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# Microbial Oxidation of Chloroaromatics in the Enantiodivergent Synthesis of Pyrrolizidine Alkaloids: Trihydroxyheliotridanes

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Both enantiomers of the pyrrolizidine alkaloid trihydroxyheliotridane 1 have been prepared in an efficient and stereocontrolled fashion in 10 steps. Key steps involve the microbial oxidation of chlorobenzene with *Pseudomonas putida* to afford chiral cyclohexadienediol 4 with high enantiomeric excess and its conversion to lactone 7, from which either enantiomer of azide 18 can be prepared. The azides are converted to the title compounds via a [4 + 1] pyrroline annulation based on an intramolecular azide–diene cycloaddition/thermal rearrangement.

## Introduction

We report a simple and efficient method for the preparation of either enantiomer of highly oxygenated pyrrolizidine alkaloids of the trihydroxyheliotridane class 1 (Figure 1).[2] Such an approach is highly desirable for two reasons: first, it provides natural or unnatural members of a class of compounds that are endowed with a vast range of biological activities, and second, it sets the stage for the preparation of the indolizidine homologues of this series such as castanospermine or swainsonine, compounds that are the focus of attention because of their cytotoxic properties.[3]

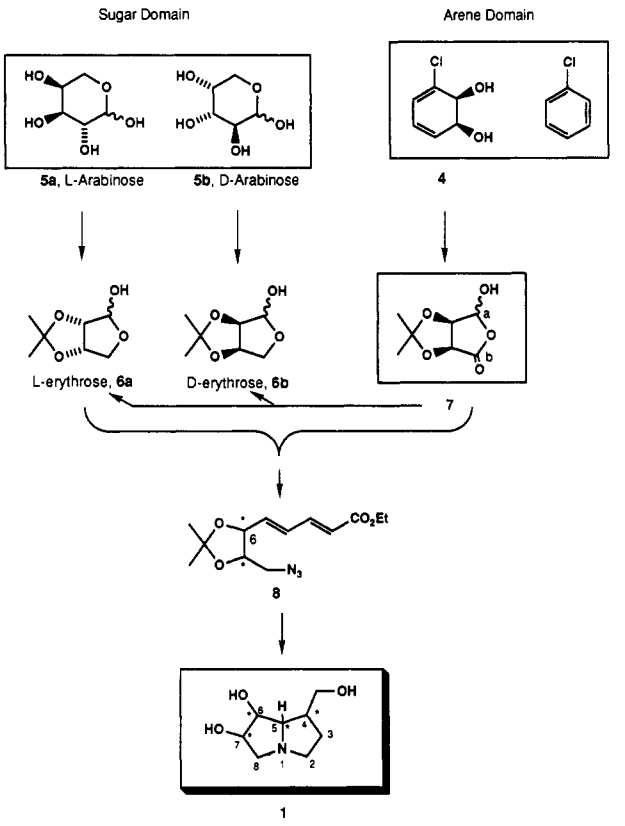
## Results and Discussion

Our approach is based on the combination of the [4 + 1] pyrroline annulation, which relies on the intramolecular azide–diene cycloaddition methodology recently developed in our laboratories,[4] with the use of chiral synthons **6a**, **6b**, and **7**. The intramolecular cyclization of azido dienes to afford vinylaziridines represents a formal [4 + 1] union of a nitrene with a 1,3-diene. Pyrolysis of the intermediate vinylaziridines, or low-temperature rearrangements using TMSI, have provided for a reliable pyrroline annulation technology.[4]

Chamberlin[5] and we have shown that complete control of stereochemistry at C-4, C-5, and C-6 can be achieved in the racemic series of pyrrolizidine diols.[4,6] The C-4 center is set endo during vinylaziridine–pyrroline rearrangement, and the ester at this center can be either reduced or epimerized quantitatively to the more stable exo configuration.[6] Chamberlin[5] and others[7] have shown that the C-5 and C-6 centers are controlled by redox manipulations and base-catalyzed epimerization of C-5 keto derivatives, thereby providing for a stereocontrolled synthesis of *any* diastereomeric combinations at C-4, -5, and -6 of pyrrolizidinediols. To achieve the control of absolute stereochemistry in **1**, it remained to set chirality at C-6 and C-7 in the precursory azido diene 8, since the C-6 center has been shown to *completely control the remaining relative stereochemistry*.[6]

The chiral synthons **6** and **7** are derived either by manipulations of chloro dienediol 4[8] or from the two enan-

**Scheme I**




(1) Recipient of the Research Career Development Award, 1984–1989, National Institutes of Health (AI-00564).

(2) (a) Dihydroxyheliotridane: Danishefsky, S.; McKee, R.; Singh, R. K. *J. Am. Chem. Soc.* **1977**, *99*, 7711 and references therein. (b) Trihydroxyheliotridane is a diastereomer of dihydrocrotanecine. (c) For a recent synthesis of crotanecine see: Bennett, R. B. III; Cha, J. K. *Abstracts of Papers*; 41st Southeast Regional Meeting of the American Chemical Society, Winston-Salem, NC; American Chemical Society: Washington, DC, 1989; Abstract 355. Recent reviews on pyrrolizidine synthesis: (d) Ikeda, M.; Sato, T.; Ishibashi, H. *Heterocycles* **1988**, *27*, 1465. (e) Hudlicky, T. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1989; Vol. 3, p 3. (f) Pearson, W. H. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1, p 323. (g) Nishimura, Y. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1, p 227.

(3) (a) Castanospermine: Hamana, H.; Ikota, N.; (b) Ganem, B. *J. Org. Chem.* **1987**, *52*, 5492 and references therein. Swainsonine: (c) Bennett, R. B. III; Choi, J.-R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2580. (d) Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron Lett.* **1984**, 1853 and references therein. Reviews: (e) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1987; Vol. 5, Chapter 1.

(4) (a) Hudlicky, T.; Seoane, G.; Seoane, A.; Frazier, J. O.; Kwart, L. D.; Tiedje, M. H.; Beal, C. *J. Am. Chem. Soc.* **1986**, *108*, 3755. (b) Hudlicky, T.; Frazier, J. O.; Kwart, L. D. *Tetrahedron Lett.* **1985**, *26*, 3527. (c) Pearson, W. H. *Tetrahedron Lett.* **1985**, 3528. (d) Hudlicky, T.; Sinai Zingde, G.; Seoane, G. *Synth. Commun.* **1987**, *17*, 1155.

