted. Baeyer–Villiger oxidation of **37**, $LiAlH_4$ reduction of the product **38**, followed by acetylation of the resulting diol gave the perhydrobenzofuran derivative **39** as a single isomer in high overall yield. The ^1H NMR spectrum of **39** revealed the H-7 signal as a triplet at δ 4.86 with $J_{6,7} = J_{7,8}$ = 10.5 Hz. From these spectral data the structure of **24** was established.

The structure of **25** was determined as follows (Scheme VII): Hydrogenation of **25** followed by PCC oxidation of the product gave the decalone derivative **40** as a single isomer. Baeyer–Villiger oxidation of **40** with *m*-CPBA gave an inseparable mixture of ϵ-lactones **41** and **42**. Reduction of the mixture using $LiAlH_4$ followed by acetylation of the products provided the acetates **43** and **44**, separated by column chromatography on silica gel, in a nearly 1 to 1 ratio. The ^1H NMR spectra of **43** and **44** revealed that both compounds possess two acetoxymethyl groups. These facts indicate that compound **40** bears two methylene groups, both of which are adjacent to the carbonyl group. Thus, the locations of the methyl and carbonyl groups in **40** were established. The stereochemistry of the ring fusion of **25** was determined as follows: Luche reduction[24] of **25** followed by acetylation of the product gave allylic acetate **45** as a single diastereomer. The hydride attack to **25** presumably occurred from the less hindered α-site. Cis-dihydroxylation of the double bond in **45** with OsO_4–NMO[25] gave diol **46** exclusively. In the ^1H NMR spectrum, the H-3 signal of **46** appears as a doublet of doublets at δ 2.04 with $J_{2,3}$ = 12.5 Hz and $J_{3,8}$ = 4.4 Hz. From these observations, the ring fusion of **25** was determined to be as depicted.

The structure of the perhydrobenzofuran derivative **26** was determined both by ^1H NMR analysis and by chemical

(24) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(25) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

Scheme VIII



modification (Scheme VIII). In the ^{1}H NMR spectrum of **26**, the proton signal at C-7 appears as a doublet at δ 2.86 with J = 9.2 Hz. This coupling constant indicates that H-7 and H-8 are disposed in a diaxial relationship. Reduction of **26** using $LiAlH_4$ followed by Swern oxidation of the resulting diol **47** gave **48**, which was subjected to intramolecular aldol condensation. Treatment of **48** with DBU followed by β-elimination provided the octahydronaphthalenone derivative **49** efficiently. By using the aforementioned reaction sequence, the aldol **49** was converted into a perhydrobenzofuran derivative, **52**. The ^{1}H NMR spectrum of **52** revealed the proton signal for H-7 as a doublet of doublets at δ 4.90 with $J_{6,7}$ = 5.1 and $J_{7,8}$ = 11.7 Hz. These facts led to the conclusion that the structure of the Michael adduct **26** is as depicted in Scheme IV.

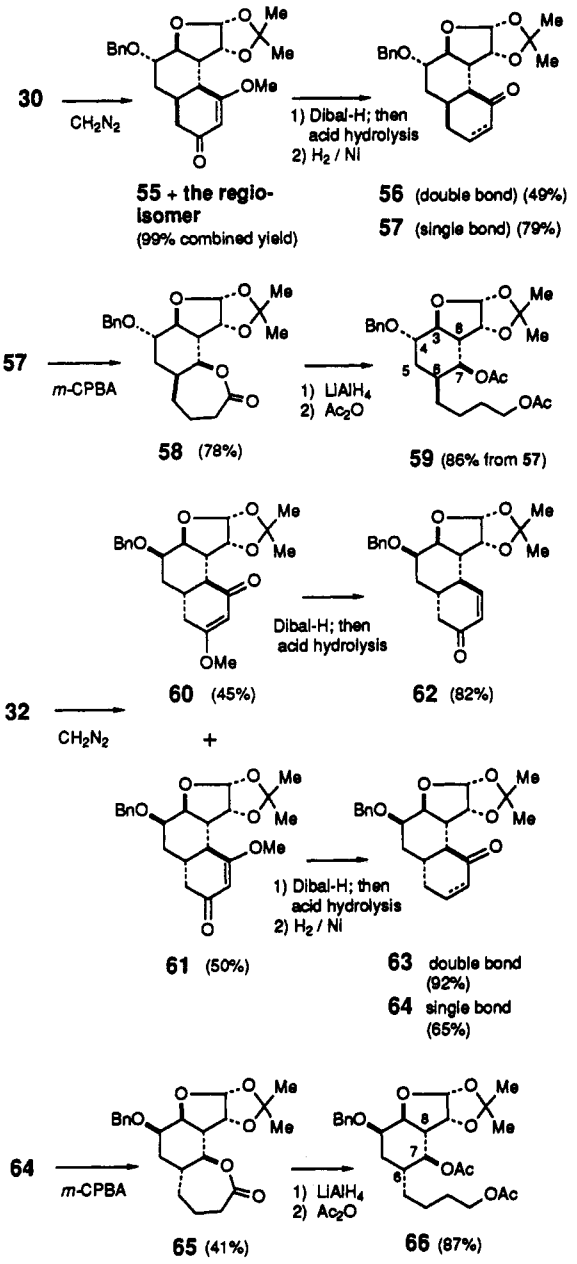
The structure of **27** was determined by analogy with the aforementioned aldol reaction product **49**. Compound **27** was treated with excess diazomethane to give an inseparable mixture of β-methoxy enones **53** and **54**. The nearly 1:1 mixture of **53** and **54** was subjected to Dibal-H reduction followed by acid hydrolysis to provide enone **49**, which was derived from **54**, in 50% yield. As the structure of **49** was established as described above, the structure of **27** was determined as depicted. In the case of the remaining cyclization product **28**, its structure was determined directly by ^{1}H NMR analysis. Compound **28** exists as a 1,3-diketo structure in $CDCl_3$ solution, as evidenced by two signals at δ 3.36 and 3.59 arising from the C-5 methylene protons. The signal due to H-3 appears at δ 2.60 as a triplet with $J_{2,3} = J_{3,8}$ = 11.4 Hz (see the conformational description in Scheme IV).

Finally, the structures of **30–33** were determined as shown in Scheme IX. Treatment of **30** with diazomethane gave a regioisomeric mixture of **55** (only one regioisomer is shown in Scheme IX), which was subjected to Dibal-H reduction/acid hydrolysis to give enone **56** and its regioisomer, which were separated, in 49% and 33% yields, respectively. Through a reaction sequence analogous to that used above, compound **56** was converted into perhydrobenzofuran derivative **59** via **57** and **58**. The structure of **59** was confirmed by ^{1}H NMR analysis, in which the signal due to H-4 appears as a doublet of triplets at δ 3.60, with $J_{4,5eq}$ = 4.4 Hz and $J_{3,4} = J_{4,5ax}$ = 9.5 Hz, and the signal due to H-7 appears as a doublet of doublets at δ 4.95, with $J_{6,7}$ = 5.3 Hz and $J_{7,8}$ = 11.4 Hz. The structure of another cyclization product, **31**, was determined directly from its ^{1}H NMR analysis. In the ^{1}H NMR spectrum the signal due to H-3 of **31** appears as a triplet at δ 2.58 with $J_{2,3} = J_{3,8}$ = 11.9 Hz. This coupling constant verified the configurations to C-3 and C-8, and the structure of **31** was determined (see the conformational description of Scheme V).

The tandem cyclization product **32** was converted into **66** via **60–65** in a manner analogous to that used in the case of **59** from **30**. The ^{1}H NMR spectrum of **66**, in which H-7 appears as a triplet at δ 4.90 with $J_{6,7} = J_{7,8}$ = 10.6 Hz, revealed that the structure of **32** was as depicted in Scheme V. The structure of **33** was determined by ^{1}H NMR analysis. When the signal due to H-1 at δ 4.72 was irradiated, the signal due to H-2 at δ 2.44 changes to a triplet with $J_{2,3} = J_{2,11}$ = 11.0 Hz. During irradiation of the signal at δ 3.80, attributable to H-11, the signal due to H-2 changed to a doublet of doublets with $J_{1,2}$ = 4.4 Hz and $J_{2,3}$ = 11.0 Hz. These observations led to the conclusion that the configuration at C-3 of **33** is *S*. Because we had isolated the 3*S*,8*S* isomer above, i.e. **32**, we also concluded that the configuration at C-8 of **33** must be *R*. Thus the structure of **33** was established.

