Serial Radical Cyclization of Pyranose-Derived Dienes in the Stereocontrolled Synthesis of Woodward's Reserpine Precursor[1]

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Received December 6, 1994[⊗]

A new strategy for the synthesis of Woodward's densely functionalized carbocyclic precursor to reserpine (**2**) that is based upon serial radical 5-*exo*/6-*exo* cyclizations of readily prepared dienic hexopyranose derivatives has been examined. The substrates **4**, **7**, **9**, and **12**, which are obtainable in simple steps from commercially available triacetylglucal, have their unsaturations on-template at C2 and off-template at C7, and the cyclization sequence is triggered by use of a silicon tether appendage placed at C-4 in the pyran ring. The first radical cyclization takes place onto the $\Delta^{2,3}$ unsaturation and serves the dual purpose of introducing a carbon branch at C-3 in a complete regio- and stereocontrolled manner as well as generating a radical at C-2 that experiences the 6-*exo-trig* ring closure to form the actual cyclohexane ring in which all but one of the required stereocenters have been established. Electron-withdrawing substituents that accelerate the 6-*exo-trig* ring closure, as in substrates **4**(**a** and **b**), were found to be necessary for the second cyclization to take place in good yields. Nevertheless, some cyclohexane formation was also obtained in the radical cyclization of substrates **9**(**a** and **b**) in which an allylic phenyl sulfide was used as the C-7 trap. The presence of an acetate substituent at C-6 in the latter cases resulted in a high degree of stereocontrol for the 6-*exo* cyclization process based in a stereochemical model that invokes release of 1,3 allylic strain in the transition state for the radical cyclization. The compounds resulting from the radical cyclizations of **4a,b** and **9a,b** were transformed to the same [2.2.2]oxabicyclic intermediate **34** that was correlated with Woodward's carbocyclic intermediate after opening of the glycosidic bond.

Introduction

Reserpine, (**1**), a prominent member of the yohimbine family of indole alkaloids, possesses a characteristic pentacyclic skeleton which contains six chiral centers. This structural complexity coupled with its remarkable physiological properties[3] has made reserpine an attractive target for a number of synthetic efforts. These have been summarized recently by Baxter and Mariano.[4]

Baxter and Mariano[4] identify two major synthetic approaches to reserpine. In the first (Scheme 1a,b), elaboration of the DE ring system is followed by condensation with a tryptophyl unit containing the AB rings, and ring C is constructed in the final stages.[5] A second general approach, which originated in the seminal work of Szantay[6] (Scheme 1c), starts with a β-carboline derivative that embodies rings ABC, rings D and E being developed sequentially.[7] In the first category, exemplified by Woodward's landmark synthesis,[8] a richly functionalized E ring is coupled directly with 6-methoxytryptamine (Scheme 1a). Recent additional examples have come from Wender's and Martin's groups, where a *cis*-hydroisoquinoline is coupled with a 6-methoxytryptophyl halide (Scheme 1b).[5d,e] By-and-large strategies in the first category have relied upon cycloaddition reactions of the 4 + 2 and 2 + 2 varieties that provide frameworks for installing the rich DE functionality.

Especially appealing to us was the E ring system of reserpine, a densely functionalized cyclohexane which, by itself, accounts for five of the six chiral centers present in the molecule. Its construction therefore provides a challenging context for exploring new synthetic methodologies. Our laboratory is interested in converting carbohydrates into densely functionalized carbocycles;[9] hence our attraction to the Woodward intermediate **2** (Scheme 2). In this paper we report fully on our efforts toward a novel strategy for the synthesis of Woodward's richly functionalized E ring,[10] the key step of which features

⊗ Abstract published in *Advance ACS Abstracts,* May 15, 1995.

(1) Supported by grants from the National Science Foundation (CHE 892003 and CHE 9311356).

(2) Financial support from the Consejo Superior de Investigaciones Científicas (C.S.I.C.) and Consejería de Educación, Comunidad Autónoma de Madrid (Spain) is gratefully acknowledged by A.M.G and J.C.L., respectively. J.C.L. is a Visiting Associate Professor and is on leave from the Instituto de Química Orgánica General (C.S.I.C.), Madrid.

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(5) For some examples, see the following and references cited therein: (a) Pearlman, B. A. *J. Am. Chem. Soc.* **1979**, *101*, 6398. (b) Kametani, T.; Suzuki, T.; Tomino, A.; Unno, K. *Chem. Pharm. Bull.* **1982**, *30*, 167. (c) Isobe, M.; Fukami, N.; Nishikawa, T.; Goto, T. *Heterocycles* **1987**, *25*, 521. (d) Martin, S. F.; Rueger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124. (e) Wender, P. A.; Schaus, J. M.; White, A. W. *Heterocycles* **1987**, *25*, 263. (f) R. P. Polniaszek, Stevens, R. V. *J. Org. Chem.* **1986**, *51*, 3023. (g) Stork, G. *Pure Appl. Chem.* **1989**, *51*, 439. (h) Baxter, E. W.; Labaree, D.; Ammon, H. L.; Mariano, P. S. *J. Am. Chem. Soc.* **1990**, *112*, 7682.

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(7) See for example: (a) Wenkert, E.; Halls, T. D. J.; Kunesh, G.; Orito, K.; Stephens, R. L.; Tempple, W. A.; Yadav, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 5371. (b) Ernst, H.; Hauser, B.; Winterfeldt, E. *Chem. Ber.* **1981**, *114*, 1894. (c) Rahman, A.-U.; Ghazala, M. *J. Chem. Soc., Perkin Trans. I* **1982**, 59. (d) Kametani, T.; Takagi, N.; Kanaya, N.; Honda, T.; Fukumoto, K. *J. Heterocycl. Chem.* **1982**, *19*, 1217. (e) Naito, T.; Tada, Y.; Ninomiya, I. *Heterocycles* **1983**, *20*, 853.

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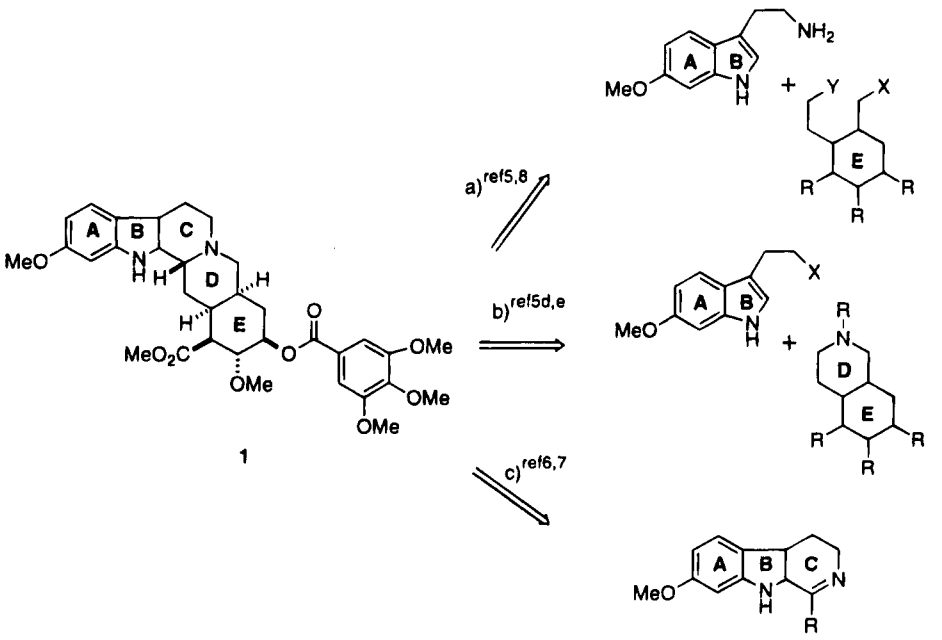
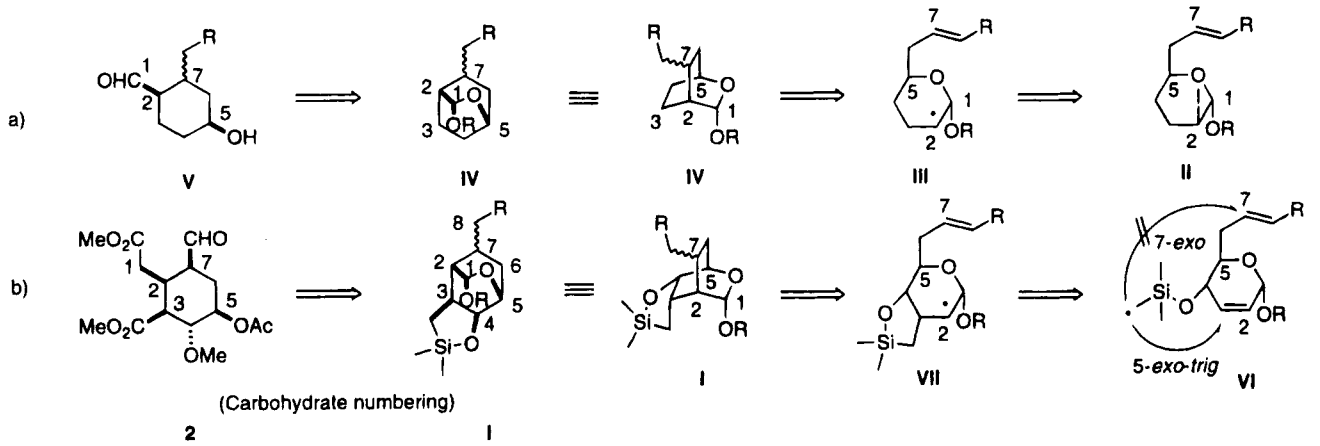
Scheme 1



Scheme 2



serial 5-*exo*/6-*exo* radical cyclizations of a dienic pyranoside.

Retrosynthetic Analysis (Scheme 2). Woodward's carbocyclic intermediate for reserpine **2** is a highly functionalized cyclohexane that incorporates three carbon branches and two oxygenated substituents. We envisaged its retron as the tricyclic cage **I**, in which all of the above-mentioned functionalities are already incorporated. This retrosynthetic plan emanated from previous work in our laboratories[11] in which a pyranosyl iodide, **II** (Scheme 2a), had been the source of a C-2-centered radical in the pyranose ring, **III**, which was found to undergo smooth 6-*exo-trig* cyclization onto an off-template C-7 double bond to furnish a cage pyranoside, **IV**, unraveling of which led to a trisubstituted cyclohexane, **V**.

The resemblance between Woodward's intermediate **2** and cyclohexane **V** is apparent. We envisaged that the extra carbon–carbon branch at C-3 in **2** could be incorporated regio- and stereoselectively by means of a 5-*exo-trig* addition of a tethered radical to a hex-2-enopyranoside, **VI**, in a process that would simultaneously generate the required carbon-centered radical at C-2, **VII**.

The issue of regiochemistry in the cyclization of the intermediate radical **VI**, which bears two unsaturations susceptible to attack, is clear cut, the 5-*exo-trig* cyclization mode being expected to prevail on the basis of kinetic control. Furthermore, comparison of Dreiding models of **III** and **VII** (Scheme 3) does not indicate any additional strain in the $B^{2,5}$ boat conformation of **III**, this being required for the subsequent 6-*exo-trig* cyclization to take place.

Choice of Pyranoside Substrates for Radical Cyclizations. In designing the pyranoside substrates for the key radical cyclization steps (i.e. **VI** → **VII** → **I**, Scheme 2), we aimed first for a precursor that would provide a latent synthon for the C-7 formyl group of the target molecule **2**. In so doing, we were mindful of Woodward's and Pearlman's problems caused by the instability of the formyl group in **2**. In view of this specter, the C-7 vinyl group (Scheme 4) was incorporated in **3** as the formyl synthon. Second, a silicon-tethered radical, as described by Nishiyama's and Stork's

(10) Part of this work has been the subject of a preliminary communication: Gómez, A. M.; López, J. C.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 4048.

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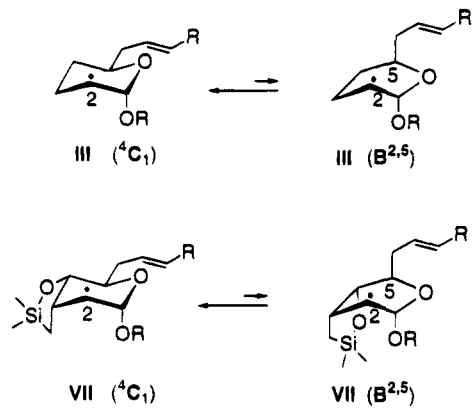
Scheme 3



groups,[12,13] was placed at C-4 since it would act as a synthetic equivalent for the one-carbon branch that is required at C-3 of **2**.

These requirements are satisfied by substrates **4a** and **4b**, which would cyclize to give the bicyclic epimers **5** (Scheme 4a), the (ethoxycarbonyl)methyl moieties of which are synthons for the vinyl group in **6**. Alternatively a more direct route is conceivable from the allylic phenyl sulfide **7**, taking advantage of the seminal work of Ueno and co-workers[14] indicating that a vinyl group is readily formed by expulsion of PhS· from an intermediate such as **8**.