(5) Chamberlin, A. R.; Chung, J. Y. L. *J. Org. Chem.* **1985**, *50*, 4425.

(6) Hudlicky, T.; Seoane, G.; Lovelace, T. C. *J. Org. Chem.* **1988**, *53*, 2094.

(7) (a) Aasen, A. J.; Culvenor, C. C. J.; Smith, L. W. *J. Org. Chem.* **1969**, *34*, 4137. (b) Aasen, A. J.; Culvenor, C. C. *Aust. J. Chem.* **1969**, *22*, 2657.

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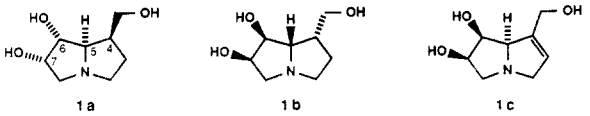
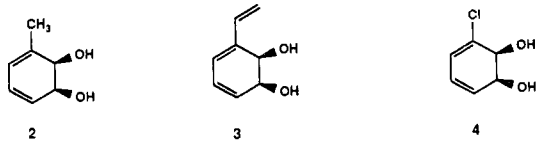


1a 1b 1c

**Figure 1.** Trihydroxyheliotridanes and crotanecine.



2 3 4

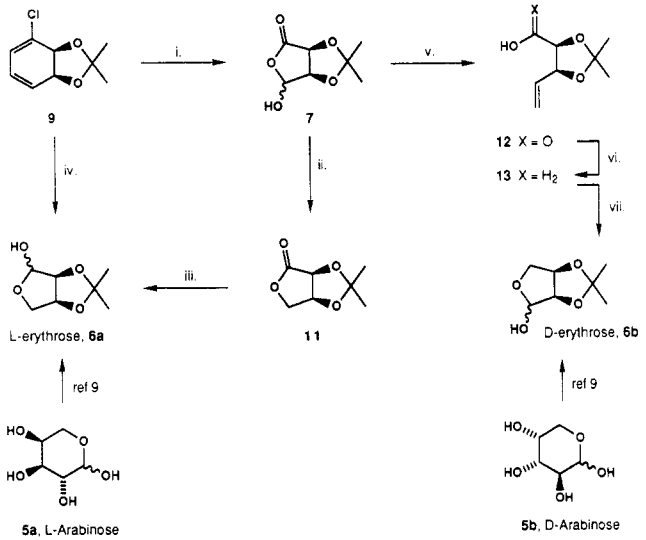
**Figure 2.** Arene-*cis*-diols.

tiomeric series of arabinose **5** (Scheme I).[9] Enantiodivergence is realized upon the recognition that *either* functionality a or b in hydroxy lactone **7** can become *either* the azide or the diene in ester **8**. Thus hydroxy lactone **7**, a formal *chiral equivalent of meso-tartaric acid*, serves the function of *either* enantiomer of tartarate through functional inversion of its carbonyl moieties, which would, of course, not be possible with meso-tartarate. The advantage of using arenediols rather than sugars to furnish precursors such as **6** or **7** is evident because of the brevity and the cost of the preparations.[8c] Although sugars have been used extensively in the preparation of chiral synthons of this type, multistep manipulations or enantiomerically different starting materials are required to cross over the enantiomeric domains. The oxidation of substituted aromatics with *Pseudomonas putida* provides additionally a possibility of preparation of sugar derivatives by simple procedures.[8c] The strategy used in the approach to the stereocontrolled synthesis of pyrrolizidines is shown in Scheme I.

Use of microorganisms for the construction of chiral synthons has become increasingly common in organic synthesis.[10] Nearly twenty years ago, Gibson and coworkers reported the controlled microbial oxidation of several benzene derivatives to cyclohexadienediols by employing genetically manipulated strains of *Pseudomonas putida*.[11] Despite the operational simplicity and complete stereospecificity of the reaction, little use of this transformation has been made in organic synthesis, save for recent reports by Ley[12] and by us.[8] The reaction proceeds under exceedingly mild conditions and tolerates a variety of functional groups attached to the benzene ring, while providing for the introduction of two chiral centers as in the *cis*-diols **2–4** (Figure 2).

Recently, we have reported a four-step enantioselective synthesis of a prostaglandin intermediate in the shortest route to $PGE_{2\alpha}$,[8a] which was obtained by combination of chiral pool reagents derived from the microbial oxidation of toluene with Johnson's procedure for the attachment

**Scheme II**[a]




[a] Reagents: (i) $O_3$, EtOAc; then DMS, 34%; (ii) $NaBH_4$, MeOH, 75%; (iii) DIBAL, $CH_2Cl_2$, 82%; (iv) $O_3$, EtOAc; then $NaBH_4$, 52%; (v) $Ph_3PBrCH_3$, BuLi, $CH_2Cl_2$, 60%; (vi) LAH, $Et_2O$, 95%; (vii) $O_3$, $CH_2Cl_2$; then DMS, 55%.

of prostaglandin side chains.[13] Styrenediol **3** has been utilized by us in an enantioselective synthesis of the cyclohexene (−)-zeylena.[8b] Herein, we report an efficient and enantiodivergent approach to both enantiomers of the pyrrolizidine alkaloid trihydroxyheliotridane **1** via chiral erythrose derivatives obtained by the microbial oxidation of chlorobenzene.

Chlorobenzene was oxidized by using the procedure adapted from toluene diol preparation.[8a] Diol **4** was protected as its acetonide. Ozonolysis, followed by reductive workup with DMS, led to hydroxy lactone **7**.[14] Divergence into both enantiomeric series of erythrose was made possible at this point by controlling the site of reduction at either carbon a or b in the hydroxy lactone (Scheme II). Reduction of **7** with $NaBH_4$ at the aldehyde site (carbon b) led to lactone **10**, which upon further reduction with DIBAL afforded protected L-erythrose **6a**. A more direct route to **6a** was obtained when the ozonide of **9** was reacted with $NaBH_4$ as opposed to DMS. In this case the lactol was obtained directly. The enantiomer of **6a** was prepared by subjecting the hydroxy lactone to Wittig olefination, followed by reduction of acid **12** at carbon a to vinyl alcohol **13**. This compound cyclized spontaneously to protected D-erythrose **6b** upon ozonolysis.