Stereochemical Interpretations for the Results of the Intramolecular Michael Addition. It is apparent from the results of the cyclization of **10** or **11** that the initial Michael addition proceeded with moderate to high stereochemical bias, giving the cis-substituted perhydrobenzofuran derivatives predominantly. Judging from the ratio of the cyclization products, the bias of the cis cyclization mode compared to the trans is estimated to be 4.8:1 (**23** + **25**:**24**) for **10** or 7.7:1 (**26** + **27**:**28**) for **11**. In the case of the allylic chloride **14**, the S_N2' type cyclization provided exclusively the cis-substituted perhydrobenzofuran **29**. Consequently, the Michael reaction achieved by using **10** or **11** provided either exclusively or predominantly

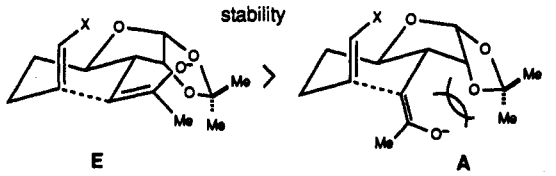
Scheme IX



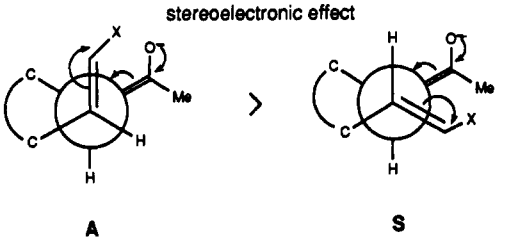
the cis vicinally substituted products under kinetically controlled conditions. The formation of the trans-fused tandem cyclization products **24** and **28** might be the consequence of thermodynamic equilibrium between the Michael and retro-Michael reactions, although we have no firm experimental basis for this assumption.

We adopt the following argument to account for the stereochemical bias observed in the Michael addition and the S_N2' cyclization. In general, a six-membered ring formation proceeds through a thermodynamically favorable chair-like transition state. As depicted in eq 1, the enolate generated from the acetonyl group in **10**, **11**, or **14** would be favorably disposed in a quasi-equatorial orientation (**E**). The quasi-axial disposition (**A**) seems to be disfavored owing to a nonbonded interaction incurred from the *O*-isopropylidene group. We assume the geometry of the enolate to be *Z* for each substrate as depicted in eqs 1 and 2, although no firm spectral evidence to support this assumption is in our hands. Once we investigated O-silylation of the enolate generated from **10**, however, the cyclization to **23–25** occurred rapidly. The silyl enol ether could not be characterized.[26] The preferred formation of the thermodynamically less stable cis cyclization products is not unusual, and this phenomenon was reported by Schlosser[27] early in the seventies. Concerning the conformation of the Michael acceptor, an argument proposed by Seebach[28] can be used to explain the stereoselectivity observed in our work. Namely, a smaller substituent in the Michael donor part (hydrogen atom of the enolate) and a carbon–carbon double bond in the acceptor part are preferably aligned antiperiplanarly (the Newman projection **A**) for stereoelectronic reasons.[29] This alignment leads to the cis-substituted Michael adduct. On the other hand, the synclinal alignment (the Newman projection **S**) leads to a disadvantageous transition state. The results obtained from our substrates can be explained well by using Seebach's proposal. However, it is likely that the retro-Michael reaction also contributes in some measure to the formation of the trans-fused cyclization products.

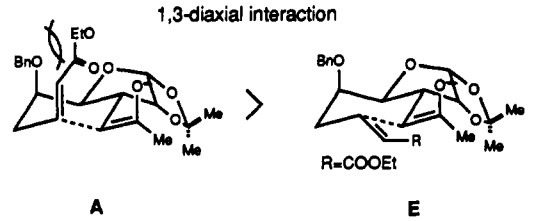
The preferential formation of the cis-fused octahydronaphthalenone **30** from **20S** can be accounted for in virtually the same manner as that adopted for substrates **10** and **11**. In the case of **20S**, the equatorially disposed benzyloxy group scarcely influences the stereochemical course of the cyclization. On the other hand, the axially disposed benzyloxy group in **20R** surely interacts with the Michael acceptor part as depicted in **A** of eq 3. This unfavorable 1,3-diaxial interaction can be avoided by changing the conformation of the transition state from **A** to **E**, in which the Michael acceptor is disposed equatorially. As a result, compound **32** was formed preferentially. The formation of **33** to a certain extent indicates that the steric effect of the benzyloxy group on the cyclization is significant, but not exclusive.



(1)



(2)



(3)

In conclusion, we have demonstrated an enantiomeric access to densely functionalized octahydronaphthalene

(26) When **10** was mixed with NaH and TMSCl–Et_3N in DMF at 0 °C, rapid formation of the cyclized products **23–25** was observed and none of the silyl enol ether(s) was isolated from the reaction mixture.

(27) Schlosser, M. *Top. Stereochem.* **1970**, *5*, 1.
(28) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.
(29) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; p 221.

derivatives. Our approaches feature tandem intramolecular Michael addition/aldol cyclizations or acylations which were realized by using enantiomerically pure substrates derived from D-glucose. These approaches may serve as novel procedures for the synthesis of naturally occurring cis- or trans-fused hydronaphthalene sesquiterpenes such as cadinene, amorphene, and related compounds.[30]

Experimental Section[31]

(1*R*,3*R*,4*R*,5*R*)-3-[(*E*)- and (*Z*)-(Ethoxycarbonyl)-ethenyl]-4-(2-oxopropyl)-7,7-dimethyl-2,6,8-trioxabicyclo-[3.3.0]octanes (7E and 7Z).[32] To a stirred solution of **2** (2.36 g, 9.07 mmol) in MeOH (25 mL) was added aqueous $NaIO_4$ (2.33 g, 10.9 mmol in H_2O 13 mL). The mixture was stirred for 30 min and then concentrated to ca. half the volume of the original. The residue was diluted with H_2O (100 mL) and extracted with EtOAc (100 mL × 3). The extracts were combined, dried, and then concentrated to provide crude aldehyde **3** (2.22 g).

A mixture of the aldehyde and Ph_3P=CHCOOEt (4.11 g, 11.8 mmol) in benzene (25 mL) was stirred for 30 min, and the solvent was evaporated. The residue was triturated with EtOAc and petroleum ether. After 30 min of stirring, the precipitated Ph_3P=O was collected by filtration and washed well with petroleum ether. The filtrate and washings were combined and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to provide 2.54 g (94% combined yield) of a mixture of **7E** and **7Z** as a colorless oil. In a small-scale experiment, **7E** and **7Z** were separated by repeated column chromatography on silica gel. **7E**: a colorless oil; TLC R_f 0.63 (EtOAc/hexane, 1:1); $[\alpha]^{26}_D$ +50.3° (*c* 2.02, $CHCl_3$); IR (neat) 2980, 2930, 1715, 1660, 1365, 1300, 1265, 1210 cm^{-1}; ^1H NMR (270 MHz) δ 1.29 (t, *J* = 7.1 Hz, 3 H), 1.30, 1.50 (2 s, 3 H × 2), 2.19 (s, 3 H), 2.15–2.28 (m, 1 H), 2.44 (dd, *J* = 3.3 and 18.0 Hz, 1 H), 2.85 (dd, *J* = 11.0 and 18.0 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 4.23 (ddd, *J* = 0.7, 6.2, and 10.6 Hz, 1 H), 4.82 (t, *J* = 4.0 Hz, 1 H), 5.87 (d, *J* = 4.0 Hz, 1 H), 6.07 (dd, *J* = 1.5 and 15.8 Hz, 1 H), 6.79 (dd, *J* = 6.2 and 15.8 Hz, 1 H). Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.07; H, 7.33. **7Z**: a colorless oil; TLC R_f 0.65 (EtOAc/hexane, 1:1); $[\alpha]^{26}_D$ −5.6° (*c* 1.09, $CHCl_3$); IR (neat) 2980, 2940, 1720, 1650, 1420, 1375, 1210 cm^{-1}; ^1H NMR (270 MHz) δ 1.30 (t, *J* = 7.3 Hz, 3 H), 1.30, 1.54 (2 s, 3 H × 2), 2.16 (s, 3 H), 2.17–2.28 (m, 1 H), 2.51 (dd, *J* = 4.0 and 18.7 Hz, 1 H), 2.93 (dd, *J* = 9.9 and 18.7 Hz, 1 H), 4.19 (q, *J* = 7.3 Hz, 2 H), 4.79 (t, *J* = 4.0 Hz, 1 H), 5.43 (dd, *J* = 8.4 and 10.3 Hz, 1 H), 5.87 (d, *J* = 4.0 Hz, 1 H), 5.91 (dd, *J* = 0.9 and 11.7 Hz, 1 H), 6.05 (dd, *J* = 8.8 and 11.7 Hz, 1 H). Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.22; H, 7.27.