However, the advantages of **4** and **7** had to be weighed against our prior experience showing that these 6-deoxy substrates engender poor stereoselectivities at C-7 of the bicyclic products.[11] By contrast, a properly oriented C-6 oxygen was found to provide a powerful stereocontrolling element, presumably because of the steric interactions in intermediate **10** (see Scheme 5). Thus **10-*anti*** is preferred because it avoids the allylic strain experienced by the **10-*syn*** rotamer.[15]

Thus the C6-oxygen (Scheme 4c) might prove advantageous for stereocontrol in spite of the steps required to remove it from product **11**.

Finally, the allene moiety, as in **12** (Scheme 4d), was chosen to explore the feasibility of a 6-hexenyl mode of cyclization of the allene (**13** → **14**) leading to a vinyl radical that would be reduced to **11**.

Preparation of the Radical Precursors. The substrates **4**, **7**, **9**, and **12** in Scheme 4 were prepared from ethyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside,[16] which is readily available in multigram amounts, without chromatographic separation, from commercially available tri-*O*-acetyl-D-glucal. This precursor was converted into unsaturated esters **15** and **16**[17] (Scheme 6a,b) according to our previous work, and these, in turn, were uneventfully transformed in the radical substrates **4a** and **4b**, respectively.

The 4-hydroxy compound **18** (Scheme 6b) was prepared from **16a**[17] by reduction of the carbethoxy group to **17a** followed by conversion of the hydroxyl function to a phenyl sulfide (**17b**) and desilylation.

Subjecting **19**[17] (Scheme 6c) to Swern oxidation in THF, followed by addition of the anion of propargyl phenyl sulfide[18] according to the Ireland–Norbeck protocol,[19] led to an epimeric mixture of phenyl sulfides **20** and **6-*epi*-20** in a 1:1.8 ratio, in 75% yield (Scheme 6c), that was separated by flash chromatography. The faster running isomer on TLC was treated with Red-Al in ether and acetylated to furnish a mixture of phenyl sulfide **24a** and allene **21b** which upon desilylation led to **21c**.

Application of a similar protocol to **19**, except for the use of propargylic alcohol dianion, afforded **22** and **6-*epi*-22** as a 1:1.6 mixture of C-6 epimers in 86% yield. Careful chromatographic separation followed by stereoselective reduction of **22** (which was faster moving on TLC than its epimer) with Red-Al in ether then afforded **23a**, which underwent regioselective reaction with PhSSPh and nBu_3P[20] to generate phenyl sulfide **23b**. Acetylation then paved the way to the desired alcohol **24b** in 72% yield.

In spite of the foregoing fortuitous separation of **23a**, the lack of stereoselectivity in the formation of **22** and **6-*epi*-22** prompted us to devise a plan to invert the configuration of the "unwanted" C-6 epimer. Accordingly, the primary hydroxyl group of the epimeric mixture was selectively esterified under Mitsunobu conditions[21] with *p*-nitrobenzoic acid[22] at 0 °C to afford the readily separable epimeric monobenzoates **25a** and **25b**. Resubjection of the latter to Mitsunobu conditions,[22] this time at room temperature, furnished dinitrobenzoate **25c**. Finally, deesterification of **25a** and **25c** and standard processing led to **23a** and then to **26** (**a** and **b**).

The silylmethylene ethers were prepared by use of $ClSi(CH_3)_2CH_2Br$ according to the procedures of Nishiyama[12] and Stork[13] and their co-workers from the corresponding 4-hydroxy compounds **15**, **16a**, **18**, **21c**, **24b**, and **26b**. Although some of the silyl ethers were not stable to silica gel (partial cleavage of the O–Si bond could be observed even on TLC plates), they could be used for the radical reactions after standard workup followed by coevaporation with toluene.

Cyclization of Radical Precursors. The silylmethylene ethers were subjected to the conditions for radical cyclization recommended by Stork and Sher[23] (Bu_3SnCl, $NaCNBH_3$, AIBN, Bu^tOH, 0.015 M, 4 h), oxidation of the crude reaction mixture according to Tamao et al.[24] followed by acetylation.

The *cis* crotonate **4a** produced bicyclic compound **27** as a 1:1.3 mixture of epimers (^1H NMR estimation) that was unresolved on TLC, in 78% yield. Some monocyclized product **28** (1.9%) along with desilylated precursor **16b** (11%) was also isolated. It is noteworthy that the pendant *cis* olefin had undergone isomerization, most

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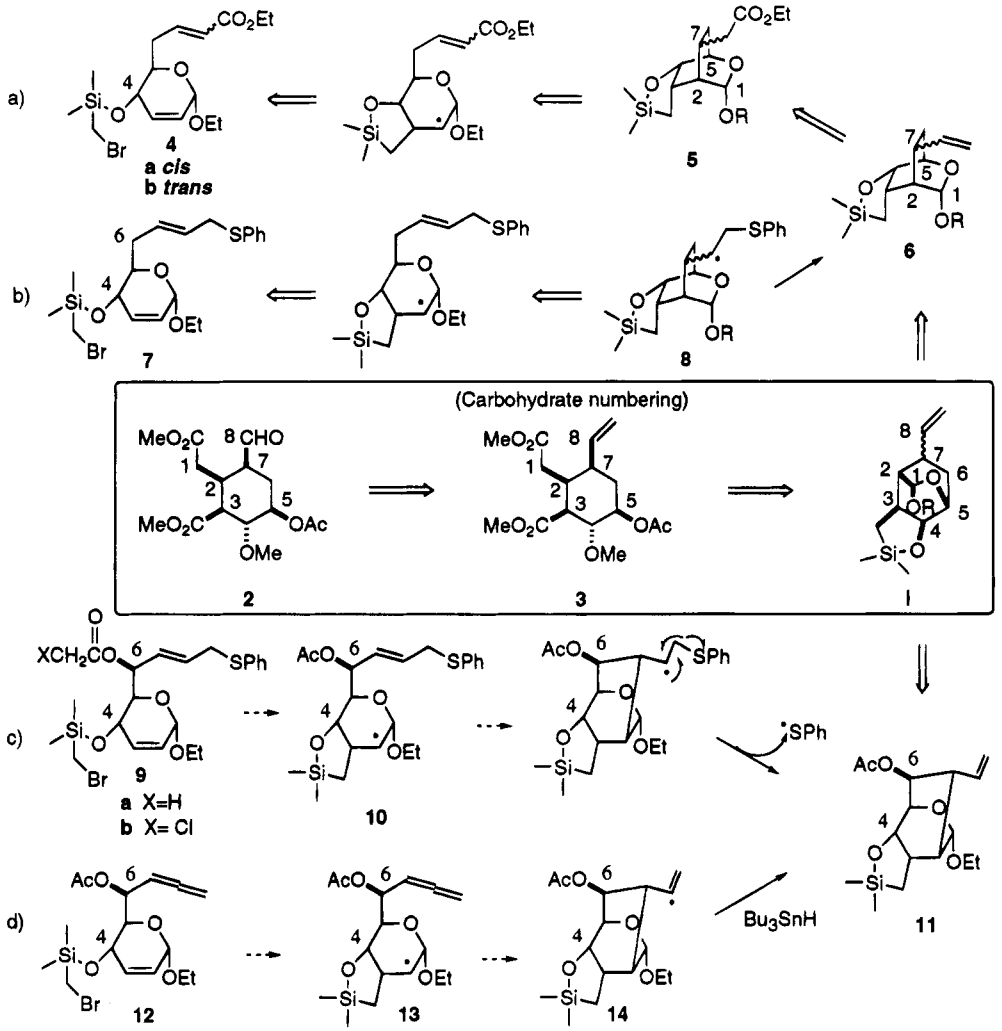
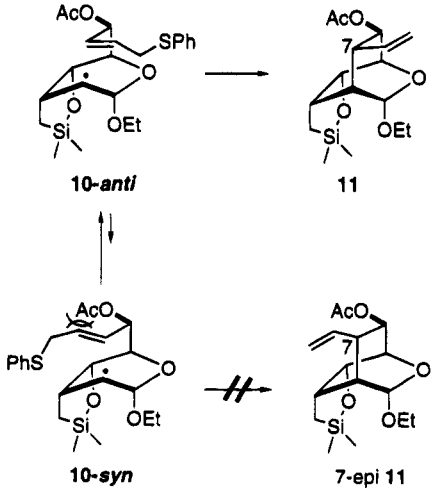
Scheme 4



Scheme 5



likely through a process of addition/elimination of $Bu_3Sn^{\bullet}$ to give the thermodynamically more stable *trans* isomer.

Subjection of the *trans* isomer **4b** to the same reaction conditions led to a similar reaction mixture where compounds **27** (1.5:1 ratio, 75%), **28** (6.6%), and **16b** (10%) were also present.

The fact that both isomers **4**(**a** and **b**) led to a similar product mixture helped to simplify the preparative procedure since the geometric mixture of olefins could be used as starting materials.

Cyclizations of silyl bromides **7** and **12** (Scheme 7c,d) stopped at the monocyclic products **29** and **30** in 41% and 55% yields respectively, resulting from 5-*exo-trig* ring closure followed by reduction of the radical at C-2.

With substrate **9a** (Scheme 7e), the oxabicyclic compound **31** was obtained as the sole non-UV-absorbing material in the crude reaction mixture in 17% yield, the C-7 configuration being established by the indicated NOE experiments.

Similarly, treatment of substrate **9b** gave a crude mixture that was divided into two portions. One, upon acetylation, gave the above-described **31**, along with a number of byproducts. The other portion was treated with Markiewicz's 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TIPSCl)[25] in pyridine. This reagent is known to react rapidly with the primary hydroxyl function followed by a slower intramolecular ring closure with a conveniently located secondary hydroxyl group to form an eight-membered ring, a trend that had been observed even in tetrols.[25c,d] Accordingly, compound **32** was isolated in 17% yield, the hydroxyl group at C-6 being ready for deoxygenation.

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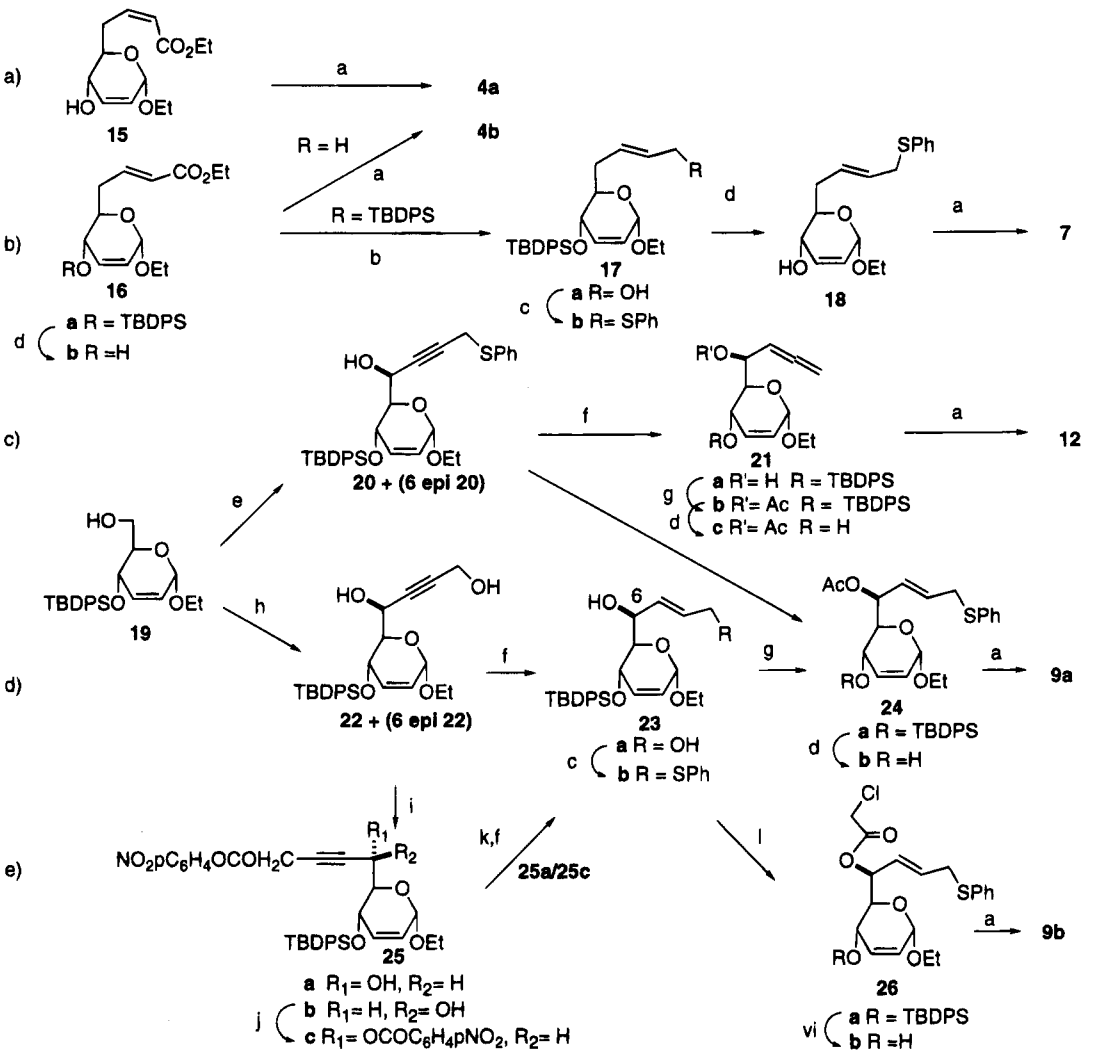
Scheme 6[a]



a Reaction conditions: (a) $BrCH_2SiMe_2Cl$, Et_3N, CH_2Cl_2; (b) DIBAL-H, CH_2Cl_2, 0 °C; (c) PhSSPh nBu_3P, Py; (d) HF–Py, THF; (e) (1) $(ClCO)_2$, DMSO, Et_3N, THF, −78 °C → 35 °C, (2) propargyl phenyl sulfide, nBuLi, −78 °C; (f) Red-Al, Et_2O, 0 °C → rt; (g) Ac_2O, DMAP, Py; (h) (1) $(ClCO)_2$, DMSO, Et_3N, THF, −78 °C → 35 °C, (2) propargyl alcohol, nBuLi, −78 °C; (i) Ph_3P, 4-nitrobenzoic acid, DEAD, THF, 0 °C; (j) Ph_3P, 4-nitrobenzoic acid, DEAD, rt; (k) K_2CO_3, MeOH; (l) $(ClCH_2CO)_2O$, Et_3N, CH_2Cl_2.