The enantiomeric integrity of the erythroses obtained from chlorobenzene was determined by their independent synthesis from L- and D-arabinose.[9] These compounds proved identical in all respects. The independent synthesis also established that optically active sugars are accessible from arenes via a protocol involving the tandem microbial oxidation/chemical synthesis. This is significant as these erythroses are frequently used as chiral synthons in the synthesis of complex natural products.[15] It should also be pointed out that an operation, such as addition of a nucleophile, that is performed on either **6a** or **6b** can be performed on **7** with identical enantiodivergence. Thus

(8) (a) Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 4735. (b) Hudlicky, T.; Seoane, G.; Pettus, T. *J. Org. Chem.* **1989**, *54*, 4239. (c) Hudlicky, T.; Luna, L.; Price, J. D.; Rulin, F. *Tetrahedron Lett.* **1989**, *30*, 4053. (d) Hudlicky, T.; Price, J. D. *Synth. Lett.* **1990**, 159.

(9) Ballou, C. E. *J. Am. Chem. Soc.* **1957**, *79*, 165.

(10) (a) Empie, M. N.; Gross, A. *Annu. Rep. Med. Chem.* **1988**, *23*, 305. (b) Klibanov, A. M. *ChemTech* **1986**, 354. (c) Butt, S.; Roberts, S. M. *Nat. Prod. Rep.* **1986**, 489; *Chem. Br.* **1987**, 127. (d) Whitesides, G. M.; et al. *Chem. Br.* **1987**, 645.

(11) (a) Gibson, D. T.; Hensley, M.; Yoshika, H.; Mabry, R. J. *Biochemistry* **1970**, *9*, 1626. (b) Gibson, D. T.; Mahaderan, V.; Davey, J. F. *J. Bacteriol.* **1974**, *119*, 1626. (c) Gibson, D. T.; Koch, J. R.; Kallio, R. E. *Biochemistry* **1968**, *7*, 2653.

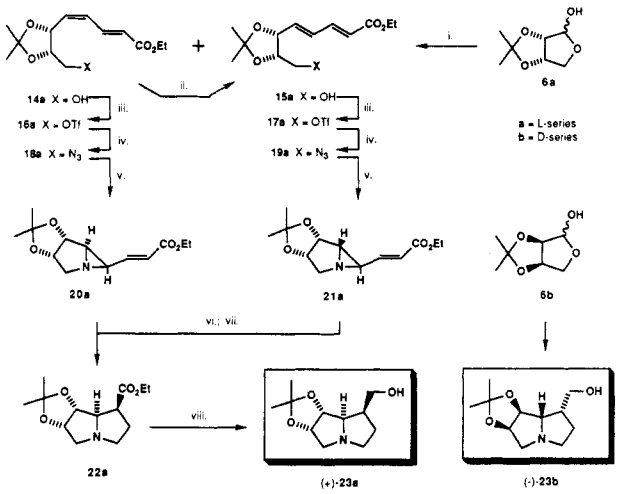
(12) (a) Ley, S. V.; Sternfeld, F. *Tetrahedron Lett.* **1988**, *29*, 5305. (b) Ley, S. V.; Sternfeld, F.; Taylor, S. *Tetrahedron Lett.* **1986**, *27*, 225. (c) Ley, S. V.; Sternfeld, F. *Tetrahedron Lett.* **1989**, 3463; **1988**, 5305. (d) Carless, H. A. J.; Busia, K. *Tetrahedron Lett.* **1990**, 1617.

(13) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1986**, *108*, 5655.

(14) Beer, D.; Meuwly, R.; Vasella, A. *Helv. Chim. Acta* **1982**, *65*, 2571.

(15) (a) For a review of carbohydrates in organic synthesis, see: Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach*; Pergamon Press: Oxford, 1983. (b) For the use of lactol **6** in organic synthesis, see: Williams, D. R.; Klinger, F. D. *J. Org. Chem.* **1988**, *53*, 2134.

**Scheme III**[a]



[a] Reagents: (i) $Ph_3P{=}CHCH{=}CHCO_2Et$, $CH_2Cl_2$ 84%; (ii) $I_2$, $CH_2Cl_2$, 94%; (iii) $Tf_2O$, py, $CH_2Cl_2$; (iv) $NaN_3$, 18-C-6, $CH_2Cl_2$, 69% two steps; (v) $C_6H_6$, reflux, 44%; (vi) FVP, 520 °C, ca. $10^{-4}$ Torr; (vii) $H_2$, Pd/C, MeOH; (viii) $LiAlH_4$, THF, 34% three steps.

a realistic estimate of yield is the preparation of **7** from chlorobenzene (50% overall), since the actual conversion to **6a** and **6b** may be unnecessary in many applications.[16]

Wittig reaction of **6a** with $Ph_3P{=}CHCH{=}CHCO_2Et$ produced a 5:1 mixture of (*Z*,*E*)- and (*E*,*E*)-dienols **14** and **15**, respectively. These proved separable by flash chromatography. Preparatively useful samples of the (*E*,*E*)-diene could be obtained by treating the mixture with $I_2$, resulting in a nearly quantitative isomerization of **14** to **15**. To investigate the diastereomeric course of the [4 + 1] pyrroline annulation, both dienyl alcohols, **14** and **15**, were converted to azido dienes **18** and **19** via their respective triflates. Subjecting **18** to reflux in benzene resulted in smooth conversion to vinylaziridine **20**. As reported for 1,3-dipolar cycloadditions of azides to olefins, the *Z* stereochemistry of the olefin was retained resulting in cis aziridine formation (cis hydrogen substitution).[6] In a similar fashion azido diene **19** was converted to trans aziridine **21**. The relative stereochemistry of these compounds was confirmed by $^1H$ NMR analysis, including NOE experiments. Irradiation of the allylic hydrogen in the cis isomer **20** resulted in a 6% enhancement of the bridgehead hydrogen, whereas irradiation of the allylic hydrogen in the trans isomer **21** resulted in no enhancement of the bridgehead hydrogen. The relative stereochemistry of the bridgehead protons with respect to the adjacent alkoxide hydrogens was determined by decoupling experiments.