Mixture of (1*R*,3*R*,4*R*,5*R*)-3-(3-Hydroxypropyl)-4-[2(*R*)- and 2(*S*)-hydroxypropyl]-7,7-dimethyl-2,6,8-trioxabicyclo-[3.3.0]octanes (8). The mixture of **7** (2.54 g, 8.51 mmol) in EtOH (25 mL) was hydrogenated in the presence of Raney nickel T-4 under H_2 (1 atm) for 20 h. The catalyst was removed through a pad of Celite and washed well with EtOH. The filtrate and washings were combined and concentrated to provide saturated ester (2.57 g) [TLC R_f 0.50 (EtOH/toluene, 1:10)].

To a stirred solution of the residue (2.57 g) in THF (50 mL) was added $LiAlH_4$ (646 mg, 17.0 mmol). After 30 min, H_2O (0.65 mL), 10% aqueous NaOH (0.65 mL), and H_2O (1.9 mL) were added successively. The solid that precipitated was removed by filtration. The filtrate was concentrated. The residue was purified by column chromatography on silica gel (EtOH/toluene, 1:20, 1:15, and then 1:8, successively) to provide compounds **8** (2.08 g, 94%): a colorless oil; TLC R_f 0.38 (EtOH/toluene, 1:5); IR (neat) 3400, 2930, 2870, 1370, 1210 cm^{-1}; ^1H NMR (270 MHz) δ 1.23, 1.24 (2 d, each *J* = 6.2 Hz, ca. 7:5, 3 H), 1.32, 1.49, 1.50 (3 s, 3 H for 1.32, total 3 H for 1.49, 1.50), 1.41–2.30 (m, 9 H), 3.65, 3.67 (2 d, *J* = 6.0 Hz, total 2 H), 3.75–3.84 (m, 1 H), 3.87–4.01 (m, 1 H), 4.68–4.72 (m, 1 H), 5.78–5.80 (m, 1 H). Anal. Calcd for $C_{13}H_{24}O_5$: C, 59.97; H, 9.29. Found: C, 60.08; H, 9.33.

(1*R*,3*R*,4*R*,5*R*)-7,7-Dimethyl-3-[(3*E*)-5-oxo-3-hexenyl]-4-(2-oxopropyl)-2,6,8-trioxabicyclo[3.3.0]octane (10). To a stirred solution of **8** (1.81 g, 6.95 mmol) in CH_2Cl_2 (40 mL) were added PCC (5.99 g, 27.8 mmol) and powdered molecular sieves, 4A (6.0 g). After 30 min, the mixture was passed through a short column of silica gel. The column was eluted with excess ether to provide **9** (1.82 g): a colorless oil; TLC R_f 0.65 (EtOH/toluene, 1:5); ^1H NMR (270 MHz) δ 1.28, 1.46 (2 s, 3 H × 2), 1.46–1.65, 1.90–2.18 (2 m, 1 H × 2), 2.20 (s, 3 H), 2.46 (dd, *J* = 3.4 and 18.5 Hz, 1 H), 2.64–2.67 (m, 2 H), 2.83 (dd, *J* = 10.2 and 18.5 Hz, 1 H), 3.72–3.80 (m, 1 H), 4.74 (t, *J* = 3.4 Hz, 1 H), 5.77 (d, *J* = 3.4 Hz, 1 H), 9.74 (d, *J* = 1.0 Hz, 1 H).

To a solution of **9** (1.82 g) in benzene (40 mL) was added Ph_3P=CHC(=O)CH_3 (3.53 g, 11.1 mmol). The mixture was refluxed for 10 h, and then the solvent was removed by concentration. The residue was triturated with excess petroleum ether. After 30 min of stirring, the precipitated Ph_3P=O was removed by filtration and washed well with petroleum ether. The filtrate and washings were combined and then concentrated. The residue was purified by column chromatography on silica gel (EtOAc/toluene, 1:10) to provide 1.38 g (67%) of **10**: a colorless oil; TLC R_f 0.44 (EtOAc/toluene, 1:2); $[\alpha]^{24}_D$ +82.4° (*c* 0.77, $CHCl_3$); IR (neat) 2980, 2930, 1715, 1695, 1670, 1625, 1370, 1250 cm^{-1}; ^1H (270 MHz) δ 1.29, 1.47 (2 s, 3 H × 2), 1.50–1.62, 1.66–1.75 (2 m, 1 H × 2), 2.08–2.19 (m, 1 H), 2.19, 2.23 (2 s, 3 H × 2), 2.26–2.49 (m, 2 H), 2.38 (dd, *J* = 3.5 and 18.3 Hz, 1 H), 2.83 (dd, *J* = 10.1 and 18.3 Hz, 1 H), 3.76 (dt, *J* = 2.6 and 10.7 Hz), 4.74 (t, *J* = 4.0 Hz, 1 H), 5.79 (d, 1 H, *J* = 4.0 Hz), 6.09 (dt, *J* = 15.8 and 1.5 Hz, 1 H), 6.81 (td, *J* = 7.0 and 15.8 Hz, 1 H). Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.86; H, 8.16. Found: C, 64.46; H, 8.22.

(1*R*,3*R*,4*R*,5*R*)-3-[(3*E*)-4-(Ethoxycarbonyl)-3-butenyl]-4-(2-oxopropyl)-7,7-dimethyl-2,6,8-trioxabicyclo[3.3.0]octane (11). The mixture of **8** (2.08 g, 7.99 mmol), which was obtained from 2.65 g of **7**, was converted into **9** (1.48 g) as described in the preparation of **10**. A mixture of **9** (1.48 g) and Ph_3P=CHCOOEt (3.02 g, 8.66 mmol) in benzene (30 mL) was stirred for 3.5 h. The solvent was removed by concentration. The residue was triturated with excess petroleum ether. The precipitated Ph_3P=O was removed by filtration. The filtrate and washings (petroleum ether) were combined, and the whole was concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8 then 1:5) to provide 1.66 g (64%) of **11**: a colorless oil; TLC R_f 0.61 (EtOAc/toluene, 1:1); $[\alpha]^{24}_D$ +74.0° (*c* 0.88, $CHCl_3$); IR (neat) 2990, 2940, 2870, 1720, 1655, 1370, 1210 cm^{-1}; ^1H NMR (270 MHz) δ 1.28 (t, *J* = 7.3 Hz, 3 H), 1.29, 1.47 (2 s, 3 H × 2), 1.50–1.76 (m, 2 H), 2.05–2.17 (m, 1 H), 2.20 (s, 3 H), 2.21–2.50 (m, 2 H), 2.38 (dd, *J* = 3.7 and 18.3 Hz, 1 H), 2.83 (dd, *J* = 10.2 and 18.3 Hz, 1 H), 3.74 (ddd, *J* = 2.6, 9.2, and 11.9 Hz, 1 H), 4.18 (q, *J* = 7.3 Hz, 2 H), 4.74 (t, *J* = 4.0 Hz, 1 H), 5.79 (d, *J* = 4.0 Hz, 1 H), 5.83 (dt, *J* = 15.8 and 1.5 Hz, 1 H), 6.96 (dt, *J* = 15.8 and 7.0 Hz, 1 H). Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.47; H, 7.98.

Mixture of (1*R*,3*R*,4*R*,5*R*)-3-[(*E*)-5-Hydroxy-3-pentenyl]-4-[2(*R*)- and 2(*S*)-hydroxypropyl]-7,7-dimethyl-2,6,8-trioxabicyclo[3.3.0]octanes (12). To a cooled (−70 °C) stirred solution of **11** (1.63 g, 4.99 mmol) in CH_2Cl_2 (35 mL) under Ar was added Dibal-H (17.5 mmol, 11.6 mL, 1.5 M solution in toluene). The mixture was stirred at −70 °C for 30 min and then quenched by addition of H_2O (1 mL). The gel that precipitated was filtered off and washed well with EtOAC. The filtrate and washings were combined, and the whole was concentrated. The residue was partitioned between EtOAc (150 mL) and 0.1 N aqueous HCl (150 mL). The aqueous phase was extracted with

(30) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley & Sons: New York, 1983; Vol. 5, pp 124–228.