From the experiments in Scheme 7a–c, two conclusions could be drawn: first that our assumption for the stereochemical model proposed in Scheme 5 was correct and, second, that when the olefin at C-7 is not deactivated with an electron-withdrawing substituent the 6-*exo-trig* cyclization (**VII** → **I**, Scheme 2b) is not a very efficient process and reduction of the intermediate radical at C-2 (i.e. **VII**, Scheme 2b) becomes an important reaction pathway.

Synthesis of Woodward's Reserpine Precursor. The caged compound **34** (Scheme 8) was set as our frontier material, since it incorporates all the synthons required in Woodward's intermediate, the formyl group being retrosynthetically correlated with the pendant vinyl group at C-7. The oxabicyclic compounds **27** and **32**, prepared as shown in Scheme 7, are plausible precursors of **34**. In the case of the latter, this required Barton–McCombie type radical deoxygenation[26] using Robins' phenyl thionoformate[27] followed by cleavage of the TIPS group (Scheme 8a).

The route from **27** (Scheme 8b) involved silylation of the hydroxyl groups to give **35a**, followed by processing of the C-7 function via hydride reduction and selenoxide elimination as the key steps leading to **35c**. Desilylation gave a mixture of diols **34** and **36** that could be readily separated by chromatography. The "wrong" C7 configuration in **36** could be corrected, if necessary, by ozonolysis–epimerization–methylenation to obtain more of **34**.

Synthesis of Woodward's Reserpine Precursor from 34. The first task in pursuit of our objective was to correct the "wrong" C-4 configuration in **34**. Attempts to effect epimerization by Mitsunobu procedures[20] and modifications thereof proved unavailing,[21,28] and so an oxidation/reduction sequence was examined. David's bromine-induced oxidation of stannylene acetals[29] proceeded with the expected regioselectivity to give ketone

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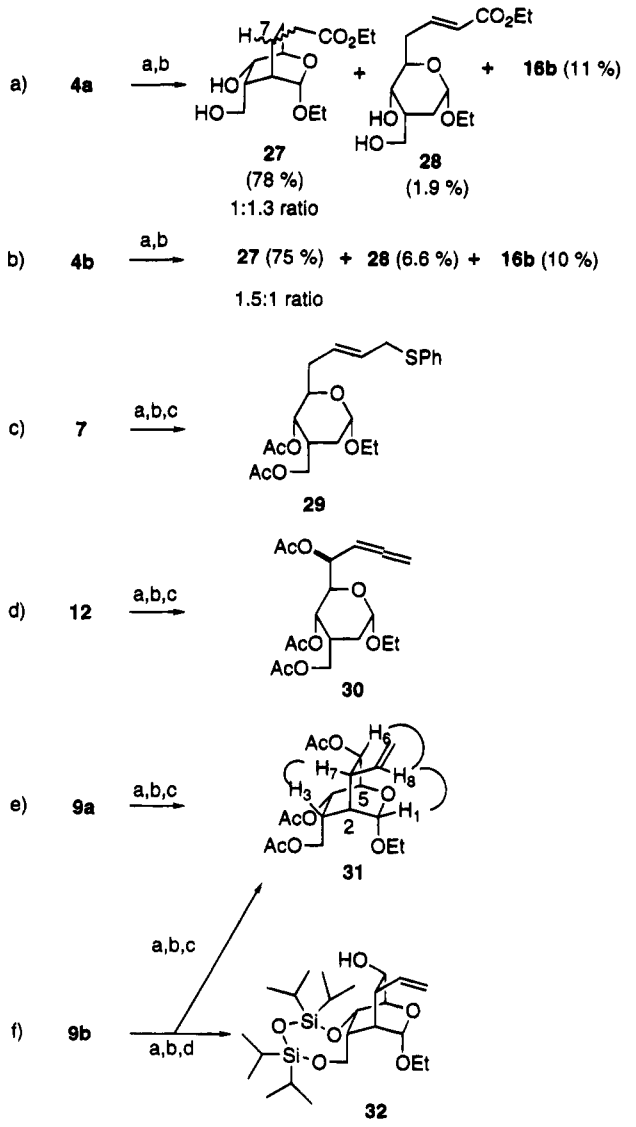
Scheme 7[a]

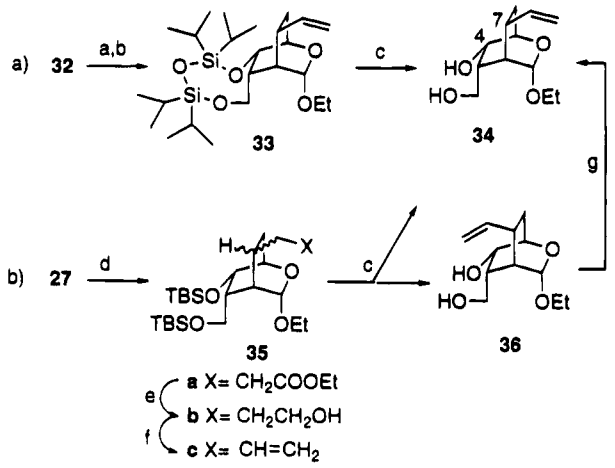


[a] Reaction conditions: (a) Bu_3SnCl, $NaCNBH_3$, AIBN, *t*-BuOH, reflux; (b) H_2O_2, $KHCO_3$, KF, THF–MeOH (1:1), reflux; (c) Ac_2O, DMAP, Py; (d) TIPSCl, Py.

37, and reduction with sodium triacetoxyborohydride[30,31] ensured hydrogen delivery from "below", as shown in **38**, to give the desired C-4 orientation in **39a**. After regioselective silylation and methylation, the anomeric center of **39c** was liberated, and use of the Levine reagent[32] paved the way to enol ether **40**.

The enol–ether function in **40** was introduced in the hope of direct transformation into **41**[33] as shown in Scheme 9; but liberation of the TBDPS protecting group in order to elaborate the C-3 branch proved unsuccessful, because of the formation of lactone **42**. In light of this situation, the carbon branch at C-3 was processed by routine methods that included deprotection of the silyl

Scheme 8[a]



[a] Reaction conditions: (a) PhOCSCl, Py; (b) Bu_3SnH, AIBN, C_6H_6, reflux; (c) nBu_4NF, THF; (d) TBSCl, imidazole, DMF; (e) LAH, Et_2O; (f) (1) MsCl, Et_3N, CH_2Cl_2, 0 °C, (2) PhSeSePh, $NaBH_4$, EtOH–THF, 0 °C → rt, (3) H_2O_2, 0 °C → reflux; (g) (1) O_3, MeOH, −78 °C, (2) Me_2S, −78 °C → rt, (3) K_2CO_3, MeOH, (4) Ph_3PCH_3Br, BuLi, THF.

group, direct oxidation to carboxylic acid,[34] and methyl ester formation with TMS–diazomethane[35] to give the methoxycarbonyl in **43b**. The enol ether was converted into the second methoxycarbonyl group of **3**, and ozonolysis led to **2**.

In spite of its central place in reserpine synthetic methodology, it is noteworthy that aldehyde **2** had not been previously characterized. The "instability" recognized by Woodward and the ready epimerization subsequently suggested by Pearlman[5a] have always been obviated by immediate reductive amination with a tryptophane derivative. Indeed, as mentioned above, we have followed that precedent to obtain the advanced intermediate **3**. Although it was not possible to obtain an ^1H NMR spectrum of **2** which had not partially epimerized, we were able to obtain data which are entirely consistent with the presumed structure **2** revealing, among other things, that **2**, **3**, and **44** exist in similar conformations.

Conclusions

We have explored the scope and limitations of serial radical cyclizations of tethered pyranosyl-derived dienes as a method for the stereocontrolled synthesis of complex cyclohexane moieties and have done so in the context of the synthesis of Woodward's densely functionalized intermediate for reserpine, **1**. The method involves an efficient 5-*exo-trig* radical cyclization onto a $\Delta^{2,3}$ unsaturation in the pyranose ring that serves dual purposes, first to introduce a carbon branch at C-3 in a regio- and stereocontrolled manner and second to generate an additional radical at C-2 that is set to undergo 6-*exo-trig* ring closure to form the cyclohexane ring. We have observed that the second radical cyclization leading to the actual cyclohexane ring requires the presence of an electron-withdrawing substituent at the terminus of the olefin at C-7. Although some cyclization was observed when an allylic phenyl sulfide was employed as the second radical trap, the main reaction course observed in this case was the reduction of the radical at C-2. We

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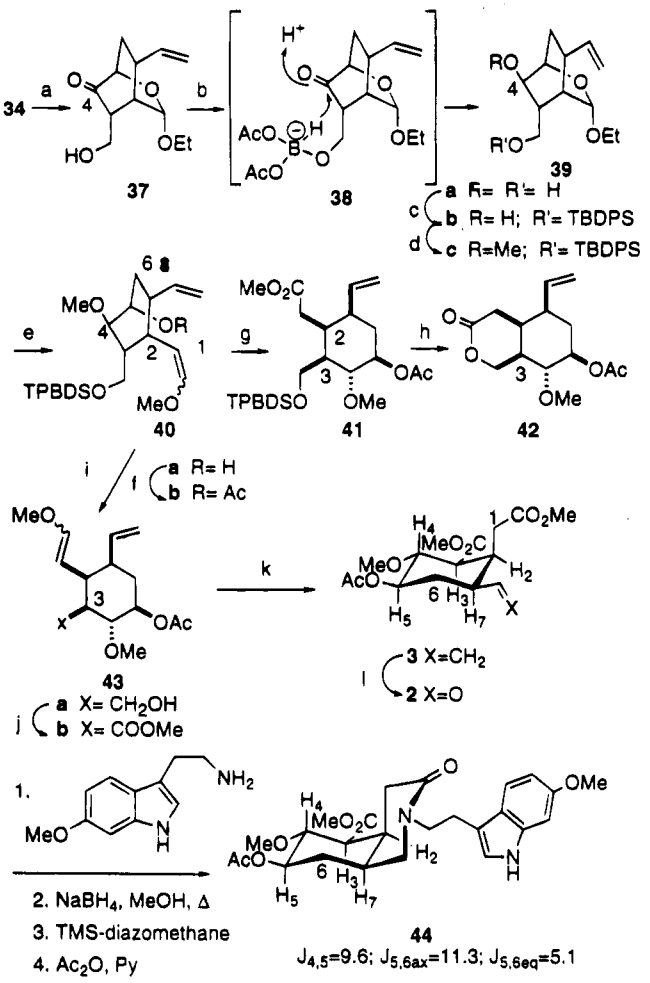
Scheme 9[a]



[a] Reaction conditions and yields: (a) (1) Bu_2SnO, toluene, reflux, (2) NBS, $CHCl_3$, 78% for two steps; (b) $NaBH(OAc)_3$, EtOAc, 0 °C → rt, 88%; (c) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 85%; (d) MeI, Ag_2O, 85%; (e) (1) AcOH, THF, H_2O, 90 °C, (2), Ph_3PCH_3OMeCl, nBuLi, THF, 0 °C, 74% for two steps; (f) Ac_2O, Py, DMAP, 95%; (g) PCC, CH_2Cl_2, 71%; (h) HF–Py, THF, 80%; (i) nBu_4NF, THF, 78%; (j) (1) PDC, DMF, (2) $TMSCHN_2$, MeOH, 78% for two steps; (k) (1) AcOH, THF, H_2O 4:2:1, 90 °C, (2) PDC, DMF, (3) $TMSCHN_2$, MeOH, 64% for three steps; (l) O_3, MeOH, −78 °C, then Me_2S.

have made use of a model based in 1,3 allylic strain[15] to control the stereoselectivity in the formation of the second stereogenic center of the radical process. In summary, two types of diene pyranoside precursors have been used in the synthesis of Woodward's carbocyclic key intermediate for reserpine.