Pyrolysis of either vinyl aziridine furnished 2,3-dehydro-**22a** as a single isomer. This unstable enamine was hydrogenated immediately to **22a**. Subsequent reduction with $LiAlH_4$ afforded (+)-trihydroxyheliotridane (**1a**) as the protected acetonide **23a**. The predicted relative stereochemistry about carbons 4, 5, 6, and 7 was confirmed by NMR analysis as well as by X-ray crystallography.[17] In an identical fashion, lactol **6b** was converted to (−)-trihydroxyheliotridane (**23b**), the protected enantiomer of **1a**.

This sequence demonstrated that the presence of additional oxygenation in the starting azido dienes does not change the steric course of the vinylaziridine formation, nor does it interfere with the stereoselectivity of pyrroline rearrangement. Thus the entire process is stereoselective and applicable to both enantiomers when absolute stereochemistry is incorporated into the starting materials. Finally, either **22** or its 2,3-dehydro isomer obtained from pyrolysis may be functionalized according to literature methods to the unsaturated pyrrolizidine crotanecine (**1c**).

## Conclusion

In summary, an enantiodivergent approach to oxygenated pyrrolizidines in under 10 steps from chlorobenzene has been furnished as a prelude to synthetic ventures toward oxygenated indolizidine bases such as castanospermine. Details of these endeavors will be reported in due course. Significantly, the [4 + 1] pyrroline annulation methodology developed within our group has been successfully coupled with the use of chiral pool reagents derived via microbial oxidation of aromatics.

## Experimental Section[19]

**(2*S*,3*S*)-2,3-*O*-Isopropylidene-1-chlorocyclohexa-4,6-diene (9).** To a solution of dienediol **4**[11a] (736.5 mg, 4.646 mmol), in 10 mL of 2,2-dimethoxypropane (DMP)–acetone (3:1) was added a catalytic amount of *p*-toluensulfonic acid, and the reaction mixture was stirred at room temperature, protected from moisture, for 30 min. To the mixture was added 5 mL of 10% aqueous NaOH, and the reaction mixture was stirred for 10 min. The reaction mixture was diluted with 10 mL of ethyl acetate, and the organic layer was washed with brine (3 × 5 mL). The organic extracts were dried over sodium sulfate, and the solvent was evaporated, yielding 832 mg (95%) of a colorless liquid: $R_f$ = 0.8 (hexane–ethyl acetate, 8:2); $[\alpha]^{25}_D$ = +45° (*c* 0.50, $CHCl_3$); IR (neat) 2988, 2935, 2898, 1652, 1380 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 6.05 (d, *J* = 5.5 Hz, 1 H), 5.85 (m, 2 H), 4.7 (dd, *J* = 3.4 Hz, *J* = 8.8 Hz, 1 H) 4.57 (d, *J* = 8.8 Hz, 1 H), 1.36 (s, 6 H); $^{13}C$ NMR ($CDCl_3$) δ 133.3, 124.0, 123.2, 121.6, 106.3, 74.7, 72.6, 26.6, 24.9.

**2,3-*O*-Isopropylidene-L-erythruronolactone (7).** A solution of diene **9** (94 mg, 0.5 mmol) in 7 mL of ethyl acetate was cooled to −78 °C, and a stream of $O_2/O_3$ was passed through until the persistance of a blue color. Nitrogen was bubbled through the solution to remove the excess ozone. Dimethyl sulfide (DMS, 1.4 mL) was added, and the temperature was immediately raised to 0 °C. The reaction was stirred for 12 h and then diluted with 30 mL of ether. The ethereal solution was washed with water (1 × 5 mL) and brine (1 × 5 mL). The solution was dried ($Na_2SO_4$) and filtered, and the solvent was evaporated, yielding 70.7 mg of crude product (80%). After purification (chromatography, 10% deactivated silica gel, methylene chloride/acetone, 7:3), 30.4 mg of clean product was obtained (34.4%): $R_f$ = 0.2 (silica gel; chloroform/methanol, 8:2); $[\alpha]^{25}_D$ = −60° (*c* 1.0, $CHCl_3$); IR (KBr) 3400, 1723 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.81 (s, 1 H), 4.91 (m, 1 H), 4.60 (d, 1 H, *J* = 5.4 Hz), 1.47 (s, 3 H), 1.40 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 174, 114, 99, 95, 80, 74, 27, 26 ppm. Spectral data were

(16) A realistic cost estimate for lactols **6a** and **6b** is $2.40/g from arabinoses, and $1.40/g from chlorobenzene. Labor is comparable for the two processes. The overall yield of lactol **6a** from chlorobenzene was 45%. This compares with a yield of 39% from arabinose.

(17) Private communication, Dr. Joseph Merola, Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061.

(18) Lager, W.; Hafele, B. *Synthesis* **1987**, 803.

(19) All nonhydrolytic reactions were carried out in a nitrogen or argon atmosphere, with standard techniques for the exclusion of air and moisture. Glassware used for moisture-sensitive reactions was flame-dried with an internal inert gas sweep. THF, ethyl ether, DME, and benzene were distilled from benzophenone ketyl, dichloromethane, and toluene from calcium hydride. Analytical TLC was performed on silica gel 60F-254 plates. Flash chromatography was performed using Kieselgel 60 (230–400 mesh). Mass spectra were recorded on a DuPont 20-491 or a Varian MAT-112 instrument (low resolution) or on a double-focusing DuPont 21-110C or VGT instrument (exact mass). Infrared spectra were recorded as neat samples (NaCl plates) on a Perkin-Elmer 1600 Series FT spectrometer. Proton NMR spectra were obtained on a Bruker WP-270 instrument. Proton chemical shifts are reported in parts per million (ppm) relative to chloroform (7.24 ppm). Carbon NMR spectra were recorded on a Bruker WP-270 instrument. Carbon chemical shifts are reported in parts per million relative to the center line of the $CDCl_3$ triplet (77.0 ppm). The multiplicity is indicated by $CH_3$, $CH_2$, CH, or C and were determined by INEPT experiments.

in agreement with literature values: $[\alpha]^{25}_D$ = −54.6° (c 1.25, $CHCl_3$).[14]