(31) **General.** Melting points are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ solution with tetramethylsilane as internal standard. Unless otherwise specified, reactions were carried out at rt. Organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed by rotary evaporator below 40 °C. Commercial NaH (60% emulsion in mineral oil) was washed with hexane, dried in vacuo, and weighed. The following reagents were used for drying solvents prior to distillation: CaH_2 (CH_2Cl_2, benzene, DMF, and DMSO); NaOH (pyridine); $LiAlH_4$ then benzophenone/Na (THF); $CaSO_4$ (acetone); P_2O_5 (HOAc).

(32) Concerning the nomenclature of the synthetic intermediates, **7–20** were named as derivatives of 7,7-dimethyl-2,6,8-trioxabicyclo[3.3.0]octane, **21**, **22**, **26**, **29**, **36**, **39**, **43**, **44**, **52**, **59**, **66** as derivatives of 11,11-dimethyl-2,10,12-trioxatricyclo[7.3.0.0^{3,8}]dodecane, and **23–25**, **27**, **28**, **30–34**, **37**, **40**, **46**, **49**, **50**, **55–57**, **60–64** as derivatives of 15,15-dimethyl-12,14,16-trioxatetracyclo[11.3.0.0^{2,11}.0^{3,8}]hexadecane, and **35**, **38**, **58**, **65** as derivatives of 16,16-dimethyl-4,13,15,17-tetraoxatetracyclo-[12.3.0.0^{2,12}.0^{3,9}]heptadecane, respectively.

EtOAc (150 mL × 2). The organic phase and the extracts were combined, dried, and concentrated. The residue was purified by column chromatography on silica gel (EtOH/toluene, 1:25) to provide a diastereomeric mixture of **12** (1.42 g, 99%): a colorless oil; TLC R_f 0.47 (EtOH/toluene, 1:5); IR (neat) 3400, 2930, 2860, 1665, 1450, 1370, 1250 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.23, 1.24 (2 d, each J = 5.8 Hz, ca. 2.5:1, total 3 H), 1.32, 1.48, 1.49 (3 s, 3 H for 1.32, total 3H for 1.48, 1.49), 1.34–1.53, 1.55–1.84, 1.88–2.00, 2.08–2.16, 2.18–2.34 (5 m, total 10 H), 3.72–4.02 (m, 1 H), 4.08 (d, J = 4.0 Hz, 1 H), 4.66–4.72 (m, 1 H), 5.62–5.71 (m, 2 H), 5.75–5.80 (m, 1 H). Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 62.74; H, 8.95.

Mixture of (1*R*,3*R*,4*R*,5*R*)-3-[(*E*)-5-Chloro-3-pentenyl]-4-[2(*R*)- and 2(*S*)-hydroxypropyl]-7,7-dimethyl-2,6,8-trioxabicyclo[3.3.0]octanes (13). A mixture of **12** (1.25 g, 4.36 mmol), *p*-toluenesulfonyl chloride (2.50 g, 13.1 mmol), and 4-(dimethylamino)pyridine (DMAP) (734 mg, 6.55 mmol) in CH_2Cl_2 (30 mL) was stirred for 32 h. The mixture was diluted with H_2O (100 mL), and then the whole was extracted with CH_2Cl_2 (100 mL × 3). The extracts were combined, dried, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/toluene, 1:20) to provide 0.634 g (48%) of **13** and 0.567 g (45%) of recovered **12**. **13**: a colorless oil; TLC R_f 0.41 (EtOAc/toluene, 1/1); IR (neat) 3450, 2925, 2870, 1660, 1440, 1370, 1245, 1210 cm^{-1}; ^{1}H NMR (270 MHz), δ 1.24, 1.25 (each d, each J = 5.9 Hz, total 3 H), 1.32, 1.50, 1.52 (each s, total 6 H), 1.29–1.94, 2.08–2.38, 3.71–3.39 (m, 10 H), 4.03 (dd, J = 0.7 and 6.6 Hz, 2 H), 4.67–4.73 (m, 1 H), 5.61–5.84 (m, 3 H). Anal. Calcd for $C_{15}H_{25}O_4Cl$: C, 59.11; H, 8.27. Found: C, 59.33; H, 7.96.

(1*R*,3*R*,4*R*,5*R*)-3-[(*E*)-5-Chloro-3-pentenyl]-4-(2-oxopropyl)-7,7-dimethyl-2,6,8-trioxabicyclo[3.3.0]octane (14). To a stirred solution of **13** (634 mg, 2.08 mmol) in CH_2Cl_2 (15 mL) were added PCC (1.79 g, 8.31 mmol) and powdered molecular sieves 4A (1.55 g). After 30 min, the mixture was passed through a short column of silica gel. The column was eluted with excess Et_2O. The eluate was concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to provide 572 mg (91%) of **14**: a colorless oil; TLC R_f 0.54 (EtOH/toluene, 1:15); $[\alpha]^{24}_D$ +75.5° (*c* 1.51, $CHCl_3$); IR (neat) 2990, 2940, 2870, 1720, 1690, 1660, 1445, 1375, 1250, 1215 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.29, 1.47 (2 s, 3 H × 2), 1.42–1.68 (m, 2 H), 2.03–2.33 (m, 3 H), 2.19 (s, 3 H), 2.38 (dd, J = 3.7 and 18.0 Hz, 1 H), 2.82 (dd, J = 10.3 and 18.0 Hz, 1 H), 3.70–3.77 (m, 1 H), 4.02 (dd, J = 0.7 and 6.6 Hz, 2 H), 4.74 (t, J = 4.0 Hz, 1 H), 5.58–5.83 (m, 2 H), 5.79 (d, J = 4.0 Hz, 1 H). Anal. Calcd for $C_{15}H_{23}O_4Cl$: C, 59.50; H, 7.66. Found: C, 59.51; H, 7.46.

(1*R*,3*S*,4*R*,5*R*)-3-[(1*R*)-1,2-(Isopropylidenedioxy)-ethyl]-4-(2-methyl-2-propenyl)-7,7-dimethyl-2,6,8-trioxabicyclo[3.3.0]octane (15). To a stirred solution of **1** (4.87 g, 16.2 mmol) in THF (25 mL) were added $Ph_3P^+CH_3Br^-$ (17.3 g, 48.6 mmol) and *t*-BuOK (5.46 g, 48.6 mmol in THF 60 mL). The mixture was stirred for 15 min and then quenched with 10% aqueous NH_4Cl (30 mL). It was diluted with EtOAc (300 mL), and the whole was washed with 10% aqueous NH_4Cl (200 mL × 3). The organic layer was drawn off, dried, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/toluene, 1:20) to provide 4.67 g (97%) of **15**: white crystals; mp 55.0–56.0 °C; TLC R_f 0.75 (EtOAc/toluene, 1:5); $[\alpha]^{26}_D$ +75.8° (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3030, 2990, 2930, 1635, 1440, 1360, 1220 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.31, 1.35, 1.43, 1.51 (4 s, 3 H × 4), 1.79 (s, 3 H), 2.00–2.10 (m, 1 H), 2.28–2.38 (m, 2 H), 3.79 (dd, J = 5.9 and 9.5 Hz, 1 H), 3.92–3.97 (m, 1 H), 4.02–4.11 (m, 2 H), 4.61 (t, J = 4.0 Hz, 1 H), 4.81 (d, J = 0.7 Hz, 2 H), 5.74 (d, J = 4.0 Hz, 1 H). Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.50; H, 8.40.