Experimental Section

General Procedures. Melting points were determined in capillary tubes and are uncorrected. Optical rotations were determined at the sodium D line and measured in chloroform. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. High-field NMR spectra were recorded at 300 MHz in $CDCl_3$; chemical shifts (δ) are relative to $CHCl_3$ as internal reference. Mass spectra were recorded by chemical ionization (with methane ammonia as the reagent gas). TLC was conducted in precoated kieselgel 60 F_{254}. Detection was first by UV (254 nm) and then charring with a solution of ammonium molybdate(VI) tetrahydrate (12.5 g) and cerium(IV) sulfate tetrahydrate (5.0 g) in 10% aqueous sulfuric acid (500 mL). Column chromatography was carried out on kieselgel (230–400 mesh) and mixtures of petroleum ether–ethyl acetate (PE–EtOAc) as eluant. All reactions were conducted under an atmosphere of argon. Anhydrous $MgSO_4$ or Na_2SO_4 was used to dry the organic solutions during workups, and the removal of the solvents was done under vacuum with a rotoevaporator. Unless otherwise noted, materials were obtained from commercially available sources and used without further purification. Solvents were dried and purified using standard methods.

General Method for the Reduction of Propargyl Alcohols with Red-Al. To a stirred, cooled (0 °C) solution of sodium bis(methoxyethoxy)aluminum hydride (Red-Al) (4 equiv) in Et_2O (1 mL/mmol) was added the propargyl alcohol in Et_2O (2 mL/mmol) over 1 h. The solution was warmed to room temperature and stirred until TLC showed complete reaction. The mixture was again cooled to 0 °C, and the reaction was quenched with H_2O. The aqueous layer was saturated with sodium chloride and was extracted with ether. The combined organic layers were dried, solvent was removed, and the residue was purified by chromatography.

General Method for the Desilylation Reaction with HF–Py. To a cooled (0 °C) solution of the silyl derivative in dry tetrahydrofuran (20 mL/mmol) was added pyridine (7 mL/mmol) followed by a hydrogen fluoride–pyridine complex (7 mL/mmol). The solution was allowed to warm to room temperature and kept at that temperature with stirring until TLC showed total consumption of the starting material. After the solution was cooled to 0 °C, saturated $NaHCO_3$ solution was added dropwise and the reaction mixture extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were washed with concd $NaHCO_3$ and water and dried. Evaporation of the solvents gave a residue that was purified by flash chromatography.

General Method for Acetylation. To a stirred solution of the alcohol in pyridine (5 mL/ mmol) was added an excess of acetic anhydride and a catalytic amount of 4-(dimethylamino)pyridine (DMAP). The mixture was stirred for 10 h. The solvent was then removed *in vacuo*, and the residue was subjected to flash chromatography.

General Procedure for the Preparation of Thioethers from Alcohols.[20] To a stirred solution of the diol in pyridine was added diphenyl disulfide (1.5 equiv) and nBu_3P (1.5 equiv) was added. The mixture was stirred until TLC showed complete reaction. The solvent was then removed *in vacuo*, and the resulting residue was subjected to flash chromatography.

General Procedure for the Preparation of (Bromomethyl)silyl Ethers.[12,13] Typically, to a ice-cooled solution of the alcohol in CH_2Cl_2 were added Et_3N (2 mL/mmol) and (bromomethyl)dimethylchlorosilane (1.2 equiv). The solution was allowed to warm to room temperature and kept at that temperature overnight. The reaction mixture was poured into aqueous $NaHCO_3$ and extracted twice with CH_2Cl_2. The combined organic extracts were washed with water and brine and dried. Evaporation of the solvent furnished crude (bromomethyl)silyl ethers that were azeotroped with toluene and without further purification were subjected to the radical cyclization reaction.

General Procedure for the Radical Cyclization Reactions.[23] To a thoroughly degassed (argon) solution of the alkyl halide, tributyltin chloride (0.1 equiv), and AIBN (0.1 equiv) in *tert*-butyl alcohol (0.04 M) was added sodium cyanoborohydride (2 equiv), and the reaction mixture was immediately refluxed in a preheated bath for 4 h. The reaction mixture was diluted with CH_2Cl_2 and shaken with a 3% aqueous ammonia solution, followed by addition of brine and separation of the organic phase. The aqueous layer was extracted twice with CH_2Cl_2 and dried. Solvents were removed by azeotroping with toluene and the residue subjected to flash chromatography.

General Procedure for the Tamao Oxidations.[24] The crude silyl ether resulting from the radical cyclization was dissolved in THF/MeOH (1:1, 1 mL/mmol) and the solution treated with potassium hydrogen carbonate (2 equiv), potassium fluoride (4 equiv) and 30% hydrogen peroxide (20 equiv). The resulting mixture was refluxed for 10 h. After cooling, the remaining hydrogen peroxide was decomposed by careful addition of well-ground $Na_2S_2O_3 \cdot 5H_2O$ (25 equiv) at room temperature. After 1 h, an iodine starch test was negative

and the mixture was then diluted with Et_2O (1 mL/mmol) and filtered through Celite. The precipitate was washed with THF/MeOH/Et_2O (1:1:2), and the filtrate was concentrated under reduced pressure. The resulting crude diols were subjected to acetylation, with acetic anhydride and catalytic DMAP in pyridine (room temperature, 24 h), for further characterization.

General Procedure for the Methanolysis of 4-Nitrobenzoyl Esters. To a stirred solution of the *p*-nitrobenzoate in methanol was added K_2CO_3. The mixture was stirred until TLC showed complete reaction. The solvent was then removed *in vacuo*, and the resulting residue was subjected to flash chromatography.

Ethyl (*E*)-4-*O*-(*tert*-Butyldiphenylsilyl)-2,3,6,7,8-pentadeoxy-α-D-*erythro*-nona-2,7-dienopyranoside (17a). To a cooled (0 °C) solution of ester **16a**[17] (400 mg, 0.81 mmol) in CH_2Cl_2 was added slowly DIBAL (1 M hexane, 1.78 mL, 1.78 mmol, 2.2 equiv). The mixture was diluted with Et_2O, and methanol was added dropwise with stirring, until a white gel formed. The solids were removed by filtration through a pad of Celite and washed thoroughly with Et_2O. The filtrate was concentrated *in vacuo* and the residue purified by flash chromatography (PE–EtOAc, 75:25) to provide 315 mg (86%) of alcohol **17a** as a clear oil: $[\alpha]^{21}_D$ +51.5° (*c* 0.8); ^{1}H NMR δ 1.07 (s, 9 H), 1.25 (t, *J* = 7.1 Hz, 3H), 2.10 (m, 1H), 2.60 (m, 1H), 3.51 (m, 1H), 3.80 (m, 1H), 3.91 (dd, *J* = 2.6, 8.5 Hz, 1H), 4.02 (m, 1H), 4.06 (d, *J* = 4.1 Hz, 2H), 4.86 (s, 1H), 5.59 (dt, *J* = 2.4, 10.2 Hz, 1H), 5.66 (m, 2H), 5.81 (d, *J* = 10.2, 1H), 7.41 (m, 6H), 7.70 (m, 4H); ^{13}C NMR δ 13.4, 19.4, 27.0, 34.3, 63.6, 63.9, 68.8, 71.1, 94.1, 125.7, 127.6, 127.8, 128.8, 129.8, 129.9, 131.5, 133.1, 133.9, 136.0, 136.1; MS *m/z* 470 $(M + NH_4)^+$.

Anal. Calcd for $C_{27}H_{36}O_4Si$: C, 71.64; H 8.02. Found: C 71.43; H, 7.84.

Ethyl (*E*)-4-*O*-(*tert*-Butyldiphenylsilyl)-2,3,6,7,8,9-hexadeoxy-9-(phenylthio)-α-D-*erythro*-nona-2,7-dienopyranoside (17b). This compound was prepared by the general method from alcohol **17a** (219 mg, 0.48 mmol) followed by chromatography (PE–EtOAc, 95:5) to give **17b** as a colorless oil (248 mg, 94%): $[\alpha]^{21}_D$ +16.5° (*c* 0.7); ^{1}H NMR δ 1.05 (s, 9 H), 1.23 (t, *J* = 7.1 Hz, 3H), 2.03 (m, 1H), 2.54 (m, 1H), 3.48 (m, 3H), 3.77 (m, 1H), 3.84 (dd, *J* = 2.4, 8.5 Hz, 1H), 3.97 (m, 1H), 4.83 (s, 1H), 5.56 (m, 3H), 5.76 (d, *J* = 10.2, 1H), 7.36 (m, 11H), 7.65 (m, 4H); ^{13}C NMR δ 15.3, 19.4, 27.0, 34.4, 36.4, 63.8, 68.9, 71.0, 94.0, 125.6, 126.0, 127.3, 127.6, 127.8, 128.7, 129.4, 129.7, 129.9, 130.2, 133.8, 133.9, 135.9, 136.0; MS *m/z* 562 $(M + NH_4)^+$.

Anal. Calcd for $C_{33}H_{40}O_3SSi$: C, 72.75; H 7.4. Found: C, 72.59; H, 7.19.

Ethyl (*E*)-2,3,6,7,8,9-Hexadeoxy-9-(phenylthio)-α-D-*erythro*-nona-2,7-dienopyranoside (18). This compound was prepared by the general method from thioether **17b** (230 mg, 0.42 mmol) followed by chromatography (PE–EtOAc, 7:3) to give **18** (124 mg, 97%) as a colorless oil: $[\alpha]^{21}_D$ +33.3° (*c* 0.9); ^{1}H NMR δ 1.21 (s, t, *J* = 7.1 Hz, 3H), 1.53 (d, *J* = 8.5 Hz, 1H), 2.25 (m, 1H), 2.52 (m, 1H), 3.51 (m, 3H), 3.60 (dt, *J* = 3.5, 7.9 Hz, 1H), 3.78 (m, 2H), 4.92 (s, 1H), 5.70 (m, 3H), 5.88 (d, *J* = 10.1 Hz, 1H), 7.30 (m, 5H); ^{13}C NMR δ 15.3, 34.8, 36.3, 63.9, 67.4, 71.1, 93.9, 126.1, 126.7, 127.9, 128.8, 128.9, 129.7, 133.3, 136.2; MS *m/z* 289 $(MH - H_2O)^+$.

Anal. Calcd for $C_{17}H_{22}O_3S$: C, 66.04; H 7.24. Found: C, 65.87; H, 7.31.

Ethyl 4-*O*-(*tert*-Butyldiphenylsilyl)-2,3,7,8,9-pentadeoxy-9-(phenylthio)-α-D-*erythro*-L-*glycero*-non-2-en-7-ynopyranoside (20). To a stirred solution of oxalyl chloride (381 μL, 4.36 mmol) in 3 mL of THF at −78 °C was added dimethyl sulfoxide (412 μL, 5.8 mmol). The solution was allowed to warm to −35 °C for 30 min and then was recooled to −78 °C. A solution of alcohol **19** (849 mg, 29 mmol) in 40 mL of THF was then added to the reaction mixture. The resultant solution was allowed to warm to −35 °C and after 15 min was treated with Et_3N (4.08 mL, 29.1 mmol). The reaction mixture was allowed to warm briefly to rt and was then recooled to −78 °C. A solution of the lithio derivative of propargyl phenyl sulfide, prepared by treatment of phenyl propargyl sulfide (2.15 g, 14.5 mmol) with *n*-BuLi (6.90 mL of a 2.1 M solution, 14.5 mmol) at −78 °C, was added via a double-ended needle. The temperature of the solution was allowed to warm to −50 °C over 1 h, recooled to −78 °C, and then treated with ethanol (5 mL) and then with a saturated solution of NH_4Cl. The warmed reaction mixture was extracted with ether. The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue (PE–EtOAc, 95:5) afforded **20** (345 mg, 27%) followed by its 6-epimer (615 mg, 48%).

For 20: $[\alpha]^{21}_D$ +47.8° (*c* 0.9); ^{1}H NMR δ 1.05 (s, 9 H), 1.22 (t, *J* = 7.2 Hz, 3H), 2.14 (d, *J* = 10.0 Hz, 1H), 3.48 (m, 1 H), 3.66 (d, *J* = 1.8 Hz, 2H), 3.92 (d, *J* = 9.0 Hz, 1H), 3.95 (m, 1H), 4.48 (dd, *J* = 1.2, 9.0 Hz, 1H), 4.72 (dd, *J* = 1.8, 10.0 Hz, 1H), 4.93 (b s, 1H), 5.53 (dt, *J* = 2.4, 10.5 Hz, 1H), 5.69 (d, J= 10.5 Hz, 1H), 7.35 (m, 15H,); ^{13}C NMR 15.2, 19.4, 23.1, 26.9, 61.1, 64.0, 65.1, 73.5, 80.4, 82.9, 94.3, 125.3, 126.8, 126.9, 127.7, 127.9, 129.0, 129.8, 129.9, 130.0, 130.1, 132.7, 133.5, 133.7, 135.9; MS *m/z* 576 $(M + NH_4)^+$.