**2,3-*O*-Isopropylidene-L-erythrose (6a). Method A.** A solution of 78.4 mg (0.5 mmol) of diene **9** in 7 mL of methanol–methylene chloride (8:2) was cooled to −78 °C, and a stream of $O_3/O_2$ was passed through until the persistance of a blue color. Nitrogen was bubbled through the solution to remove excess ozone. To the stirred reaction, at −78 °C under nitrogen atmosphere, was added 36 mg (0.5 mmol) of $NaBH_4$, stirring was continued for 1 h, the temperature was raised to 0 °C, and the solution was stirred for an additional hour. After that, 10 drops of a saturated aqueous solution of $NH_4Cl$ was added, and the solvent was removed under reduced pressure, without heating. The semisolid residue was taken up in ethyl acetate (5 mL) and filtered; this operation was repeated twice. The combined organic extracts were evaporated to produce 74 mg of a colorless viscous liquid. Separation by preparative TLC (silica gel; hexanes–ethyl acetate, 6:4) produced the following. **2,3-*O*-Isopropylidene-4-*O*-methyl-L-erythruronolactone** (11.6 mg, 12%): $R_f$ = 0.55 (silica gel; ethyl acetate–hexane, 1:1); mp 76–78 °C; $[\alpha]^{25}_D$ = −66.35° (c 4.75, MeOH); IR (neat) 2985, 2920, 1710 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.34 (s, 1 H), 4.8 (d, J = 5.5 Hz, 1 H), 4.55 ( d, J = 5.5 Hz, 1 H), 3.53 (s, 3 H), 1.46 (s, 3 H), 1.38 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 114 (C), 105 (C), 79 (CH), 74 (CH), 60 (CH), 26 (CH), 25 (CH); MS (CI) calcd for $C_8H_{12}O_5$ 188.07629, found 188.07574. **2,3-*O*-Isopropylidene-L-erythrose (6a)** (41.6 mg, 52%): $R_f$ = 0.34; $^1H$ NMR ($CDCl_3$) δ 5.4 (d, 1 H), 4.85 (m, 1 H), 4.59 (d, 1 H), 4.05 (m, 2 H), 1.48 (s, 3 H), 1.32 (s, 3 H); spectral data were in agreement with literature values $[\alpha]^{25}_D$ = +75° (c 1.0, $CH_3OH$).[9]

**Method B.** To a solution of L-erythruronolactone **7** (17.4 mg, 0.10 mmol) in methanol (2 mL) was added 5 mg (0.13 mmol) of $NaBH_4$. The mixture was stirred at room temperature for 15 min and diluted with a further 4 mL of methanol, and MeI was added (0.5 mL). This solution was heated to reflux for 8 h and evaporated to dryness, and the residue was extracted with $CHCl_3$ (3 × 10 mL). After evaporation, purification by chromatography (silica gel; EtOAc–hexane, 1/1) afforded 9.1 mg (0.075 mmol, 75%) of **2,3-*O*-isopropylidene-L-erythrolactone (11)**: $R_f$ = 0.50 (hexane–EtOAc, 1:1); mp 64 °C $[\alpha]^{25}_D$ = +106° (c 0.91, acetone). Spectral data were in agreement with literature values: $[\alpha]^{25}_D$ = +105° (c 1.0, $H_2O$).[18] To a solution of lactone **11** (9.1 mg, 0.057 mmol) in 4 mL of $CH_2Cl_2$ at −78 °C was added 0.08 mL of a 1 M hexane solution of DIBAL. The reaction was stirred for 4 h and quenched by the addition of MeOH and $H_2O$. The solution was diluted with EtOAc (5 mL), and the pH was carefully adjusted to 3 by the addition of dilute sulfuric acid. The organic fraction was concentrated, leaving a yellow oil which after chromatography (silica gel; EtOAc–hexane, 6:4) afforded 7.5 mg (0.047 mmol, 82%) of 2,3-isopropylidene-L-erythrose **6a**, identical with material obtained by method A above.

**(2*S*,3*S*)-2,3-*O*-Isopropylidene-4-pentenoic Acid (12).** To a solution of triphenylmethylphosphonium bromide (1.07 g, 3.0 mmol) in THF was added 3.1 mmol of *n*-BuLi (1.2 mL, 2.5 M in hexane) at 0 °C. After warming to 25 °C, 174 mg (1.0 mmol) of hydroxy lactone (**7**) in 5 mL of THF was added. The solution was heated to relfux for 1 h and then stirred at 25 °C for 8 h. The reaction mixture was poured into $H_2O$ (30 mL). The aqueous layer was washed with ether (3 × 15 mL), acidified with acidic resin (Amberlite IR-120), and extracted with $CH_2Cl_2$ (3 × 30 mL). The $CH_2Cl_2$ fractions were combined, dried ($Na_2SO_4$), and concentrated. Purification by Kugelrohr distillation (90–100 °C, 0.005 mm) afforded 103 mg (60%) of the vinyl acid **12** as a colorless oil: $[\alpha]^{25}_D$ = +22.8° (c 2.60, $CHCl_3$). Spectral data were in agreement with literature values: $[\alpha]^{20}_D$ = +24° (c 1.56, $CHCl_3$).[18]

**(2*R*,3*S*)-2,3-*O*-Isopropylidene-4-pentenol (13).** To a solution of 52 mg (0.30 mmol) of pentenoic acid **12** in ether (10 mL) was added 45 mg (1.2 mmol) of LAH at 0 °C. The mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched by the addition of $H_2O$ (45 μL) and 15% aqueous NaOH (150 μL), and the solution was filtered through a short column of silica gel. Concentration afforded 45 mg (95%) of pure alcohol **13**: $[\alpha]^{25}_D$ = +41.0° (c 2.25, $CHCl_3$); $R_f$ = 0.50 (hexane–EtOAc, 1:1) Spectral data were in agreement with literature values: $[\alpha]^{20}_D$ = +44° (c 4.89, $CHCl_3$).[18]

**2,3-*O*-Isopropylidene-D-erythrose (6b).** Pentenol **13** (158 mg, 1.00 mmol) was dissolved in $CH_2Cl_2$ (10 mL), and ozone was bubbled through the solution at −78 °C until persistance of a blue color. Excess ozone was removed by a stream of $N_2$. Dimethyl sulfide (0.2 mL) was added, and the solution was stirred for 4 h at room temperature. The reaction mixture was washed with $H_2O$ (5 × 5 mL), dried ($Na_2SO_4$), and concentrated. Purification by flash chromatography (silica gel; EtOAc–hexane, 6:4) afforded 88 mg (0.55 mmol, 55%) of lactol **6b**: $[\alpha]^{25}_D$ = −71° (c 3.02, $CHCl_3$); $R_f$ = 0.50. Spectral data were in agreement with literature values: $[\alpha]^{25}_D$ = −77.0° (c 2.09, $CHCl_3$).[6] Additionally, this material proved identical to a sample prepared from D-arabinose.[9]