(1*R*,3*S*,4*R*,5*R*)-3-[(1*R*)-1,2-Dihydroxyethyl]-4-(2-methyl-2-propenyl)-7,7-dimethyl-2,6,8-trioxabicyclo[3.3.0]-octane (16). Compound **15** (4.63 g, 15.5 mmol) was dissolved in 60% aqueous HOAc (80 mL), and the solution was stirred for 16 h and then concentrated. The residue was purified by column chromatography on silica gel (EtOAc/toluene, 1:25) to provide 3.49 g (87%) of **16**: a colorless oil; TLC R_f 0.46 (EtOH/toluene, 1:5); $[\alpha]^{26}_D$ +120.0° (*c* 0.40, $CHCl_3$); IR (neat) 3400, 3000, 2940, 1650, 1450, 1380, 1370, 1215 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.32, 1.52 (2 s, 3 H × 2), 1.78 (s, 3 H), 2.08–2.45 (m, 5 H), 3.73–3.77 (m, 3 H), 3.94 (dd, J = 4.0 and 10.0 Hz, 1 H), 4.63 (t, J = 4.0 Hz, 1 H), 4.82 (s, 2 H), 5.76 (d, J = 4.0 Hz, 1 H). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.16; H, 8.45.

Mixture of (1*R*,3*S*,4*R*,5*R*)-3-[(1*R*)- and (1*S*)-1-Hydroxy-3-butenyl]-4-(2-methyl-2-propenyl)-7,7-dimethyl-2,6,8-trioxabicyclo[3.3.0]octanes (17). To a stirred solution of **16** (3.34 g, 12.9 mmol) in MeOH (50 mL) was added aqueous $NaIO_4$ (3.32 g, 15.5 mmol in H_2O 25 mL). After 30 min, the solid that precipitated was removed by filtration. The filtrate and washings (MeOH) were combined, and the whole was concentrated. The residue was partitioned between EtOAc (200 mL) and H_2O (200 mL). The aqueous layer was extracted with EtOAc (200 mL × 2). The organic layers were combined, dried, and concentrated to provide crude 3-aldehyde (3.23 g) [TLC R_f 0.60 (EtOAc/hexane, 1:5)].

To a stirred solution of the crude aldehyde (3.23 g) in THF (80 mL) was added under Ar allylmagnesium chloride (19.35 mL, 38.7 mol, 2.0 M solution in THF). The mixture was stirred for 1 h, quenched with 10% aqueous NH_4Cl (10 mL), and concentrated to ca. a 10-mL volume. The residue was diluted with H_2O (200 mL), and the whole was extracted with CH_2Cl_2 (200 mL × 4). The extracts were combined, dried, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to provide 3.23 g (93%) of a diastereomeric mixture of **17**: a colorless oil; TLC R_f 0.48 and 0.54 (EtOAc/hexane, 1:2); IR (neat) 3470, 3080, 2990, 2945, 1650, 1640, 1445, 1380, 1375, 1220 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.317, 1.325, 1.50, 1.52 (4 s, 3 H × 2), 1.78 (s, 3 H), 2.02–2.49 (m, 6 H), 3.57–3.64, 3.76–3.81, 3.84–3.90 (m, total 2 H), 4.60–4.64 (m, 1 H), 4.81 (s, 2 H), 5.08–5.20 (m, 2 H), 5.75–5.94 (m, 2 H).

(1*R*,3*S*,4*R*,5*R*)-3-[(1*S*)- and (1*R*)-1-(Benzyloxy)-3-butenyl]-4-(2-methyl-2-propenyl)-7,7-dimethyl-2,6,8-trioxabicyclo[3.3.0]octanes (18S and 18R). To a cold (0 °C), stirred solution of the mixture of **17** (3.23 g, 12.0 mmol) in DMF (20 mL) was added NaH (1.16 g, 48.1 mmol). After 10 min, benzyl bromide (5.0 mL, 42.1 mmol) was added. The mixture was stirred for 1.5 h, quenched with EtOH (10 mL), and then diluted with EtOAc (200 mL). The whole was washed with H_2O (200 mL × 3). The organic layer was drawn off, dried, and the concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:35) to provide 1.91 g (44%) of **18S** and 2.26 g (52%) of **18R**. **18S**: a pale yellow oil; TLC R_f 0.34 (EtOAc/hexane, 1:7); $[\alpha]^{25}_D$ +63.3° (*c* 1.07, $CHCl_3$); IR (neat) 3070, 2990, 2940, 2880, 1645, 1640, 1495, 1450, 1375, 1370, 1210 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.30, 1.47 (2 s, 3 H × 2), 1.72 (s, 3 H), 1.80–1.87, 2.19–2.60 (2 m, 1 H, 5 H), 3.43–3.49 (m, 1 H), 3.85 (dd, J = 1.5 and 9.9 Hz, 1 H), 4.48, 4.68 (AB q, J = 11.7 Hz, 2 H), 4.60 (t, J = 4.0 Hz, 1 H), 4.78–4.80 (m, 2 H), 5.05–5.30 (m, 2 H), 5.79 (d, J = 4.0 Hz, 1 H), 5.76–5.91 (m, 1 H), 7.30–7.33 (m, 5 H). Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.76; H, 8.40. **18R**: a pale yellow oil; TLC R_f 0.46 (EtOAc/hexane, 1:5); $[\alpha]^{26}_D$ +47.6° (*c* 1.15, $CHCl_3$); IR (neat) 3075, 2990, 2940, 1645, 1640, 1495, 1450, 1375, 1370, 1240 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.31, 1.49 (2 s, 3 H × 2), 1.74 (s, 3 H), 2.15–2.44 (m, 5 H), 3.57–3.63 (m, 1 H), 3.95 (dd, J = 4.8 and 9.5 Hz, 1 H), 4.55–4.66 (m, 3 H), 4.78 (d, J = 0.7 Hz, 2 H), 5.05–5.17 (m, 2 H), 5.72 (d, J = 3.3 Hz, 1 H), 5.80–5.96 (m, 1 H), 7.31–7.33 (m, 5 H). Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.83; H, 8.39.

(1*R*,3*S*,4*R*,5*R*)-3-[(1*S*)- and (1*R*)-1-(Benzyloxy)-2-formylethyl]-4-(2-oxopropyl)-7,7-dimethyl-2,6,8-trioxabicyclo[3.3.0]octanes (19S and 19R). Through a cold (−78 °C) stirred solution of **18S** (296 mg, 0.34 mmol) in CH_2Cl_2 (10 mL) was bubbled ozone (O_2 containing ca. 3% O_3) for 20 min. Then Ph_3P (867 mg, 3.31 mmol) was added. The mixture was maintained for 1.5 h at −78 °C. The solvent was evaporated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to provide 266 mg (89%) of **19S**: a colorless oil; TLC R_f 0.28 (EtOAc/hexane, 1:1); IR (neat) 2950, 2940, 2860, 1720, 1500, 1370, 1205 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.27, 1.43 (2 s, 3 H × 2), 2.05 (s, 3 H), 2.15 (dd, J = 3.4 and 18.1 Hz, 1 H), 2.43–2.54 (m, 1 H), 2.65 (dd, J = 10.3 and 18.1 Hz, 1 H), 2.77–2.95 (m, 2 H), 3.83 (dd, J = 2.4 and 10.3 Hz, 1 H), 4.07 (dt, J = 2.6 and 9.2 Hz, 1 H), 4.42, 4.65 (AB q, J = 11.7 Hz, 2 H), 4.76 (t, J = 3.7 Hz, 1 H), 5.77 (d, J = 3.7 Hz, 1 H), 7.30–7.34 (m, 5 H), 9.80 (s, 1 H).

Analogously as described for **19S**, 639 mg of **18R** was ozonolyzed to provide 612 mg (89%) of **19R**. **19R**: a colorless oil; TLC R_f 0.47 (EtOAc/hexane, 1:1); IR (neat) 2990, 2940, 2820, 2720, 1720,

1495, 1450, 1405, 1400, 1380, 1370, 1210 cm^{-1}, ^{1}H NMR (270 MHz) δ 1.28, 1.47 (2 s, 3 H × 2), 2.04 (s, 3 H), 2.28–2.38 (m, 1 H), 2.66 (dd, J = 3.9 Hz and 18.6 Hz, 1 H), 2.73–2.88 (m, 3 H), 3.84–3.97 (m, 2 H), 4.44, 4.62 (AB q, J = 11.2 Hz, 2 H), 4.73 (t, J = 4.0 Hz, 1 H), 5.74 (d, J = 4.0 Hz, 1 H), 7.27–7.34 (m, 5 H), 9.82 (t, J = 2.0 Hz, 1 H).