Anal. Calcd for $C_{33}H_{38}O_4SSi$: C, 70.93; H 6.85. Found: C, 71.06; H, 6.73.

Reduction of Propargyl Alcohol 20. According to the general method, propargyl alcohol **20** (1.250 g, 2.24 mmol) was treated with Red-Al to give after flash chromatography (PE–EtOAc, 95:5) a mixture of allene **21a** (423 mg, 42%) and alkene **24a** (see below, 477 mg, 38%).

For 21a: colorless oil; $[\alpha]^{21}_D$ +56.6° (*c* 0.7); ^{1}H NMR δ 1.07 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H), 3.51 (m, 1H), 3.83 (d, *J* = 9.2 Hz, 1H), 3.84 (m, 1H), 4.51 (ddd, *J* = 1.5, 2.2, 9.0 Hz, 1H), 4.58 (m, 1 H), 4.90 (dd, *J* = 2.7, 10.0 Hz, 1H), 4.93 (b s, 1 H), 5.37 (q, *J* = 6.6 Hz, 2H), 5.55 (dt, *J* = 2.2, 10.2 Hz, 1H), 5.75 (d, *J* = 10.2 Hz, 1H), 7.62 (m, 15H); ^{13}C NMR 15.2, 19.4, 26.9, 64.0, 65.3, 67.3, 73.5, 77.5, 92.5, 94.3, 125.2, 127.6, 127.8, 127.9, 129.8, 129.9, 132.9, 133.8, 133.9, 135.9, 136.0, 207.5; MS *m/z* 468 $(M + NH_4)^+$.

Anal. Calcd for $C_{27}H_{34}O_4Si$: C, 71.96; H 7.61. Found: C, 71.68; H, 7.48.

Ethyl 6-Acetyl-2,3,7,8,9-pentadeoxy-α-D-*erythro*-L-*glycero*-nona-2,6,8-trienopyranoside (21c). Alcohol **21a** (370 mg, 0.82) was submitted to the standard conditions of acetylation to afford after chromatography (PE–EtOAc, 9:1) the acetyl ester **21b** (342 mg, 85%), and treatment of a portion (300 mg) under the general method, followed by chromatography (PE–EtOAc, 7:3) afforded **21c** (132 mg, 85%) as a colorless oil: $[\alpha]^{21}_D$ +77.6° (*c* 0.7); ^{1}H NMR δ 1.21 (t, *J* = 7.1 Hz, 3H), 2.14 (s, 3H), 2.84 (d, *J* = 6.0 Hz, 1H), 3.54 (m, 1H), 3.99 (m, 1H), 4.89 (m, 2H), 5.04 (m, 1H), 5.41 (q, *J* = 6.8 Hz, 2H), 5.72 (m, 2H), 5.95 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR δ 15.2, 21.1, 63.6, 64.1, 70.2, 73.4, 77.5, 87.6, 94.6, 126.2, 133.1, 171.5, 208.6; MS *m/z* 272 $(M + NH_4)^+$.

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H 7.13. Found: C, 61.63; H, 7.22.

Ethyl (*E*)-4-*O*-(*tert*-Butyldiphenylsilyl)-2,3,7,8-tetradeoxy-α-D-*erythro*-L-*glycero*-nona-2-eno-7-ynopyranoside (22). To a stirred solution of oxalyl chloride (3.17 mL, 36.4 mmol) in 25 mL of THF at −78 °C was added dimethyl sulfoxide (3.44 mL, 48.5 mmol). The solution was allowed to warm to −35 °C for 30 min and then was recooled to −78 °C. A solution the alcohol **19** (10 g, 24.2 mmol) in 500 mL of THF was then added to the reaction mixture. The resultant solution was allowed to warm to −35 °C and after 15 min was treated with Et_3N (20.45 mL, 145.5 mL). The reaction mixture was allowed to warm briefly to rt and was then recooled to −78 °C. A solution of dilithio derivative of propargyl alcohol, prepared by treatment of propargyl alcohol (4.05 mL, 69.4 mmol) with *n*-BuLi (34.5 mL of a 2.1 M solution, 69.4 mmol) at −78 °C, was added via a double-ended needle. The temperature of the solution was allowed to warm to rt, allowed to react for 3 h, recooled to −78 °C, and then treated with 15 mL of ethanol and then with 500 mL of a saturated solution of NH_4Cl. The warmed reaction mixture was extracted with ether. The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. Careful chromatography of the residue with PE–EtOAc, 7:3, afforded 6-epimer **22** (3.74 g, 33%) followed by **6-*epi*-22** (6.02 g, 53%).

For 22: mp 116–118 °C; $[\alpha]^{21}_D$ +32.6° (*c* 1.3); ^{1}H NMR δ 1.05 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H), 3.52 (m, 1H), 3.95 (m, 2H), 4.30 (s, 2H), 4.48 (dd, *J* = 1.2, 9.0 Hz, 1H), 4.76 (bs, 1H), 4.82 (s, 1H), 5.53 (dt, *J* = 2.1, 10.3 Hz, 1H), 5.70 (d, *J* = 10.3

Hz, 1H), 7.35 (m, 6H), 7.69 (m, 4H); ^{13}C NMR δ 15.3, 19.4, 26.9, 50.7, 60.9, 64.0, 65.0, 73.8, 83.6, 84.8, 94.4, 125.2, 127.7, 127.9, 129.9, 130.1, 132.6, 133.4, 133.6, 133.8, 135.9, 136.2; MS *m/z* 484 $(M + NH_4)^+$.

Anal. Calcd for $C_{27}H_{34}O_5Si$: C, 69.49; H 7.34. Found: C, 69.40, H, 7.35.

Ethyl (*E*)-4-*O*-(*tert*-Butyldiphenylsilyl)-2,3,7,8,9-pentadeoxy-9-(phenylthio)-α-D-*erythro*-L-*glycero*-nona-2,7-dienopyranoside (23b). Reduction with Red-Al of alcohol **22** (1.55 g, 3.3 mmol) according to the standard method gave after flash chromatography (PE−EtOAc, 7:3) the alkene **23a** (1.315 g, 85%). Deesterification of *p*-nitrobenzoates **25a** and **25c** with dilute KOH in MeOH, followed by reduction of the alkyne by the standard procedure, also gave **23a**. This compound (300 mg, 0.61 mmol) was subjected to the general method for thioether formation, and chromatography (PE−EtOAc,8:2) afforded **23b** (572 mg, 70%) as a colorless oil: $[\alpha]^{21}_D$ +46.8° (*c* 0.8); ^{1}H NMR δ 1.06 (s, 9 H), 1.21 (t, J = 7.1 Hz, 3H), 3.45 (m, 1H), 3.58 (d, J = 5.9 Hz, 2H), 3.73 (m, 1H), 3.77 (d, J = 6.6 Hz, 1H), 4.45 (m, 2H), 4.88 (s, 1H), 5.54 (dt, J = 2.1, 10.2 Hz, 1H), 5.76 (d, J = 10.2, 1H), 5.81 (m, 2H), 7.38 (m, 5H), 7.45 (m, 6H), 7.68 (m, 4H); ^{13}C NMR δ 15.3, 19.4, 26.9, 35.9, 64.0, 65.1, 69.2, 73.3, 94.2, 125.2, 126.2, 126.6, 127.7, 127.8, 128.9, 129.6, 129.8, 129.9, 133.0, 133.8, 133.9, 135.9; MS *m/z* 578 $(M + NH_4)^+$.

Anal. Calcd for $C_{33}H_{40}O_4SSi$: C, 70.68; H 7.19. Found: C, 70.49; H, 7.02.

Ethyl 6-Acetyl-2,3,7,8,9-pentadeoxy-9-(phenylthio)-α-D-*erythro*-L-*glycero*-nona-2,7-dienopyranoside (24b). Alcohol **23b** (2.12 g, 3.84 mmol) was submitted sequentially to the standard conditions for acetylation and desilylation to afford after flash chromatography (PE−EtOAc, 8:2) the alcohol **24b** (1.06 g, 72%): $[\alpha]^{21}_D$ +52.1° (*c* 0.6); ^{1}H NMR δ 1.18 (t, J = 7.1 Hz, 3H), 2.11 (s, 3H), 2.76 (bs, 1H), 3.48 (m, 1H), 3.55 (d, J = 6.3 Hz, 2H), 3.69 (dd, J = 2.4, 9.3 Hz, 1H), 3.75 (m, 1H), 3.93 (bd, J = 8.4 Hz, 1H), 5.00 (s, 1H), 4.63 (dd, J = 1.8, 6.3 Hz, 1H), 5.69 (dt, J = 2.4, 10.2 Hz, 1H), 5.78 (dd, J = 6.6, 15.3 Hz, 1H), 5.92 (m, 2H), 7.25 (m, 5H); ^{13}C NMR δ 15.2, 21.1, 35.9, 63.5, 64.1, 72.0.2, 73.2, 94.5, 126.2, 126.5, 128.0, 128.9, 129.8, 130.0, 133.0, 135.6, 171.5; MS *m/z* 382 $(M + NH_4)^+$.

Anal. Calcd for $C_{19}H_{24}O_5S$: C, 62.62; H 6.64. Found: C, 62.98; H, 6.52.

Ethyl 4-*O*-(*tert*-Butyldiphenylsilyl)-9-(4-nitrobenzoyl)-2,3,7,8-tetradeoxy-α-D-*erythro*-L-*glycero*-non-2-en-7-ynpyranoside (25a). To a cooled (0 °C) and stirred solution of the mixture of **22** and **6-*epi*-22** (7.96 g, 17.1 mmol), Ph_3P (7.61 g, 29.0 mmol), and 4-nitrobenzoic acid (5.42 g, 32.42 mmol) in dry THF (500 mL) was added a solution of DEAD (4.51 mL, 29.0 mmol) in THF (10 mL). The reaction mixture was stirred for 10 min, after which time methanol (20 mL) was added. Concentration *in vacuo* and flash chromatography (PE−EtOAc, 85:15) afforded **25a** (3.72 g, 35%) and **25b** (5.55 g, 52%).

For 25a: mp 106−107 °C; $[\alpha]^{21}_D$ +44.0° (*c* 0.7); ^{1}H NMR δ 1.05 (s, 9H), 1.18 (t, J = 7.1 Hz, 3H), 2.22 (d, J = 10.2 Hz, 1H), 3.51 (m, 1H), 3.94 (m, 2H), 4.48 (dd, J = 1.3, 8.9 Hz, 1H), 4.79 (d, J = 10.0 Hz, 1H), 4.94 (s, 1H), 5.02 (s, 2H), 5.53 (dt, J = 2.2, 10.2 Hz, 1H), 5.70 (d, J = 10.2 Hz, 1H), 7.42 (m, 6H), 7.70 (m, 4H), 8.26 (m, 4H); ^{13}C NMR δ 15.3, 19.4, 26.9, 53.6, 61.0, 63.9, 64.9, 73.4, 77.8, 87.0, 94.4, 123.6, 125.3, 127.7, 127.9, 129.9, 130.1, 130.9, 132.6, 133.4, 133.6, 134.8, 135.8, 163.9; MS *m/z* 633 $(M + NH_4)^+$.

Anal. Calcd for $C_{34}H_{37}O_8NSi$: C, 66.32; H 6.06; N, 2.29. Found: C, 66.01; H, 5.87; N, 2.37.

Ethyl 4-*O*-(*tert*-Butyldiphenylsilyl)-6,9-bis-(4-nitrobenzoyl)-2,3,7,8-tetradeoxy-α-D-*erythro*-L-*glycero*-non-2-en-7-ynopyranoside (25c). To a cooled (0 °C) and stirred solution of **25b** (3.16 g, 5.13 mmol), Ph_3P (2.29 g, 8.73 mmol), and *p*-nitrobenzoic acid (1.63 g, 9.75 mmol) in dry THF (300 mL) was added a solution of DEAD (1.36 mL, 8.73 mmol) in THF (3 mL). The reaction mixture was stirred for 2 h at rt, the solution was concentrated *in vacuo*, and the residue was chromatographed (PE−EtOAc, 85:15) to afford **25c** (3.61 g, 93%): $[\alpha]^{21}_D$ −19.1° (*c* 0.8); ^{1}H NMR δ 1.00 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H), 3.56 (m, 1H), 4.00 (m, 1H), 4.29 (s, 2H), 5.05 (m, 3H), 5.66 (m, 1H), 5.84 (d, J = 10.2 Hz, 1H), 6.03 (s, 1H), 7.02 (m, 3H), 7.32 (m, 3H), 7.46 (m, 2H), 7.56 (m, 2H), 8.04 (m, 2H), 8.24 (m, 8H); ^{13}C NMR δ 15.2, 19.1, 26.8, 53.3, 63.5, 64.1, 64.9, 72.7, 79.8, 82.4, 94.7, 123.4, 123.6, 125.8, 127.5, 127.7, 129.9, 130.9, 131.1, 131.6, 132.9, 133.7, 134.5, 134.6, 135.6, 135.7, 135.8, 135.9, 150.7, 163.3, 163.8; MS *m/z* 782 $(M + NH_4)^+$.

Anal. Calcd for $C_{41}H_{40}O_{11}N_2Si$: C, 64.38; H 5.27; N, 3.66. Found: C, 64.97; H, 4.88; N, 3.25.