**Ethyl 8-Hydroxy-(6*R*,7*S*)-6,7-*O*-isopropylidene-(2*E*,4*Z*)-octadienoate (14a) and Ethyl 8-Hydroxy-(6*R*,7*S*)-6,7-*O*-isopropylidene-(2*E*,4*E*)-octadienoate (15a).** To a solution of (4-ethoxy-4-oxobut-2-enylidene)triphenylphosphorane (3.0 g, 7.5 mmol) in 25 mL of $CH_2Cl_2$ was added lactol (**6a**) (800 mg, 5.0 mmol) in 10 mL of $CH_2Cl_2$. The mixture was stirred at room temperature for 12 h. After evaporation, the residue was dissolved in EtOAc (15 mL) and precipitated by the addition of hexane (15 mL). This procedure was repeated two times. The EtOAc–hexane fractions were combined and concentrated. Purification by column chromatography (silica gel; hexane–EtOAc, 1:1) afforded dienol **14a**: yield 895 mg (3.5 mmol, 70%); $R_f$ = 0.42; $[\alpha]^{25}_D$ = −18.7° (c 2.42, $CHCl_3$); IR (neat) 3420, 2970, 2920, 1710, 1640, 1610, 1460, 1370, 1310, 1270, 1180, 1040 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.31 (t, J = 8.1 Hz, 3 H), 1.43 (s, 3 H), 1.54 (s, 3 H), 2.16 (broad s), 3.56 (d, J = 4.5 Hz, 2 H), 4.22 (q, J = 4.0 Hz, 2 H), 4.35 (m, 1 H), 5.23 (dd, $J_1$ = 5.8 Hz, $J_2$ = 5.6 Hz, 1 H), 5.87 (dd, $J_1$ = 5.8 Hz, $J_2$ = 5.8 Hz, 1 H), 5.96 (d, J = 15.0 Hz, 1 H), 6.30 (dd, $J_1$ = 14.3 Hz, $J_2$ = 5.6 Hz, 1 H), 7.54 (dd, $J_1$ = 14.3 Hz, $J_2$ = 5.8 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) δ 14.2 ($CH_3$), 25.1 ($CH_3$), 27.7 ($CH_3$), 60.54 ($CH_2$), 61.8 ($CH_2$), 73.2 (CH), 78.7 (CH), 109.2 (C), 124.4 (CH), 129.5 (CH), 134.2 (CH), 137.8 (CH), 166.6 (C); Ms (EI mode) *m/e* 257 (p + 1, 0.20), 256 (+, 0.10), 241 (0.60), 217 (0.20) 196 (0.17), 156 (0.30), 101 (1.00), 59 (0.85); high-resolution mass spectrum calcd for $C_{13}H_{20}O_5$ 256.2980, found 256.2986, error 2.3 ppm.

Dienol **15a**: yield 180 mg (0.70 mmol, 14%); $R_f$ = 0.40; $[\alpha]^{25}_D$ = −14.2° (c 1.20, $CHCl_3$); IR (neat) 3420, 2970, 2920, 1710, 1640, 1610, 1460, 1370, 1310, 1240 (br), 1040 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) δ 1.28 (t, J = 8.1 Hz, 3 H), 1.37 (s, 3 H), 1.47 (s, 3 H), 3.50 (d, J = 5.7 Hz, 2 H), 4.15 (q, J = 8.1 Hz, 2 H), 4.26 (m, 1 H), 4.72 (dd, $J_1$ = 6.8 Hz, $J_2$ = 6.8 Hz, 1 H), 5.84 (d, J = 13.4 Hz, 1 H), 6.04 (dd, $J_1$ = 15.4 Hz, $J_2$ = 11.1 Hz, 1 H), 6.37 (dd, $J_1$ = 15.3 Hz, $J_2$ = 6.8 Hz, 1 H), 7.20 (dd, $J_1$ = 15.4 Hz, $J_2$ = 11.1 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) δ 14.2 ($CH_3$), 25.1 ($CH_3$), 27.7 ($CH_3$), 60.5 ($CH_2$), 62.0 ($CH_2$), 72.8 (CH), 78.5 (CH), 122.7 (CH), 130.6 (CH), 136.2 (CH), 142.8 (CH); MS (CI mode) *m/e* 257 (p + 1, 0.12), 256 (p), 241 (0.60), 217 (0.26) 196 (0.17), 156 (0.26), 101 (1.00), 59 (0.81); high-resolution mass spectrum calcd for $C_{13}H_{20}O_5$ 256.2980, found 256.2976, error −1.6 ppm.

**Ethyl 8-Hydroxy-(6*S*,7*R*)-6,7-*O*-isopropylidene-(2*E*,4*Z*)-octadienoate (14b) and Ethyl 8-Hydroxy-(6*S*,7*R*)-6,7-*O*-isopropylidene-(2*E*,4*E*)-octadienoate (15b).** Reaction of (4-ethoxy-4-oxobut-2-enylidene)triphenylphosphorane with lactol **6b** proceeded as above to afford dienols **14b** and **15b**, $[\alpha]^{25}_D$ = +19.7° (c 2.40, $CHCl_3$) and $[\alpha]^{25}_D$ = +15.6° (c 2.00, $CHCl_3$), respectively.

**Ethyl 8-Hydroxy-(6*R*,7*S*)-6,7-*O*-isopropylidene-(2*E*,4*E*)-octadienoate (15a).** To a mixture of dienes **14a** and **15a** (ratio 6:1, 105 mg) in 25 mL of $CH_2Cl_2$ was added a single crystal of $I_2$. The resulting purple solution was stirred for 30 min, washed with saturated aqueous $Na_2S_2O_3$, dried ($Na_2SO_4$), and concentrated. Purification by flash chromatography (silica gel; EtOAc–hexane 1:1) afforded 92 mg (0.36 mmol, 88%) of **15a**.