(1*R*,3*S*,4*R*,5*R*)-3-[(1*S*,3*E*)- and (1*R*,3*E*)-1-(Benzyloxy)-4-(ethoxycarbonyl)-3-butenyl]-4-(2-oxopropyl)-7,7-dimethyl-2,6,8-trioxabicyclo[3.3.0]octanes (20S and 20R). To a stirred solution of **19S** (245 mg, 0.68 mmol) in benzene (10 mL) was added Ph_3P=CHCOOEt (308 mg, 0.88 mmol). The mixture was stirred for 7 h and then concentrated. The residue was triturated with excess petroleum ether, and Ph_3P=O that precipitated was removed by filtration and washed well with petroleum ether. The filtrate and washings were combined, and the whole was concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8 and then 1:5) to provide 288 mg (98%) of **20S**: a colorless oil; TLC R_f 0.37 (EtOAc/hexane, 1:2); $[\alpha]^{28}_D$ +71.3° (*c* 0.50, $CHCl_3$); IR (neat) 2990, 2940, 2875, 1715, 1650, 1455, 1370, 1210 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.28 (t, J = 7.1 Hz, 3 H), 1.27, 1.41 (2 s, 3 H × 2), 1.94–2.18 (m, 1 H), 2.04 (s, 3 H), 2.43–2.64 (m, 4 H), 3.50 (dt, J = 2.2 and 6.6 Hz, 1 H), 3.76 (dd, J = 2.2 and 10.3 Hz, 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 4.42, 4.66 (AB q, J = 11.7 Hz, 2 H), 4.76 (t, J = 4.0 Hz, 1 H), 5.79 (d, J = 4.0 Hz, 1 H), 5.93 (dt, J = 15.7 and 1.1 Hz, 1 H), 6.94 (dt, J = 15.7 and 7.3 Hz, 1 H), 7.26–7.33 (m, 5 H). Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.52; H, 7.37.

As described for **20S**, 596 mg of **19R** was converted into 697 mg (98%) of **20R**. **20R**: a colorless oil; TLC R_f 0.62 (EtOAc/hexane, 1:1); $[\alpha]^{25}_D$ +38.7° (*c* 1.03, $CHCl_3$); IR (neat) 2990, 2940, 1720, 1645, 1370, 1270 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.28 (t, J = 7.3 Hz, 3 H), 1.28, 1.45 (2 s, 3 H × 2), 2.00 (s, 3 H), 2.32–2.43 (m, 1 H), 2.48–2.87 (m, 4 H), 3.51–3.57 (m, 1 H), 3.78 (dd, J = 6.9 and 9.9 Hz, 1 H), 4.19 (q, J = 7.3 Hz, 2 H), 4.37, 4.62 (AB q, J = 11.3 Hz, 2 H), 4.73 (t, J = 4.0 Hz, 1 H), 5.75 (d, J = 4.0 Hz, 1 H), 5.94 (dd, J = 15.8 and 1.1 Hz, 1 H), 7.03 (dt, J = 15.8 and 7.7 Hz, 1 H), 7.26–7.33 (m, 5 H). Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.41; H, 7.32.

(1*R*,3*R*,6*S*,7*R*,8*R*,9*R*)-7-Acetyl-6-hydroxy-11,11-dimethyl-2,10,12-trioxatricyclo[7.3.0.0^{3,8}]dodecane (21S) and Its 6*R* Isomer (21R). The mixture of **8** (193 mg, 0.74 mmol) was treated with PCC (640 mg) as described in the preparation of **10** to give 135 mg of **9**. Compound **9** (135 mg) thus obtained was dissolved in benzene (5 mL), and the solution was refluxed in the presence of DBU (0.079 mL, 0.53 mmol) for 4 h. The solvent was evaporated. The residue was diluted with EtOAc (40 mL) and then washed with 1 N aqueous HCl (40 mL), saturated aqueous $NaHCO_3$ (40 mL), and H_2O (40 mL), successively. The aqueous layers were combined, and the whole was extracted with EtOAc (40 mL × 3). The organic layer and the extracts were combined, dried, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:15) to provide 105 mg (53%) of **21S** and 25 mg (13%) of **21R**. **21S**: colorless crystals; mp 113.0–113.5 °C; TLC R_f 0.15 (EtOAc/hexane, 1:1); $[\alpha]^{27}_D$ +106.9° (*c* 1.89, $CHCl_3$); IR (KBr) 3480, 2990, 2960, 2920, 1710, 1450, 1365, 1210 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.31, 1.51 (2 s, 3 H × 2), 1.72–2.07 (m, 4 H), 2.32 (s, 3 H), 2.74 (s, 1 H), 2.77 (dd, J = 2.2 and 12.1 Hz, 1 H), 3.65 (dt, J = 4.0 and 10.5 Hz, 1 H), 4.35 (t, J = 2.5 Hz, 1 H), 4.72 (t, J = 3.6 Hz, 1 H), 5.83 (d, J = 3.6 Hz, 1 H). Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.70; H, 7.70. **21R**: colorless crystals; mp 97.0–99.0 °C; TLC R_f 0.26 (EtOAc/hexane, 1:1); $[\alpha]^{25}_D$ +87.1° (*c* 0.62, $CHCl_3$); IR (KBr) 3470, 3000, 2960, 2900, 1705, 1450, 1415, 1360, 1295, 1230 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.30, 1.54 (2 s, 3 H × 2), 1.41–1.55, 2.05–2.19 (2 m, total 5 H), 2.34 (s, 3 H), 2.81 (dd, J = 9.9 and 11.4 Hz, 1 H), 3.73 (dt, J = 4.0 and 10.6 Hz, 1 H), 3.86–3.92 (m, 1 H), 4.49 (t, J = 3.6 Hz, 1 H), 5.82 (d, J = 3.6 Hz, 1 H).

(1*R*,3*R*,6*S*,7*R*,8*R*,9*R*)-6-Acetoxy-7-acetyl-11,11-dimethyl-2,10,12-trioxatricyclo[7.3.0.0^{3,8}]dodecane (22S) and Its 6*R* Isomer (22R). Compound **21S** (31.5 mg, 0.12 mmol) was treated with Ac_2O (0.5 mL) in pyridine (0.5 mL) for 18 h, and then the mixture was concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to provide 41.3 mg (95%) of **22S**: colorless crystals; mp 125.5–127 °C; TLC R_f 0.44 (EtOAc/hexane, 1:1); $[\alpha]^{23}_D$ +49.1° (*c* 0.54, $CHCl_3$); IR (KBr) 3000, 2975, 2880, 1745, 1715, 1440, 1245 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.28, 1.47 (2 s, 3 H × 2), 1.63–1.66 (m, 3 H), 2.01 (s, 3 H), 2.20 (s, 3 H), 1.90–2.30 (m, 2 H), 2.82 (dd, J = 2.9 and 11.7 Hz, 1 H), 3.64 (dt, J = 4.0 and 11.0 Hz), 4.83 (t, J = 4.0 Hz, 1 H), 5.59 (dd, J = 2.2 and 4.0 Hz, 1 H), 5.82 (d, J = 4.0 Hz, 1 H). Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.09; H, 7.26.

Analogously as described for **22S**, compound **21R** (12.8 mg) was converted into 13.1 mg (88%) of **22R**: colorless crystals; mp 144.5–145.0 °C; TLC R_f 0.48 (EtOAc/hexane, 1:1); $[\alpha]^{23}_D$ +82.7° (*c* 0.60, $CHCl_3$); IR (neat) 2990, 2955, 2940, 1735, 1715, 1455, 1240 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.30, 1.54 (2 s, 3 H × 2), 1.33–1.63, 2.11–2.31 (2 m, total 5 H), 2.01 (s, 3 H), 2.28 (s, 3 H), 3.01 (t, J = 11.0 Hz, 1 H), 3.72 (dt, J = 4.0 and 11.0 Hz, 1 H), 4.49 (t, J = 4.0 Hz, 1 H), 4.93 (dt, J = 4.8 and 10.6 Hz, 1 H), 5.83 (d, J = 4.0 Hz, 1 H).