Ethyl (*E*)-6-(Chloroacetyl)-2,3,7,8,9-pentadeoxy-9-(phenylthio)-α-D-*erythro*-L-*glycero*-nona-2,7-dieno-1,5-pyranoside (26b). To a solution of **23b** (3.57 g, 6.37 mmol) in CH_2Cl_2 were added Et_3N (3.22 mL, 31.8 mmol) and chloroacetic anhydride (1.63 g, 9.55 mmol). The mixture was allowed to react for 48 h, poured over aqueous $NaHCO_3$, and extracted twice with CH_2Cl_2. The combined organic extracts were washed with water and brine and dried. Flash chromatography (PE−EtOAc, 9:1) afforded **26a** (2.19 g, 54%). This material was subjected to the general method of desilylation to afford after flash chromatography (PE−EtOAc, 9:1) compound **26b** (870 mg, 60%): $[\alpha]^{21}_D$ +75.9° (*c* 1.0); ^{1}H NMR δ 1.19 (t, J = 7.1 Hz, 3H), 2.22 (m, 1H), 3.50 (m, 1H), 3.55 (m, 2H), 3.75 (m, 2H), 3.98 (m, 1H), 4.09 (d, J = 4.1 Hz, 2H), 4.99 (s, 1H), 5.73 (m, 3H), 5.96 (m, 2H), 7.34 (m, 5H); ^{13}C NMR δ 15.2, 35.9, 41.0, 63.2, 64.2, 72.7, 74.1, 94.4, 126.2, 126.6, 127.0, 128.9, 130.9, 131.3, 133.1, 135.3, 167.3; MS *m/z* 416 $(M + NH_4)^+$.

Anal. Calcd for $C_{19}H_{23}O_5ClS$: C, 57.21; H 5.81. Found: C, 57.63; H, 5.93.

Radical Cyclization, Tamao Oxidation, and Acetylation of the (Bromomethyl)dimethylsilyl Ether (4a,b). Application of the standard procedure for the radical cyclization of **4a,b**, prepared from a 1:3 mixture of alcohols **15** and **16b** (13.9 g, 52.2 mmol), afforded a material that was subjected to sequential Tamao oxidation (carried out in EtOH/THF instead in MeOH/ THF to avoid transesterification reaction). Purification of the residue by flash column chromatography (PE−EtOAc, 1:1) gave recovered **16b** (1.3 g, 11%); elution then with (PE−EtOAc, 2:8) gave **27** (6.1 g, 78%) as a 1.5:1 mixture of diastereoisomers followed by **28** (451 mg, 3.2%).

For 27: ^{1}H NMR (for two isomers, selected data) δ 1.21 (t, J = 7.1, Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 3.47 (m, 1H), 3.65 (m, 2H), 3.93 (m, 2H), 4.12 (m, 3H), 4.86 and 4.74 (d, J = 2.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, for two isomers) δ 14.1, 15.2, 28.7, 29.0, 30.1, 32.4, 35.0, 35.3, 35.4, 37.4, 39.4, 42.8, 60.4, 62.1, 62.3, 64.0, 67.9, 68.3, 71.2, 71.6, 97.8, 101.9, 172.0, 172.1; MS *m/z* 306 $(M + NH_4)^+$, 289 $(MH)^+$.

Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.32; H 8.39. Found: C, 58.23; H, 8.19.

Ethyl (*E*)-4-Acetoxy-3-(acetoxymethyl)-2,3,6,7,8,9-pentadeoxy-9-(phenylthio)-α-D-*allo*-non-7-enopyranoside (29). Application of the standard procedure for the radical cyclization of the (bromomethyl)silyl ether **7**, prepared from alcohol **18** (130 mg, 0.42 mmol), afforded a reaction crude that was subjected to sequential Tamao oxidation and acetylation. Flash chromatography (PE−EtOAc, 9:1) of the residue gave **29** (42 mg, 42%): ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7.1 Hz, 3H), 1.80 (m, 2H), 2.01 (s, 3H), 2.03 (m, 1H), 2.06 (s, 3H), 2.28 (m, 1H), 2.41 (m, 1H), 3.37 (m, 1H), 3.54 (d, J = 5.6 Hz, 2H), 3.68 (m, 1H), 3.87 (m, 1H), 4.19 (m, 2H), 4.73 (m, 2H), 5.61 (m, 1H); ^{13}C NMR 15.1, 20.9, 30.2, 33.2, 34.1, 36.0, 63.2, 64.2, 68.9, 70.6, 95.9, 126.0, 127.8, 127.9, 128.0, 128.7, 128.9, 170.1, 170.8; MS *m/z* 440 $(M + NH_4)^+$.

Ethyl 3-(Acetoxymethyl)-4,6-diacetoxy-2,3,7,8,9-pentadeoxy-α-D-*allo*-L-*glycero*-nona-7,8-dieno-1,5-pyranoside (30). Application of the standard procedure for the radical cyclization of the (bromomethyl)silyl ether **12** prepared from allene **21c** (100 mg, 0.39 mmol) afforded a product that was subjected to sequential Tamao oxidation and acetylation. Flash chromatography (PE−EtOAc, 95:5) of the residue gave compound **30** (80 mg, 55%); $[\alpha]^{21}_D$ +106.0° (*c* 0.8); ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7.0 Hz, 3H), 1.92 (m, 2H), 2.01 (s, 3H), 2.03 (s, 3H), 2.08 (s, 3H), 2.50 (m, 1H), 3.42 (m, 1H), 3.73 (m, 1H), 3.98 (dd, J = 3.2, 9.0 Hz, 1H), 4.29 (d, J = 7.6 Hz, 2H), 4.90 (m, 2H), 4.97 (dd, J = 5.2, 8.8 Hz, 1H), 5.30 (q, J = 6.8 Hz, 2H), 5.60 (m, 1H); ^{13}C NMR 12.7, 14.0, 19.9, 29.5, 32.6, 62.2, 63.1, 66.6, 68.0, 68.2, 76.5, 86.4, 95.7, 169.0, 169.8, 207.8; MS *m/z* 388 $(M + NH_4)^+$.

Anal. Calcd for $C_{18}H_{26}O_8$: C, 58.37; H 7.08. Found: C, 58.63; H, 7.13.

(3*S*,5*R*,6*S*,7*S*,8*S*)-3-Ethoxy-5-(acetoxymethyl)-6,7-diacetoxy-8-vinyl-2-oxabicyclo[2.2.2]octane (31). Application of the standard procedure for the radical cyclization of the (bromomethyl)silyl ether **9a** prepared from the alcohol **24b** (170 mg, 0.47 mmol) afforded a reaction crude that was subjected to sequential Tamao oxidation and acetylation. Flash chromatography (PE–EtOAc, 8:2) gave **31** (29 mg, 17%): $[\alpha]^{21}_D$ +17.0° (*c* 1.7.0); ^{1}H NMR δ 1.19 (t, *J* = 7.1 Hz, 3H), 2.00 (s, 3H), 2.05 (s, 3H), 2.07 (m, 1H), 2.08 (s, 3H), 2.31 (m, 1H), 2.37 (m, 1H), 3.39 (m, 1H), 3.45 (q, *J* = 7.1 Hz, 2H), 3.81 (m, 1H), 4.03 (dd, *J* = 2.4, 4.7 Hz, 1H), 4.27 (dd, *J* = 5.5, 11.1 Hz, 1H), 4.56 (dd, *J* = 9.2, 11.1 Hz, 1H), 4.88 (s, 1H), 5.00 (t, *J* = 4.8 Hz, 1H), 5.19 (m, 2H), 5.37 (dd, *J* = 2.1, 9.7 Hz, 1H), 5.88 (m, 1H); ^{13}C NMR δ 15.3, 21.0, 21.1, 37.6, 38.31, 47.3, 63.1, 64.1, 65.6, 68.6, 71.4, 96.3, 116.8, 137.2, 170.0, 170.6, 170.9; MS *m/z* 388 $(M + NH_4)^+$.

Anal. Calcd for $C_{18}H_{26}O_8$: C, 58.37; H, 7.08. Found: C, 58.63; H, 7.33.

(3*S*,5*R*,6*S*,7*S*,8*S*)-3-Ethoxy-5-(hydroxymethyl)-6-hydroxy-5,6-*O*-(tetraisopropyl-2-oxa-1,3-disilapropylene)-7-hydroxy-8-vinyl-2-oxabicyclo[2.2.2]octane (32). Application of the standard procedure for the radical cyclization of the (bromomethyl)silyl ether **9b** derivative of thioether **26b** (870 mg, 2.18 mmol) afforded a reaction crude that was subjected to the general Tamao oxidation and then divided into two portions. One upon acetylation gave the above-described **32** (68 mg, 17%) along with several byproducts.

The other fraction was treated at 0 °C with TIPSCl (437 mL, 1.42 mmol) in pyridine (5 mL). The solution was stirred at rt until TLC analysis showed disappearance of the starting material. The reaction was then quenched with methanol and the pyridine evaporated. The residue was dissolved in chloroform, washed with water, and dried. Concentration of the solvent and flash chromatography (PE–EtOAc, 8:2) gave **32** (29 mg, 17%): $[\alpha]^{21}_D$ +19.0° (*c* 0.7); ^{1}H NMR δ 1.07 (m, 28H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.79 (m, 3H), 2.16 (t, *J* = 8.6 Hz, 1H), 2.24 (m, 1H), 3.31 (m, 1H), 3.57 (dd, *J* = 1.9, 10.9 Hz, 1H), 3.86 (m, 2H), 3.86 (m, 2H), 3.98 (m, 1H), 4.57 (dd, *J* = 2.4, 9.0 Hz, 1H), 4.61 (dd, *J* = 9.7, 10.9 Hz, 1H), 4.77 (d, *J* = 1.5 Hz, 1H0, 5.14 (m, 2H), 5.87 (m, 1H); ^{13}C NMR δ 12.5, 12.6, 12.8, 13.4, 15.1, 17.1, 17.4, 17.5, 17.6, 17.7, 41.0, 43.6, 51.5, 62.4, 63.7, 63.9, 71.5, 74.5, 95.6, 115.9, 139.0; MS *m/z* 487 $(MH)^+$.

Anal. Calcd for $C_{24}H_{46}O_6Si_2$: C, 59.22; H, 9.52. Found: C, 58.89; H, 9.71.

(3*S*,5*R*,6*S*,7*S*,8*S*)-3-Ethoxy-5-(hydroxymethyl)-6-hydroxy-5,6-O-(tetraisopropyl-2-oxa-1,3-disilapropylene)-7-hydroxy-8-vinyl-2-oxabicyclo[2.2.2]octane (33). A solution of alcohol **32** (38 mg, 0.08 mmol) was treated with pyridine (18.96 μL, 0.23 mmol) and phenyl chlorothionoformate (16.22 μL, 0.12 mmol) in pyridine (5 mL). The solution was allowed to react overnight, and then the reaction mixture was poured over aqueous $NaHCO_3$ and extracted twice with CH_2Cl_2. The combined organic extracts were washed with water and brine and dried. Evaporation of the solvent furnished a residue which was filtered through silica gel and used without further characterization. A thoroughly degassed (argon) solution of the resulting thionoformate in benzene (5 mL) was heated to reflux under argon. A solution of tributyltin hydride (31.54 μL, 0.12 mmol) and AIBN (1.3 mg, 0.01 mmol) was added. The solution was then heated for two additional hours and cooled, the solvent removed *in vacuo*, and the residue was purified by flash chromatography (PE–EtOAc, 9:1) to give **33** (22 mg, 60%): $[\alpha]^{21}_D$ +14.5° (*c* 0.7); ^{1}H NMR δ 1.05 (m, 31H), 1.74 (m, 3H), 2.00 (t, *J* = 9.0 Hz, 1H), 2.45 (m, 1H), 3.29 (m, 1H), 3.56 (dd, *J* = 1.5, 10.8 Hz, 1H), 3.86 (m, 2H), 4.12 (dd, *J* = 2.1, 8.8 Hz, 1H), 4.61 (t, *J* = 10.2 Hz, 1H), 4.85(s, 1H), 5.07 (m, 2H), 5.90 (m, 1H); ^{13}C NMR δ 12.5, 12.6, 12.8, 13.4, 15.1, 17.1, 17.4, 17.5, 17.6, 17.7, 17.8, 28.6, 39.7, 39.8, 44.4, 61.9, 63.7, 68.0, 71.6, 96.2, 114.8, 141.6; MS *m/z* 488 $(M + NH_4)^+$.

Anal. Calcd for $C_{24}H_{46}O_5Si_2$: C, 61.23; H, 9.85. Found: C, 61.64; H, 9.63.