**Ethyl (6*R*,7*S*)-8-Azido-6,7-*O*-isopropylidene-(2*E*,4*Z*)-octadienoate (18a).** A solution of the dienol **14a** (2.07 g, 8.20 mmol) in 10 mL of $CH_2Cl_2$ was added to a cooled (−78 °C) solution of $CH_2Cl_2$ (50 mL), pyridine (6 mL), and trifluoromethanesulfonic anhydride (2.07 mL, 3.47 g, 12.3 mmol) under argon. The reaction mixture was allowed to warm to room temperature and was stirred for an additional 15 min. The organic phase was washed with 1 N aqueous HCl (2 × 50 mL) and $H_2O$ (50 mL), dried, and concentrated to afford 2.64 g of a clear pink oil, which was used immediately without further purification. To a solution of trilfate **16a** in 25 mL of $CH_2Cl_2$ were added sodium azide (486 mg, 7.48 mmol, 1.1 molar equiv) and 18-crown-6 (1.97 g, 7.48 mmol, 1.1

molar equiv). The mixture was stirred overnight. After dilution with 25 mL of $CH_2Cl_2$, the organic phase was washed with brine (3 × 25 mL), dried, and concentrated, leaving a yellow oil, which was chromatographed (10% deactivated silica gel; hexane–EtOAc, 80:20) to give 1.60 g (5.69 mmol, 69%) of pure vinyl azide **18a** as an oil: $R_f$ = 0.46 (hexane–EtOAc, 80:20); $[\alpha]^{25}_D$ = +112° (*c* 1.10, $CHCl_3$); IR (neat) 3000, 2950, 2100, 1715, 1640, 1610, 1450, 1380, 1375 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) δ 1.31 (t, *J* = 7.1 Hz, 3 H), 1.42 (s, 3 H), 1.55 (s, 3 H), 3.19 (dd, $J_1$ = 4.6 Hz, $J_2$ = 12.9 Hz, 1 H), 3.28 (dd, $J_1$ = 7.0 Hz, $J_2$ = 12.9 Hz, 1 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 4.35–4.42 (m, 1 H), 5.18–5.24 (m, 1 H), 5.78–5.86 (m, 1 H), 5.98 (d, *J* = 15.2 Hz, 1 H), 6.33 (t, *J* = 11.5 Hz, 1 H), 7.52 (dd, $J_1$ = 11.8 Hz, $J_2$ = 15.2 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) δ 14.3 ($CH_3$), 25.2 ($CH_3$), 27.7 ($CH_3$), 51.3 ($CH_2$), 60.6 ($CH_2$), 73.4 (CH), 77.4 (CH), 109.8 (C), 124.7 (CH), 129.9 (CH), 133.4 (CH), 137.6 (CH), 166.5 (C); MS (CI mode) *m/e* 282 (p + 1, 0.25), 281 (p), 254 (0.47), 196 (0.43) 169 (0.48); high-resolution mass spectrum, calcd for $C_{13}H_{19}N_3O_4$ 282.1462, found 282.1467, error −1.9 ppm.

**Ethyl (6*S*,7*R*)-8-Azido-6,7-*O*-isopropylidene-(2*E*,4*Z*)-octadienoate (18b).** Reaction of dienol **14b** as above afforded azido diene **18b**: $[\alpha]^{25}_D$ = −109° (*c* 2.21, $CHCl_3$).

**Ethyl (6*R*,7*S*)-8-Azido-6,7-*O*-isopropylidene-(2*E*,4*E*)-octadienoate (19a).** A solution of the (*E*,*E*)-dienol **15a** (310 mg, 1.19 mmol) in 1 mL of $CH_2Cl_2$ was added to a cooled (−78 C) solution of $CH_2Cl_2$ (10 mL), pyridine (1 mL), and trifluoromethanesulfonic anhydride (0.30 mL, 0.50 g, 1.78 mmol) under argon. The reaction mixture was allowed to warm to room temperature and was stirred for an additional 15 min. The organic phase was washed with 1 N aqueous HCl (2 × 10 mL) and $H_2O$ (10 mL), dried ($MgSO_4$), and concentrated to afford 0.46 g of a clear pink oil, which was used immediately without further purification. To a solution of triflate **17a** in 10 mL of $CH_2Cl_2$ were added sodium azide (85 mg, 1.30 mmol, 1.1 molar equiv) and 18-crown-6 (0.34 g, 1.30 mmol, 1.1 molar equiv). The mixture was stirred overnight. After dilution with 10 mL of $CH_2Cl_2$, the organic phase was washed with brine (3 × 10), dried ($MgSO_4$), and concentrated, leaving a yellow oil, which was chromatographed (10% deactivated silica gel; hexane–EtOAc, 80:20) to give 280 mg (0.99 mmol, 83%) of pure azido diene **19a** as an oil: $R_f$ = 0.46 (hexane–EtOAc, 80:20); $[\alpha]^{25}_D$ = +30.4° (*c* 1.15, $CHCl_3$); IR (neat) 3000, 2955, 2102, 1715, 1635, 1610, 1453, 1385, 1375 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) δ 1.27 (t, *J* = 7.0 Hz, 3 H), 1.37 (s, 3 H), 1.51 (s, 3 H), 3.14 (dd, $J_1$ = 4.9 Hz, $J_2$ = 12.8 Hz, 1 H), 3.26 (dd, $J_1$ = 7.2 Hz, $J_2$ = 12.8 Hz, 1 H), 4.18 (q, *J* =7.0 Hz, 2 H), 4.34–4.22 (m, 1 H), 4.84–4.60 (m, 1 H), 5.90 (d, *J* = 15.4 Hz, 1 H), 6.00 (dd, $J_1$ = 6.9 Hz, $J_2$ = 15.4 Hz, 1 H), 6.44 (dd, $J_1$ = 10.9 Hz, $J_2$ = 14.7 Hz, 1 H), 7.24 (dd, $J_1$ = 11.0 Hz, $J_2$ = 14.7 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) δ 14.2 ($CH_3$), 25.3 ($CH_3$), 27.7 ($CH_3$), 51.5 ($CH_2$), 60.4 ($CH_2$), 66.0 (CH), 80.6 (CH), 109.5 (C), 123.0 (CH), 130.9 (CH), 135.3 (CH), 142.6 (CH), 166.6 (C); MS (CI mode) *m/e* 282 (p + 1, 0.20), 281 (p), 254 (0.40), 196 (0.40) 169 (0.50); high-resolution mass spectrum calcd for $C_{13}H_{19}N_3O_4$ 282.1462, found 282.145, error 2.8 ppm.