(1*R*,2*R*,3*S*,8*R*,11*R*,13*R*)-6,15,15-Trimethyl-12,14,16-trioxatetracyclo[11.3.0.0^{2,11}.0^{3,8}]hexadec-5-en-4-one (23), (1*R*,2*R*,3*S*,8*S*,11*R*,13*R*)-6,15,15-Trimethyl-12,14,16-trioxatetracyclo[11.3.0.0^{2,11}.0^{3,8}]hexadec-5-en-4-one (24), and (1*R*,2*R*,3*S*,8*R*,11*R*,13*R*)-4,15,15-Trimethyl-12,14,16-trioxatetracyclo[11.3.0.0^{2,11}.0^{3,8}]hexadec-4-en-6-one (25). To a cold (0 °C) stirred suspension of NaH (42 mg, 1.76 mmol) in DMF (4 mL) was added under Ar a solution of **10** (1.30 g, 4.40 mmol) in DMF (10 mL). After 45 min, the mixture was neutralized by adding 0.1 N aqueous HCl. It was diluted with H_2O (50 mL), and the whole was extracted with EtOAc (100 mL × 3). The extracts were combined, dried, and concentrated. The residue was purified by column chroamtography on silica gel (EtOAc/hexane, 1:3) followed by preparative TLC (EtOAc/hexane, 1:3) to provide 245 mg (20%) of **23**, 137 mg (11%) of **24**, and 402 mg (33%) of **25**. **23**: colorless crystals; mp 203.0–203.5 °C; TLC R_f 0.37 (EtOAc/hexane, 1:1); $[\alpha]^{29}_D$ −6.7° (*c* 1.11, $CHCl_3$); IR ($CHCl_3$) 3010, 2940, 1660, 1435, 1380, 1250 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.34, 1.56 (2 s, 3 H × 2), 1.41–1.78, 1.97–2.15 (2 m, 6 H), 1.97 (s, 3 H), 2.35–2.55 (m, 2 H), 2.61 (dd, J = 4.4 and 11.4 Hz, 1 H), 3.70 (dt, J = 4.4 and 10.6 Hz, 1 H), 4.45 (t, J = 3.6 Hz, 1 H), 5.73 (d, J = 3.6 Hz, 1 H), 5.91 (s, 1 H). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.81; H, 7.79. **24**: colorless crystals; mp 97–99.5 °C; TLC R_f 0.60 (EtOAc/hexane, 1:1); $[\alpha]^{25}_D$ +127° (*c* 1.03, $CHCl_3$); IR (KBr) 2975, 2930, 1675, 1630, 1380, 1215 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.34, 1.49 (2 s, 3 H × 2), 1.26–1.49 (m, 3 H), 1.74–1.91 (m, 2 H), 1.94 (s, 3 H), 2.11–2.36 (m, 4 H), 3.67 (dt, J = 3.7 and 11.0 Hz, 1 H), 5.24 (t, J = 4.0 Hz, 1 H), 5.83 (d, J = 4.0 Hz, 1 H), 5.85 (s, 1 H). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.00; H, 7.83. **25**: colorless crystals; mp 158.0–158.5 °C; TLC R_f 0.49 (EtOAc/hexane, 1:1); $[\alpha]^{23}_D$ +183° (*c* 1.29, $CHCl_3$); IR ($CHCl_3$) 3010, 2945, 1655, 1630, 1380, 1250 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.34, 1.55 (2 s, 3 H × 2), 1.47 (dt, J = 3.6 and 11.0 Hz, 1 H), 1.52–1.80, 2.00–2.20 (2 m, 5 H), 2.11 (s, 3 H), 2.40–2.55 (m, 3 H), 3.72 (dt, J = 4.0 and 10.6 Hz, 1 H), 4.58 (t, J = 3.5 Hz, 1 H), 5.81 (d, J = 3.5 Hz, 1 H), 5.91 (s, 1 H). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.73; H, 7.71.

(1*R*,3*R*,6*R*,7*S*,8*R*,9*R*)-7-Acetyl-6-[(Ethoxycarbonyl)-methyl]-11,11-dimethyl-2,10,12-trioxatricyclo[7.3.0.0^{3,8}]dodecane (26), (1*R*,2*R*,3*S*,8*R*,11*R*,13*R*)-6-Hydroxy-15,15-dimethyl-12,14,16-trioxatetracyclo[11.3.0.0^{2,11}.0^{3,8}]hexadec-5-en-4-one (27), and (1*R*,2*R*,3*S*,8*S*,11*R*,13*R*)-15,15-Dimethyl-12,14,16-trioxatetracyclo[11.3.0.0^{2,11}.0^{3,8}]hexadecane-4,6-dione (28). To a cold (0 °C) stirred suspension of NaH (40 mg, 1.65 mmol) in DMF (3 mL) was added under Ar a solution of **11** (540 mg, 1.65 mmol) in DMF (5 mL). After 30 min, the mixture was neutralized by adding HOAc, and then the whole was concentrated. The residue was purified by column chromatography on silica gel (EtOH/toluene, 1:5) followed by preparative TLC (EtOH/toluene, 1:10) to provide 280 mg (52%) of **26**, 80 mg (17%) of **27**, and 43 mg (9%) of **28**. **26**: a colorless oil; TLC R_f 0.61 (EtOAc/hexane, 1:1); $[\alpha]^{28}_D$ +45.9° (*c* 0.63, $CHCl_3$); IR (neat) 2980, 2940, 2870, 1730, 1710, 1375, 1250 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.24 (t, J = 7.6 Hz, 3 H), 1.27, 1.47 (2 s, 3 H × 2), 1.45–2.35 (m, 7 H), 2.22 (s, 3 H), 2.86 (d, J = 9.2 Hz, 2 H), 3.57 (dt, J = 4.0 and 11.0 Hz, 1 H), 4.12 (q, J = 7.6 Hz, 2 H), 4.75 (t, J = 3.6 Hz, 1 H), 5.79 (d, J = 3.6 Hz, 1 H). Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.30; H, 7.86. **27**: colorless crystals; mp 213–215 °C; TLC R_f 0.31 (MeOH/$CHCl_3$, 1:50); $[\alpha]^{22}_D$ +144.5° (*c* 0.79, $CHCl_3$); IR ($CHCl_3$) 3420, 2980, 2950, 2910, 2880, 1625, 1575, 1515, 1465, 1350, 1300 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$)

δ 1.36, 1.57 (2 s, 3 H × 2), 1.59–1.76 (m, 5 H), 2.09 (dd, J = 3.4 and 11.7 Hz, 1 H), 2.18 (d, J = 12.7 Hz, 1 H), 2.47 (t, J = 14.0 Hz, 1 H), 2.60 (dd, J = 4.4 and 11.7 Hz, 1 H), 3.69 (dt, J = 3.9 and 11.2 Hz, 1 H), 4.63 (t, J = 3.9 Hz, 1 H), 5.52 (s, 1 H), 5.86 (d, J = 3.9 Hz, 1 H), 6.70 (br s, 1 H). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 63.98; H, 7.02. **28**: colorless crystals; mp 180–182 °C; TLC R_f 0.40 (MeOH/$CHCl_3$, 1:50); $[\alpha]^{23}_D$ +127.9° (c 0.63, $CHCl_3$); IR (KBr) 3450, 3010, 2975, 2940, 2880, 1610, 1540, 1270, 1215 cm^{-1}; ^1H NMR (270 MHz) δ 1.33, 1.51 (2 s, 3 H × 2), 1.34–1.54 (m, 4 H), 2.04–2.36 (m, 2 H), 2.47 (dd, J = 15.4 and 13.0 Hz, 1 H), 2.60 (t, J = 11.4 Hz, 1 H), 2.72 (ddd, J = 2.2, 3.7, and 15.4 Hz, 1 H), 3.36 (dd, J = 2.2 and 16.5 Hz, 1 H), 3.59 (d, J = 16.5 Hz, 1 H), 3.71 (dt, J = 3.7 and 10.6 Hz, 1 H), 5.08 (t, J = 3.7 Hz, 1 H), 5.87 (d, J = 3.7 Hz, 1 H). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.15; H, 7.32.

When a solution of **11** (292 mg, 0.89 mmol) in DMF (10 mL) was treated with NaH (97 mg 4.03 mmol) at 0 °C for 30 min, followed by column chromatography of the reaction mixture on silica gel, 139 mg (56%) of **27** and 33 mg (13%) of **28** were obtained.

When a solution of **11** (202 mg, 0.62 mmol) in benzene and DMF (v/v, 1:1, 4 mL) was stirred in the presence of Cs_2CO_3 (202 mg, 0.62 mmol) at 80 °C for 4.5 h, extractive workup (EtOAc) and a silica gel chromatographic separation of the reaction mixture gave a nearly 8:1 inseparable mixture of **26** and its 6*S* isomer (149.5 mg, 74%). The structure of the major product **26** was determined by spectral comparison to an authentic sample obtained as above.