(3*S*,5*R*,6*S*,8*S*)-3-Ethoxy-5-(hydroxymethyl)-6-hydroxy-8-vinyl-2-oxabicyclo[2.2.2]octane (34). A solution of **33** (22 mg, 0.046 mmol) in THF (2 mL) was treated at 0 °C with a solution of 1 M tetrabutylammonium fluoride in THF (230 mL, 0.23 mmol). The mixture was allowed to warm to rt and kept at that temperature overnight. The solvent was then evaporated and the residue subjected to flash chromatography (PE–EtOAc, 6:4) to afford **34** (8 mg, 76%): $[\alpha]^{21}_D$ +5.5° (*c* 0.9); ^{1}H NMR δ 1.22 (t, *J* = 6.9 Hz, 3H), 1.71 (m, 2H), 1.84 (dt, *J* = 14.4, 4.2 Hz, 1H), 2.04 (m, 1H), 2.46 (m, 1H), 3.46 (m, 1H), 3.66 (dd, *J* = 11.4, 5.7 Hz, 1H), 3.77 (bs, 1H), 3.92 (m, 2H), 4.02 (dd, *J* = 4.2, 3.3 Hz, 1H), 4.19 (dd, *J* = 11.4, 9.3 Hz, 1H), 4.89 (d, *J* = 2.1 Hz, 1H), 5.09 (m, 2H), 5.87 (ddd, *J* = 17.1, 10.2, 6.9, 1H); ^{13}C NMR δ 15.4; 27.6, 37.6, 39.7, 42.3, 62.3, 64.1, 68.6, 71.9, 98.2, 115.5, 140.8; MS 228.1 (M^+); HRMS *m/z* calcd for $C_{12}H_{19}O_4$ $(M - H)^+$ 227.1282, found 227.1285.

(3*S*,5*R*,6*S*,8*R*/*S*)-3-Ethoxy-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]-6-[(*tert*-butyldimethylsilyl)oxy]-8-vinyl-2-oxabicyclo[2.2.2]octane (35c). A solution of diol **27** (6.1 g, 21.2 mmol) in dry DMF (100 mL) was treated sequentially with imidazole (7.2 g, 106 mmol) and *tert*-butyldimethylsilyl chloride (12.8 g, 84.7 mmol). After 16 h, the reaction was quenched by the addition of saturated sodium bicarbonate and the mixture was extracted with Et_2O (2 × 250 mL). The aqueous layer was back-extracted with Et_2O (300 mL), and the combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (PE–EtOAc, 98:2) to provide 10.5 g (96%) of disilylated derivative **35a** as a colorless oil. A solution of the mixture **35a** (10.5 g, 20.3 mmol) in 200 mL of Et_2O was added dropwise to a cooled (0 °C) suspension of lithium aluminum hydride (1.54 g, 40.6 mmol) in Et_2O (30 mL). The mixture was allowed to warm to rt, stirring was continued for 1 h, and then the mixture was recooled to 0 °C. The mixture was diluted with Et_2O (300 mL), and saturated sodium sulfate solution was added dropwise with stirring, until a grainy white precipitate forms. The solids were removed by filtration through a pad of Celite and washed thoroughly with Et_2O. The filtrate was concentrated *in vacuo* and the residue purified by flash chromatography (PE–EtOAc, 8:2) to provide 9.5 g (99%) of a mixture of alcohols **35b** as a clear oil. A cooled solution (0 °C) of these alcohols in 150 mL of dry CH_2Cl_2 was treated sequentially with Et_3N (5.6 mL, 40.0 mmol) and mesyl chloride (2.3 mL, 30.0 mmol). After 30 min, the resulting solution was partitioned between CH_2Cl_2 and water. The aqueous layer was reextracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Diphenyl diselenide (9.4 g, 30.0 mmol) in ethanol (220 mL) was treated with sodium borohydride (2.2 g, 60.0 mmol) in small portions until the solution became colorless. The solution was cooled in an ice bath, the previously prepared mesylates in THF (55 mL) were added and the resulting solution was stirred for 7 h. After the solution was cooled again to 0 °C, 30% hydrogen peroxide (6.8 mL, 200 mmol) was added dropwise. The mixture was stirred at room temperature for 30 min and then heated at 70 °C for 2 h. After cooling, the solution was poured into water and extracted with Et_2O (2 × 300 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (PE–EtOAc, 98:2) to furnish **35c** (7.2 g, 79%): ^{1}H NMR (for two isomers) δ 0.02 (s, 6H), 0.03 (s, 6H), 0.90 (s, 9H), 0.91 (s, 9H), 1.16 (t, *J* = 7.0 Hz, 3H), 1.18 (t, *J* = 7.0 Hz, 3H), 1.64 and 1.73 (m, 1H), 1.85 and 2.08 (m, 1H), 2.01 (m, 1H), 2.36 (m, 1H), 3.28 (m, 1H), 3.81 (m, 3H), 3.95 (m, 1H), 4.10 (m, 1H), 4.82 and 4.93 (m, 1H), 5.08 (m, 2H), 5.76 and 5.93 (m, 1H); ^{13}C NMR (two isomers) δ −4.5, −3.6, 15.1, 15.2, 18.1, 18.4, 25.7, 26.1, 28.4, 28.7, 34.7, 35.7, 36.5, 36.9, 39.6, 44.0, 62.1, 62.2, 62.8, 63.4, 69.2, 69.6, 71.0,71.4, 97.7, 102.0, 114.2, 114.3, 140.3, 141.7; MS *m/z* 474 $(M + NH_4)^+$, 411 $(MH - EtOH)^+$.

Anal. Calcd for $C_{24}H_{48}O_4Si_2$: C, 63.10; H, 10.59. Found: C, 62.96; H, 10.89.

(3*S*,5*R*,6*S*,8*R*)-3-Ethoxy-5-(hydroxymethyl)-6-hydroxy-8-vinyl-2-oxabicyclo[2.2.2]octane (36). A solution of the silyl ethers **35c** (7.2 g, 15.8 mmol) in THF (200 mL) was treated at 0 °C with a solution of 1 M tetrabutylammonium fluoride in THF (63.2 mL, 63.2 mmol). The mixture was allowed to warm to room temperature and kept at that temperature overnight. The solvent was then evaporated and

the residue subjected to flash chromatography (PE–EtOAc, 6:4) to afford 1.2 g (34%) of **36** and 2.2 g (61%) of **34** described above.

For 36: $[\alpha]^{21}_D$ −51.2° (*c* 1.2); ^{1}H NMR δ 1.25 (t, *J* = 7.1, 3H), 1.68 (bs, 1H), 2.11 (m, 2H), 2.37 (m, 2H), 3.53 (m, 2H'), 3.69 (bs, 1H), 3.82 (m, 1H), 3.93 (m, 1H), 4.03 (dd, *J* = 5.8, 3.2 Hz, 1H), 4.22, (t, *J* = 10.5, 1H), 4.78 (d, *J* = 2.2 Hz, 1H)5.11 (m, 2H), 5.81 (ddd, *J* = 16.6, 10.5, 5.8, 1H); ^{13}C NMR δ 15.4, 27.6, 37.6, 39.7, 42.3, 62.8, 64.1, 68.6, 71.9, 98.2, 115.5, 140.8.

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.79; H, 8.96.

The stereochemistry at C-8 was assigned by NOE 9.2% enhancement on H-8 upon irradiation at H-3.

Isomerization of 36 to 34. Ozone was bubbled through a cold (−78 °C) solution of **36** (200 mg, 0.88 mmol) in 10 mL of MeOH until the solution appeared faintly blue. A stream of argon gas was then bubbled through the reaction mixture until the blue color had disappeared. To this solution was added dropwise 2 mL of Me_2S at −78 °C. The mixture was then allowed to warm to room temperature and stirred for 3 h. Concentration *in vacuo* provided the crude aldehyde as a colorless oil. This oil was immediately taken up in 10 mL of methanol, treated with potassium carbonate, and allowed to stir at room temperature for 24 h. The solids were removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was taken up in EtOAc and washed with brine. The aqueous extracts were back-extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. A thoroughly flame-dried flask was charged with a suspension of methyltriphenylphosphonium bromide (1.2 g, 3.52 mmol) in anhydrous THF (10 mL). The mixture was cooled to −20 °C, and BuLi was added dropwise (2.1 mL, 1.6 M solution in hexanes, 3.45 mmol). The mixture was allowed to warm to room temperature for 1 h. A solution of the previously prepared aldehyde in THF (10 mL) was added to the reaction mixture at −20 °C, and this solution was stirred for 3 h while the temperature gradually came to room temperature. Excess reagent-grade acetone was added and after the solution was stirred for 5 min, Et_2O was added and the precipitated solid was filtered off with the aid of Celite. The Celite pad was washed with excess of Et_2O, and the ether solution was concentrated. Purification on silica gel (PE–EtOAc, 6:4) provided **36** (70 mg, 35% yield) and **34** (72 mg, 36% yield).

(3*S*,5*R*,8*S*)-3-Ethoxy-5-(hydroxymethyl)-6-oxo-8-vinyl-2-oxabicyclo[2.2.2]octane (37). Diol **34** (1.06 g, 46 mmol) was refluxed with dibutyltin oxide (1.20 g, 4.8 mmol) for 2 h in toluene (30 mL) in the presence of molecular sieves. The toluene was removed in a vacuum line, and the residue was dried under reduced pressure (0.1 Torr). The residue was taken up in dry chloroform (45 mL), and *N*-bromosuccinimide (827 mg, 4.6 mmol) was added. After 30 min the mixture was concentrated *in vacuo* and the residue purified through a very fast flash chromatography (PE–EtOAc, 8:2) to afford the keto alcohol **37** (818 mg, 78%): ^{1}H NMR δ 1.20 (t, *J* = 7.1 Hz, 3H), 3.20 (dd, *J* = 8.5, 2.7 Hz, 1H), 3.49 (m, 2H), 3.93 (m, 4H), 5.12 (m, 2H), 5.20 (dd, *J* = 6.6, 1.1 Hz, 1H), 5.92 (ddd, *J* = 17.3, 10.4, 6.5 Hz, 1H); ^{13}C NMR δ 15.1, 28.4, 38.4, 41.2, 53.9, 62.1, 64.1, 74.1, 96.8, 116.0, 139.2, 209.5; MS *m/z* 244 $(M + NH_4)^+$, 227 $(MH)^+$, 181 $(MH - EtOH)^+$.

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.52; H, 7.88.

(3*S*,5*R*,6*R*,8*S*)-3-Ethoxy-5-[[(*tert*-butyldiphenylsilyl)-oxy]methyl]-6-hydroxy-8-vinyl-2-oxabicyclo[2.2.2]-octane (39c). A solution of the keto alcohol **37** (816 mg, 3.6 mmol) in EtOAc (10 mL) was added to a solution of sodium triacetoxyborohydride prepared by dissolving sodium borohydride (490 mg, 12.9 mmol) in glacial acetic acid (20 mL) at 0 °C. The resultant mixture was stirred at room temperature for 1 h and then concentrated *in vacuo*. Flash chromatography (PE–EtOAc, 1:2) gave the diol **39a** (722 mg, 88% yield) which was dissolved in dry CH_2Cl_2 (30 mL) and treated with NEt_3 (644 μL, 4.6 mmol), *tert*-butyldiphenylchlorosilane (936 μL, 3.6 mmol), and (dimethylamino)pyridine (DMAP) (36 mg, 0.3 mmol). The mixture stirred at room temperature for 16 h and then diluted with CH_2Cl_2 (100 mL) and washed with water (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography (PE–EtOAc, 9:1) gave **39b** (1.25 g, 85%) as a colorless oil. This material was dissolved in methyl iodide (6 mL), and treated with silver(I) oxide (2.3 g, 10.7 mmol), and stirred in the dark for 2 days at room temperature. The methyl iodide was removed *in vacuo* and the residue was taken up in Et_2O (150 mL). After filtration through Celite, concentration *in vacuo* and flash chromatography (PE–EtOAc, 95:5) afforded **39c** (1.09 g, 85%): $[\alpha]^{21}_D$ +41.7° (*c* 0.8); ^{1}H NMR δ 1.05 (t, *J* = 7.3 Hz, 3H), 1.06 (s, 9H), 1.62 (m, 1H), 1.82 (m, 1H), 2.00 (m, 1H), 2.07 (bs, 1H), 2.49 (m, 1H), 3.29 (m, 1H), 3.32 (s, 3H), 3.67 (m, 1H), 3.96 (m, 3H), 4.82 (d, *J* = 0.9, 1H), 5.09 (m, 2H), 5.88 (ddd, *J* = 17.3, 10.2, 6.9 Hz, 1H), 7.42 (m, 6H), 7.76 (m, 4H); ^{13}C NMR δ 15.3, 19.3, 25.7, 26.9, 37.0, 39.3, 47.7, 57.2, 62.9, 66.8, 67.5, 79.2, 97.9, 114.6, 129.5, 134.1, 135.5, 135.6, 141.6; MS *m/z* 498 $(M + NH_4)^+$, 481 $(MH)^+$.

Anal. Calcd for $C_{29}H_{40}O_4Si$: C, 72.46; H, 8.39. Found: C, 72.28; H, 8.33.