**(2*R*,3*R*,4*S*,5*R*)-1-Aza-2-(2-carbethoxyethenyl)-4,5-*O*-isopropylidenebicyclo[3.1.0]hexane (20a).** To 100 mL of benzene at reflux was added the azido diene **18a** (960 mg, 3.42 mmol) in 5 mL of benzene. Heating was continued overnight. The resulting deep yellow solution was evaporated, leaving a viscous oil, which was chromatographed (10% deactivated silica gel; hexane–EtOAc, 1:1) to give 385 mg (1.52 mmol, 44%) of pure vinylaziridine **20a**: $R_f$ = 0.50 (hexane–EtOAc, 1:1); $[\alpha]^{25}_D$ = +129° (*c* 5.10, $CHCl_3$); IR (neat) 2950, 2905, 1710, 1650, 1450, 1370 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) δ 1.26 (t, *J* = 7.2 Hz, 3 H), 1.34 (s, 3 H), 1.52 (s, 3 H), 1.65 (dd, $J_1$ = 2.9 Hz, $J_2$ = 7.7 Hz, 1 H), 2.72 (d, *J* = 2.9 Hz, 1 H), 3.18 (dd, $J_1$ = 6.1 Hz, $J_2$ = 13.7 Hz, 1 H), 3.29 (dd, $J_1$ = 3.7 Hz, $J_2$ = 13.7 Hz, 1 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 4.68–4.70 (m, 1 H), 4.93 (d, *J* = 5.8 Hz, 1 H), 5.96 (d, *J* = 15.7 Hz, 1 H), 6.56 (dd, $J_1$ = 7.7 Hz, $J_2$ = 15.7 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) δ 14.2 ($CH_3$), 25.4 ($CH_3$), 27.2 ($CH_3$), 44.0 (CH), 53.3 (CH), 60.4 ($CH_2$), 61.9 ($CH_2$), 82.0 (CH), 28.5 (CH), 113.0 (C), 122.4 (CH), 145.9 (CH), 165.8 (C); mass spectrum (70 eV, rel intensity) 253 ($M^+$, 10), 238 (55), 180 (36), 150 (29), 122 (69), 105 (52), 94 (100), 81 (57); high-resolution mass spectrum calcd for $C_{13}H_{19}NO_4$ 253.1314, found 253.1314, error 0.0 ppm. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56. Found: C, 60.05; H, 7.52.

**(2*R*,3*R*,4*S*,5*R*)-1-Aza-2-(2-carbethoxyethenyl)-4,5-*O*-isopropylidenebicyclo[3.1.0]hexane (20b).** Thermolysis of azido diene **18b** as above afforded vinylaziridine **20b**: $[\alpha]^{25}_D$ = −101° (*c* 1.50, $CHCl_3$).

**(+)-Trihydroxyheliotridane 6,7-*O*-Acetonide (23a). Method A.** Vinylaziridine **20a** (90 mg, 0.36 mmol) was evaporated through a horizontal Vycor tube (0.6 × 55 cm) at 520 °C and ca. $10^{-4}$ Torr, and the condensate was collected in a trap cooled with liquid $N_2$. The total time of evaporation was kept under 15 min by gently warming the distillation flask. The crude enamine was taken up in dry MeOH (25 mL) and hydrogenated over 10% Pd/C (20 mg) at 50 psi for 12 h. The mixture was filtered through Celite, the filter was washed with MeOH, and the filtrate was evaporated to yield 77 mg of a pale yellow oil. The crude ester was dissolved in anhydrous THF (5 mL) and slowly added to a suspension of $LiAlH_4$ (50 mg, 1.32 mmol) in anhydrous THF (7 mL) 0 °C. The mixture was allowed to warm to room temperature and was then heated at reflux for 12 h. $H_2O$ (50 μL) was added, followed by 15% aqueous NaOH (50 μL) and $H_2O$ (150 μL). The mixture was filtered, and the precipitate was washed with $Et_2O$ (3 × 20 mL). The combined organic fraction was concentrated, leaving an orange semicrystalline mass. Purification by recrystallization (hexane–EtOAc, 1:1) afforded 17 mg (22% overall) of **23a** as colorless crystals: mp 134–135 °C; $R_f$ = 0.20 (silica gel; hexane–EtOAc, 1:1) $[\alpha]^{25}_D$ = +13.1° (*c* 2.03, $CHCl_3$); IR (KBr) 330, 2945, 2840, 1640, 1590, 1445, 1355 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) δ 1.30 (s, 3 H), 1.51 (s, 3 H), 1.56–1.67 (m, 1 H), 1.78–1.89 (m, 1 H), 2.43–2.59 (m, 1 H), 2.60–2.69 (m, 1 H), 2.85–2.97 (m, 2 H), 3.13 (dd, $J_1$ = 2.1 Hz, $J_2$ = 12.1 Hz, 1 H), 3.44 (dd, $J_1$ = 3.8 Hz, $J_2$ = 8.2 Hz, 1 H), 3.78 (d, *J* = 6.0 Hz, 1 H), 4.65 (dd, $J_1$ = 3.8 Hz, $J_2$ = 6.4 Hz, 1 H), 4.76 (td, $J_1$ = 2.1 Hz, $J_2$ = 5.5 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) δ 25.2, 27.3, 27.5, 42.3, 53.0, 58.8, 63.4, 73.0, 80.5, 81.8, 112.5; mass spectrum (70 eV, rel intensity), *m/e* 213 ($M^+$, 47), 198 (30), 155 (35), 124 (65), 113 (58), 82 (100); high-resolution mass spectrum calcd for $C_{11}H_{19}NO_3$ 213.1365, found 213.1371, error 2.7 ppm. Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.87; H, 8.96; N, 6.55.

**Method B.** Vinylaziridine **21a** (110 mg, 0.44 mmol) was treated as above to afford 25 mg (0.12 mmol, 27%) of trihydroxyheliotridane **23a**.

**(−)-Trihydroxyheliotridane 6,7-*O*-Acetonide (23b).** Reaction of vinylaziridine **20b** as above afforded (−)-trihydroxyheliotridane **23b**: $[\alpha]^{25}_D$ = −13.1° (*c* 1.21, $CHCl_3$).

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**Supplementary Material Available:** $^{13}C$ and $^1H$ NMR spectra of key compounds (18 pages). Ordering information is given on any current masthead page.