

## Synthetic Studies Related to Compactin: Use of Tri-*O*-acetyl-D-glucal for Preparation of Chiral Cyclohexenes

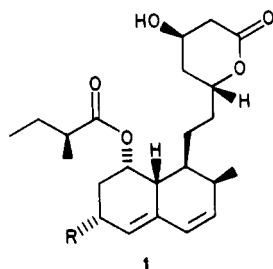
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The Diels-Alder adduct ethyl 6-*O*-(2,2-dimethyl-1-oxopropyl)-2,3-*C*-(2-butene-1,4-diyl)-2,3-dideoxy- $\alpha$ -D-lyxo-hexopyranosid-4-ulose (11) formed from ethyl 6-*O*-(2,2-dimethyl-1-oxopropyl)-2,3-dideoxy- $\alpha$ -D-glycero-hex-2-enopyranosid-4-ulose (10) and butadiene was degraded to (1*R*,6*S*)-6-methyl-3-cyclohexenemethanol (16). Benzene-1,2-dithiol was found to be a useful reagent in a short sequence of reactions that served to convert the anomeric carbon (C-1) of 11 into a methyl group. Alcohol 16 was oxidized to (1*R*,6*S*)-6-methyl-3-cyclohexene-carboxylic acid (4), needed for the synthesis of the hexahydronaphthalene portion of compactin.

Compactin (1, R = H)<sup>1</sup> and mevinolin (1, R = Me)<sup>2</sup> are fungal metabolites that have attracted considerable attention<sup>3-7</sup> because of their ability to lower<sup>2,8</sup> blood levels of cholesterol in mammals. A structure-activity study of



(1) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* 1976, 1165.

(2) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffmann, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirschfeld, J.; Hoogsteen, K.; Liesch, J.; Springer, J. *Proc. Natl. Acad. Sci. U.S.A.* 1980, 77, 3957.

(3) Synthesis of compactin: (a) Wang, N.-T.; Hsu, C.-T.; Sih, C. J. *J. Am. Chem. Soc.* 1981, 103, 6538. (b) Hirama, M.; Uei, M. *J. Am. Chem. Soc.* 1982, 104, 4251. (c) Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* 1982, 23, 5501. (d) Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* 1983, 24, 3687. (e) Hau, C.-T.; Wang, N.-Y.; Latimer, L.; Sih, C. J. *J. Am. Chem. Soc.* 1983, 105, 593. (f) Grieco, P. A.; Zelle, R. E.; Lis, R.; Finn, J. J. *J. Am. Chem. Soc.* 1983, 105, 1403. (g) Girotra, N. N.; Reamer, R. A.; Wendler, N. L. *Tetrahedron Lett.* 1984, 25, 5371. (h) Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* 1985, 107, 3731.

(4) Synthesis of mevinolin: Hirama, M.; Iwashita, M. *Tetrahedron Lett.* 1983, 24, 1811.

(5) Synthesis of analogues: (a) Lee, T.-J.; Holtz, W. J.; Smith, R. L. *J. Org. Chem.* 1982, 47, 4750. (b) Kuo, C. H.; Patchett, A. A.; Wendler, N. L. *J. Org. Chem.* 1983, 48, 1991. (c) Falk, J. R.; Yang, Y.-L. *Tetrahedron Lett.* 1984, 25, 3563. (d) Yang, Y.-L.; Manna, S.; Falck, J. R. *J. Am. Chem. Soc.* 1984, 106, 3811. (e) Sletzing, M.; Verhoeven, T. R.; Volante, R. P.; McNamara, J. M.; Corley, E. G.; Liu, T. M. H. *Tetrahedron Lett.* 1985, 26, 2951.

(6) Approaches to the lactone unit: (a) Prugh, J. D.; Deana, A. A. *Tetrahedron Lett.* 1982, 23, 281. (b) Danishefsky, S.; Kobayashi, S.; Kerwin, J. F., Jr. *J. Org. Chem.* 1982, 47, 1982. (c) Danishefsky, S.; Kerwin, J. F.; Kobayashi, S. *J. Am. Chem. Soc.* 1982, 104, 358. (d) Yang, Y.-L.; Falck, J. R. *Tetrahedron Lett.* 1982, 23, 4305. (e) Wareing, J. R.; Fuller, C. E.; Kathawala, F. G. *Abstracts of Papers, 185th National Meeting of the American Chemical Society, Seattle, WA, March, 1983; American Chemical Society: Washington, DC, 1983; ORGN 11.* (f) Majewski, M.; Clive, D. L. J.; Anderson, P. C. *Tetrahedron Lett.* 1984, 25, 2101. (g) Rosen, T.; Taschner, M. J.; Heathcock, C. H. *J. Org. Chem.* 1984, 49, 3994. (h) Ho, P.-T.; Chung, S. *Carbohydr. Res.* 1984, 125, 318. (i) Prasad, K.; Repič, O. *Tetrahedron Lett.* 1984, 25, 2435. (j) Prasad, K.; Repič, O. *Tetrahedron Lett.* 1984, 25, 3391. (k) Kozikowski, A. P.; Li, C.-S. *J. Org. Chem.* 1985, 50, 778.