(1*R*,2*R*,3*S*,4*S*,5*S*)-1-Acetyl-3-[[(*tert*-butyldiphenylsilyl)-oxy]methyl]-2-methoxy-4(*E*)-(methoxymethylene)-5-vinylcyclohexan-1-ol (40b). A stirred solution of **39c** (1.09 g, 2.27 mmol) in THF (20 mL) and water (10 mL) was treated with glacial acetic acid (40 mL), heated in an oil bath to 95 °C for 5 h, and concentrated *in vacuo*. The lactols were used without purification in the next step. A flask thoroughly flame dried was charged with a suspension of recrystallized, powdered, and dried (methoxymethyl)triphenylphosphonium chloride (3.1 g, 9.08 mmol) in anhydrous THF (15 mL). The mixture was cooled to 0 °C, and BuLi (5.6 mL, 1.6 M in hexane, 8.99 mmol) was added dropwise. The mixture was stirred at 0 °C to room temperature for 30 min. A solution of the lactols previously prepared (2.27 mmol) in THF (5 mL) was added to the reaction mixture at 0 °C, and the mixture was stirred for 5 h while the temperature came to room temperature. An excess of reagent-grade acetone was added, and the mixture was stirred for 5 min, Et_2O (250 mL) was added, the precipitated solid was washed with excess Et_2O, and the combined ether solutions were washed with saturated sodium bicarbonate, sodium chloride, and water, dried, and concentrated. The residue was purified by flash chromatography (PE–EtOAc, 8:2) to provide a 1:8 mixture of *Z* and *E* methyl vinyl ethers **40a** (795.4 mg, 74% yield). A solution of the material in pyridine (25 mL) was treated with an excess of acetic anhydride. The resulting mixture was stirred for 10 h at room temperature. The reaction was then quenched with saturated aqueous sodium bicarbonate, and the mixture was extracted several times with CH_2Cl_2. The combined extracts were washed with water and dried. Filtration and concentration *in vacuo* gave a residue which was purified by flash chromatography (PE/ethyl acetate, 95:5) to give 815 mg (95% yield) of **40b** as a colorless oil. Major *E*-isomer: $[\alpha]^{21}_D$ −1.7° (*c* 0.4); ^{1}H NMR δ 1.04 (s, 9H), 1.44 (m, 1H), 1.95 (m, 1H), 2.06 (s, 3H), 2.36 (m, 1H), 2.77 (m, 1H), 3.02 (dd, *J* = 11.4, 9.5 Hz, 1H), 3.18 (s, 3H), 3.53 (s, 3H), 3.58 (t, *J* = 9.5 Hz, 1H), 3.88 (dd, *J* = 9.5, 3.7 Hz, 1H), 4.53 (t, *J* = 11.6 Hz, 1H), 4.88 (ddd, *J* = 11.4, 9.3, 5.2 Hz, 1H), 4.96 (2H, m), 5.71 (ddd, *J* = 17.6 Hz, 9.8, 6.8, 1H), 6.35 (d, *J* = 12.4 Hz, 1H), 7.42 (m, 6H), 7.76 (m, 4H); ^{13}C NMR δ 19.3, 21.4, 26.9, 31.0, 39.3, 42.4, 47.6, 56.5, 58.8, 62.1, 76.4, 79.0, 96.1, 113.9, 127.6, 127.7, 129.5, 129.6, 135.6, 140.9, 150.7, 170.4.

Anal. Calcd for $C_{31}H_{42}O_5Si$: C, 71.23; H, 8.10. Found: C, 70.97; H, 8.22.

(1*R*,2*R*,3*S*,4*S*,5*S*)-1-Acetyl-3-(hydroxymethyl)-2-methoxy-4(*E*)-(methoxymethylene)-5-vinylcyclohexan-1-ol (43a). A solution of **40b** (500 mg, 0.95 mmol) in THF (20 mL) was treated at 0 °C with a solution of 1 M tetrabutylammonium fluoride in THF (2.85 mL, 2.85 mmol). The mixture was allowed to warm to room temperature and kept at that temperature overnight. The reaction was then quenched with water and the mixture extracted several times with Et_2O. The organic layer was dried, filtered, and concentrated *in vacuo*. Purification by flash chromatography (PE–EtOAc, 6:4) provided 229.3 mg (85% yield) of desilylated **43a** as a colorless oil. Major isomer: $[\alpha]^{21}_D$ +28.3° (*c* 0.95); ^{1}H NMR δ 1.44 (q, *J* = 12.0 Hz, 1H), 1.84 (m, 1H), 1.97 (m, 1H), 2.09 (s, 3H), 2.40

(m, 2H), 3.34 (dd, J = 10.9, 9.5 Hz, 1H), 3.51 (s, 3H), 3.54 (s, 3H), 3.60 (m, 1H), 3.72 (dd, J = 11.0, 6.4 Hz, 1H), 4.58 (dd, J = 12.2, 10.7 Hz, 1H), 4.88 (ddd, J = 11.5, 9.5, 5.2, Hz, 1H), 4.93 (m, 2H), 5.60 (ddd, J = 17.2, 10.7, 6.6 Hz, 1H), 6.24 (d, J = 12.2 Hz, 1H); ^{13}C NMR δ 20.9, 30.4, 41.1, 42.2, 46.6, 56.1, 59.8, 64.7, 76.6, 81.9, 96.1, 113.9, 139.6 149.4, 169.8.

Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.03; H, 8.14.

(2*S*,3*R*,4*R*,6*R*,7*S*)-4-Acetoxy-3-methoxy-7-(methoxymethylene)-6-vinylcyclohexanecarboxylic Acid Methyl Ester (43b). A solution of 90 mg of the hydroxyl compound **43a** (0.31 mmol) in 6 mL of DMF was treated with pyridinium dichromate (PDC) (700 mg, 1.86 mmol) for 24 h. The reaction was then diluted with Et_2O (200 mL) and washed with 0.5 N HCl (2 × 20 mL). The organic layers were washed with brine (20 mL), and the combined aqueous layers were back-extracted with Et_2O. The organic layers were dried, filtered, and concentrated *in vacuo*. The residue was then taken up in 15 mL of methanol and treated at 0 °C with (trimethylsilyl)-diazomethane (TMS-CHN_2) (0.31 mL of a 2 M solution in hexanes, 0.62 mmol). After 30 min, the mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (PE−EtOAc, 9:1) to provide 77 mg (78% yield) of pure **43a** as white needles: mp 70−72 °C; $[\alpha]^{21}_D$ −66.6° (*c* 0.40); ^{1}H NMR δ 1.44 (q, J = 12.7 Hz, 1H), 1.95 (m, 1H), 2.09 (s, 3H), 2.41 (m, 1H), 2.60 (m, 1H), 2.68 (dd, J = 11.0, 4.6 Hz, 1H), 3.51 (s, 3H), 3.65 (s, 3H), 3.66 (m, 1H), 4.57 (t, J = 12.0 Hz, 1H), 4.80 (ddd, J = 11.4, 9.5, 4.9 Hz, 1H), 4.94 (m, 2H), 5.58 (ddd, J = 10.7, 7.0, 1.3 Hz, 1H), 6.16 (d, J = 12.0, 1H); ^{13}C NMR δ 20.9, 30.0, 41.5, 41.9, 51.1,52.2, 55.6, 60.2, 77.0, 95.5, 114.3, 139.2, 149.4 ,169.8, 171.2; MS *m/z* 330 $(M + NH_4)^+$; HRMS *m/z* calcd for $C_{16}H_{24}O_6$ $(MH)^+$ 313.1573, found 313.1649.

Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.50; H, 7.74. Found: C, 61.28; H, 7.52.

(3*S*,4*S*,5*R*,6*R*,8*S*)-6-Acetoxy-4-carbomethoxy-5-methoxy-8-vinylcyclohexane Acetic Acid Methyl Ester (3). A stirred solution of **43b** (60 mg, 19 mmol) in THF (860 μL) and water (430 μL) was treated with glacial acetic acid (1.71 mL), heated in an oil bath to 90 °C for 9 h, and concentrated *in vacuo*. The resulting aldehyde was taken up in DMF (4 mL), treated with PDC (214 mg, 0.57 mmol), and allowed to stir at room temperature for 48 h. The reaction was then diluted with Et_2O (150 mL) and washed with 0.5 N HCl (2 × 20 mL). The organic layers were washed with brine (20 mL), and the combined aqueous layers were back-extracted with Et_2O. The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was then taken up in 15 mL of methanol and treated at 0 °C with a 2 M solution of TMS-CHN_2 in hexane (0.19 mL, 0.38 mmol). After 30 min, the mixture was concentrated *in vacuo*, and the residue was purified by flash chromatography (PE−EtOAc, 9:1) to provide 40 mg of **3** (64% yield) as a colorless oil: $[\alpha]^{21}_D$ −35.5° (*c* 0.8); ^{1}H NMR δ 2.07 (m, 1H) 2.10 (s, 3H), 2.46 (m, 2H), 2.68 (dd, J = 11.2, 4.1 Hz, 1H), 2.81 (m, 1H), 3.46 (s, 3H), 3.63 (s, 3H), 3.65 (m, 1H), 3.67 (s, 3H), 4.57 (t, J = 12.0 Hz, 1H), 4.79 (ddd, J = 11.5, 9.5, 5.1 Hz, 1H), 5.04 (m, 2H), 5.72 (1H, ddd, J = 17.3, 10.7, 4.7 Hz, 1H); ^{13}C NMR δ 21.3, 29.1, 29.2, 36.1, 41.1, 51.2, 51.7, 52.0, 60.4, 76.6, 78.3, 115.9, 138.3, 170.2, 172.7, 173.0; MS *m/z* 346 $(M + NH_4)^+$; HRMS *m/z* calcd for $C_{16}H_{24}O_7$ $(MH)^+$ 329.1600, found 329.1586.

Anal. Calcd for $C_{16}H_{24}O_7$: C, 58.5; H, 7.37. Found: C, 58.15; H, 7.09.

Amide 44. Ozone gas was bubbled through a cold (−78 °C) solution of **3** (20 mg, 0.06 mmol) in 5 mL of MeOH until the solution appeared faintly blue. A stream of argon gas was then bubbled through the reaction mixture until the blue color had dissipated. To this colorless solution was added dropwise 0.5 mL of Me_2S at −78 °C. The mixture was then slowly warmed to room temperature and stirred for 2 h. Concentration *in vacuo* provided the crude aldehyde **2** as an oil. Following the procedure of Woodward,[6] the above-mentioned **2** was taken up in 1.0 mL of 5:1 benzene/MeOH, treated with a solution of 6-methoxytryptamine (14 mg, 0.07 mmol) in 1 mL of 5: benzene/MeOH, and allowed to stir at room temperature for 15 min. The solvents were then evaporated (the temperature of the solution being kept below 45 °C at all times) to give a yellow oil. This oil was immediately taken up in 5 mL of methanol and treated with $NaBH_4$ (44 mg, 1.1 mmol) at 0 °C until the last of the $NaBH_4$ had been consumed; the reaction mixture was then refluxed for 8 min, poured into 50 mL of 5% HCl, and extracted with CH_2Cl_2 (2 × 20 mL) and the extracts were dried ($MgSO_4$) and concentrated. To recover any material which might have been lost by saponification, the oil was treated with an excess of TMS-CHN_2 and the solvents were evaporated. The residue was taken up in 1.2 mL of pyridine, treated with 0.8 mL of Ac_2O, and allowed to stand for 12 h. The reaction was concentrated and the residue dissolved in CH_2Cl_2, shaken with $NaHCO_3$, washed with HCl and brine and dried. Preparative TLC (EtOAc) afforded lactam **44** (7 mg, 26%) as a yellow foam: $[\alpha]^{21}_D$ −7.3° (*c* 0.6); ^{1}H NMR δ 1.42 (q, J = 11.3 Hz, 1H), 1.59 (dt, J = 11.3, 5.1 Hz, 1H), 1.94 (m, 1H), 2.09 (s, 3H), 2.28 (m, 2H), 2.38 (m, 2H), 2.59 (dd, J = 10.9, 3.9 Hz, 1H), 2.86 (d, J = 12.5 Hz, 1H), 2.96 (t, J = 7.3 Hz, 2H), 3.39 (dd, J = 12.5 Hz, 4.9 Hz, 1H), 3.48 (s, 3H), 3.70 (m, 3H), 3.72 (s, 3H), 3.84 (s, 3H), 4.66 (ddd, J = 11.3, 9.6, 5.1 Hz, 1H), 6.79 (d, J = 8.3 Hz, 1H), 6.80 (s, 1H), 6.90 (s, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.89 (bs, 1H); ^{13}C NMR δ 21.3, 23.0, 28.9, 29.9, 32.1, 33.9, 48.3, 50.9, 52.0, 52.3, 55.6, 61.0, 76.4, 77.2, 94.7, 109.4, 113.0, 119.3, 120.6, 122.0, 136.9, 156.6, 167.2, 170.4, 171.4; MS *m/z* 473 $(MH)^+$; HRMS *m/z* calcd $C_{25}H_{32}O_7N_2$ $(MH)^+$ 473.5483, found 473.2278.

Anal. Calcd for $C_{25}H_{32}O_7N_2$: C, 63.55; H, 6.83. Found: C, 63.12; H, 6.42.

Supplementary Material Available: Listings of analytical data for **6-*epi*-20**, **21b**, **6-*epi*-22**, **23a**, **25b**, **26a**, **28**, **35a**, **35b**, **39b**, **39c**, and **40a** (6 pages). This material is contained in 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.

JO942069T