(1*R*,3*R*,6*R*,7*S*,8*R*,9*R*)-7-Acetyl-11,11-dimethyl-6-vinyl-2,10,12-trioxatricyclo[7.3.0.0^{3,8}]dodecane (29). To a cold (0 °C) stirred suspension of NaH (88 mg, 3.67 mmol) in DMF (6 mL) was added a solution of **14** (222 mg, 0.74 mmol) in DMF (6 mL). After 1 h, the mixture was neutralized by adding 0.1 N aqueous HCl. It was diluted with H_2O (50 mL), and then the whole was extracted with EtOAc (60 mL × 3). The extracts were combined, dried, and concentrated. The residue was purified by column chromatography on silica gel (EtOH/toluene, 1:50) to provide 187 mg (96%) of **29**: colorless crystals; mp 115.0–117.0 °C; TLC R_f 0.50 (EtOH/toluene, 1:15); $[\alpha]^{28}_D$ +70.3° (c 0.49, $CHCl_3$); IR (neat) 2980, 2950, 2875, 1710, 1375, 1255 cm^{-1}; ^1H NMR (270 MHz) δ 1.28, 1.47 (2 s, 3 H × 2), 1.53–1.81, 1.92–2.03 (2 m, total 5 H), 2.14 (s, 3 H), 2.83 (dd, J = 4.8 and 11.4 Hz, 1 H), 2.92–2.95 (br s, 1 H), 3.64 (dt, J = 4.0 and 11.0 Hz, 1 H), 4.85 (t, J = 3.7 Hz, 1 H), 5.07 (dd, J = 1.0 and 10.0 Hz, 1 H), 5.10 (dd, J = 1.0 and 17.0 Hz, 1 H), 5.79 (ddd, J = 8.5, 10.0 and 17.0 Hz, 1 H), 5.80 (d, J = 3.7 Hz, 1 H). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.41; H, 8.18.

(1*R*,2*R*,3*S*,8*R*,10*S*,11*S*,13*R*)-10-(Benzyloxy)-6-hydroxy-15,15-dimethyl-12,14,16-trioxatetracyclo[11.3.0.0^{2,11}.0^{3,8}]hexadec-5-en-4-one (30) and the 8*S* Diastereomer (31). To a cold (0 °C) stirred suspension of NaH (12 mg, 0.47 mmol) in DMF (1 mL) was added a solution of **20S** (204 mg, 0.47 mmol) in DMF (2 mL). After 1.5 h, the mixture was neutralized by adding Amberlyst-15 (H^+). The resin was removed by filtration through a pad of Celite. The filtrate was concentrated. The residue was purified by column chromatography on silica gel (acetone/toluene, 1:5 and then 1:3) to provide 104 mg (57%) of **30** and 28 mg (15%) of **31**. **30**: colorless crystals; mp 192.0–193.0 °C; TLC R_f 0.23 (acetone/toluene, 1:1); $[\alpha]^{28}_D$ +39.6° (c 0.52, $CHCl_3$); IR (KBr) 3435, 2985, 2945, 2870, 1610, 1530, 1385, 1370, 1210 cm^{-1}; ^1H NMR (270 MHz) δ 1.36, 1.58 (2 s, 3 H × 2), 1.48–1.80 (m, 2 H), 1.98 (dd, J = 4.4 and 13.7 Hz, 1 H), 2.18–2.42 (m, 2 H), 2.54–2.68 (m, 2 H), 3.69 (dt, J = 4.7 and 9.9 Hz, 1 H), 3.78 (t, J = 9.9 Hz, 1 H), 4.59 (t, J = 3.7 Hz, 1 H), 4.63, 4.88 (AB q, J = 12.1 Hz, 2 H), 5.50 (s, 1 H), 5.87 (d, J = 3.7 Hz, 1 H), 7.26–7.37 (m, 5 H). Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.06; H, 6.80. **31**: colorless crystals; mp 108.0–109.0 °C; TLC R_f 0.40 (acetone/toluene, 1:1); $[\alpha]^{28}_D$ +43.3° (c 1.31, $CHCl_3$); IR (KBr) 3435, 2990, 2945, 2870, 1610, 1530, 1450, 1380, 1370, 1315, 1285 cm^{-1}; ^1H NMR (270 MHz) δ 1.33, 1.52 (2 s, 3 H × 2), 1.35–1.71, 2.13–2.72 (m, 6 H), 2.58 (t, J = 11.9 Hz, 1 H), 3.34 (dd, J = 1.8 and 16.5 Hz, 1 H), 3.58 (d, J = 16.5 Hz, 1 H), 3.48–3.57 (m, 1 H), 3.79 (t, J = 9.9 Hz, 1 H), 4.66, 4.88 (AB q, J = 12.1 Hz, 2 H), 5.06 (t, J = 4.0 Hz, 1 H), 5.90 (d, J = 4.0 Hz, 1 H), 7.26–7.35 (m, 5 H); HRMS calcd for $C_{22}H_{26}O_6$ (M^+) m/z 386.1729, found m/z 386.1729.

(1*R*,2*R*,3*S*,8*S*,10*R*,11*S*,13*R*)-10-(Benzyloxy)-15,15-dimethyl-12,14,16-trioxatetracyclo[11.3.0.0^{2,11}.0^{3,8}]hexadecane-4,6-dione (32) and the 8*R* Diastereomer (33). To a cold (0 °C), stirred suspension of NaH (32 mg, 1.32 mmol) in DMF (3 mL) was added a solution of **20R** (571 mg, 1.32 mmol) in DMF (6 mL). After 30 min, the mixture was neutralized by adding Amberlyst-15 (H^+). The resin was filtered off, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (acetone/toluene, 1:7 and then 1:5) to provide 280 mg (55%) of **32** and 56 mg (11%) of **33**. **32**: colorless crystals; mp 158.5–159.5 °C; TLC R_f 0.44 (acetone/toluene, 1:2); $[\alpha]^{25}_D$ +85.0° (c 0.25, $CHCl_3$); IR (KBr) 2980, 1740, 1615, 1545, 1205 cm^{-1}; ^1H NMR (270 MHz) δ 1.34, 1.49 (2 s, 3 H × 2), 1.25–1.55, 1.97–2.65 (m, total 7 H), 3.36 (dd, J = 1.9 and 16.9 Hz, 1 H), 3.55 (d, J = 16.9 Hz, 1 H), 3.82 (dd, J = 2.2 and 11.5 Hz, 1 H), 4.15 (br s, 1 H), 4.58, 4.78 (AB q, J = 12.1 Hz, 2 H), 5.09 (t, J = 3.7 Hz, 1 H), 5.89 (d, J = 3.7 Hz, 1 H), 7.25–7.37 (m, 5 H). Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.26; H, 6.77. **33**: colorless crystals; mp 109.0–110.0 °C; TLC R_f 0.25 (acetone/toluene, 1:2); $[\alpha]^{27}_D$ +58.6° (c 1.14, $CHCl_3$); IR (KBr) 3470, 2935, 1605, 1345, 1220 cm^{-1}; ^1H NMR (270 MHz) for the keto enol form (ca. 25% of **33** exists as the diketo form in $CDCl_3$) δ 1.39, 1.57 (2 s, $^3/_4$ × 3 H × 2), 1.25–1.82, 1.95–2.03, 2.27–2.64 (3 m, total 6 H), 2.44 (dt, J = 3.7 and 11.0 Hz, $^3/_4$ H), 3.80 (dd, J = 2.0 and 11.0 Hz, $^3/_4$ H), 4.15–4.18 (m, 1 H), 4.59, 4.74 (AB q, J = 12.5 Hz, $^3/_4$ H × 2), 4.72 (t, J = 3.7 Hz, $^3/_4$ H), 5.52 (s, $^3/_4$ H), 5.96 (d, J = 3.7 Hz, $^3/_4$ H), 7.23–7.36 (m, 5 H). HRMS calcd for $C_{22}H_{26}O_6$ (M^+) m/z 386.1730, found m/z 386.1727.

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Supplementary Material Available: The experimental procedures and spectroscopic data (mp, TLC, $[\alpha]_D$, IR, and ^1H NMR) for **34–40, 43, 44, 46, 49, 50, 52,** and **55–66** (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.