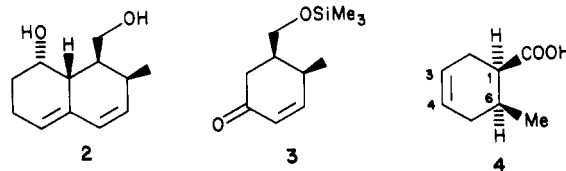
(7) Approaches to the hexahydronaphthalene unit: (a) Funk, R. L.; Zeller, W. E. *J. Org. Chem.* 1982, 47, 180. (b) Deutsch, E. A.; Snider, B. E. *J. Org. Chem.* 1982, 47, 2682. (c) Heathcock, C. H.; Taschner, M. J.; Rosen, T.; Thomas, J. A.; Hadley, C. R.; Popják, G. *Tetrahedron Lett.* 1982, 23, 4747. (d) Anderson, P. C.; Clive, D. L. J.; Evans, C. F. *Tetrahedron Lett.* 1983, 24, 1373. (e) Deutsch, E. A.; Snider, B. E. *Tetrahedron Lett.* 1983, 24, 3701. (f) Funk, R. L.; Mossman, C. J.; Zeller, W. E. *Tetrahedron Lett.* 1984, 25, 1655. (g) Rosen, T.; Taschner, M. J.; Thomas, J. A.; Heathcock, C. H. *J. Org. Chem.* 1985, 50, 1190.

(8) Mabuchi, H.; Haba, T.; Tatami, R.; Miyamoto, S.; Sakai, Y.; Wakasugi, T.; Watanabe, A.; Koizumi, J.; Takeda, R. *N. Engl. J. Med.* 1981, 305, 478.

this property, which is also manifest in humans, may help in the design of valuable drugs, since elevated levels of blood cholesterol represent a significant risk factor for atherosclerosis and its associated coronary artery diseases.<sup>9</sup> Accordingly, much effort has been devoted to total and partial synthetic work<sup>3-7</sup> that can lead not only to the natural products but also to structurally related analogues.

Our own synthetic work<sup>6f,7d</sup> in this area is aimed at preparing compactin and mevinolin by a route that can be modified easily so as to generate analogues that differ in the nature of the ring A substituent, R (see 1). It is known that mevinolin, in which R = Me, is 3 to 5 times as active as compactin (1, R = H);<sup>2</sup> possibly, further modifications to the group R will lead to more potent hypocholesterolemic agents.

We have previously reported<sup>7d</sup> a synthesis of the hexahydronaphthalene unit 2, which represents the bottom

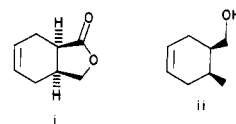


portion of compactin. The substance was made in racemic form from 3, which, in turn, was prepared from the racemic acid 4. Synthesis of the hexahydronaphthalene unit optically pure and with the correct absolute configuration would require the acid 4 in its optically pure 1*R*,6*S* form (shown). Of several synthetic approaches to chiral 4 that we considered,<sup>10</sup> we report here a method that uses a

(9) Dawber, T. R. *The Framingham Study*; Harvard University Press: Cambridge, MA, 1980.

(10) Initially, we attempted to resolve racemic 4 by classical means, i.e., through fractional crystallization of its salts with optically active amines [quinine, strychnine, dehydroabietylamine, (S)-(-)-1-phenylethylamine] or by chromatographic separation of amides formed by treating the corresponding acid chloride with (S)-(-)-1-phenylethylamine or with (S)-(-)-1-(4-nitrophenyl)ethylamine. The crystallization route was too inefficient and the diastereoisomeric amides were both difficult to separate and to hydrolyze.

The racemic lactone **i** was treated with (S)-(-)-1-phenylethylamine but the resulting hydroxy amides could not be separated in a satisfactory manner, notwithstanding extensive precedent<sup>11</sup> for separation of diastereoisomeric hydroxy amides. Use of (S)-(-)-1-(4-nitrophenyl)ethylamine in this connection was not practicable in our hands.

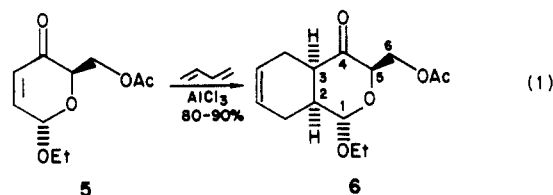


The racemic alcohol **ii** was treated with (+)-NOE-lactol dimer<sup>12</sup> and, in another experiment with  $\omega$ -camphanic acid chloride,<sup>13</sup> but in neither case was the diastereoisomer mixture separable.

(11) Helmchen, G.; Nill, G.; Flockerzi, D.; Schühle, W.; Youssef, S. K. *Angew. Chem., Int. Ed. Engl.* 1979, 18, 62, 63.

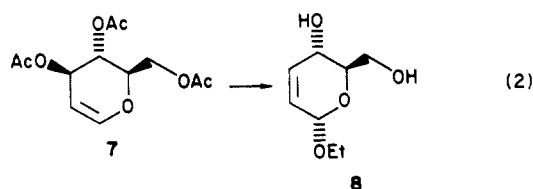
carbohydrate for generation of the chiral centers of 4.<sup>14</sup>

Our starting point was the observation<sup>15</sup> that the hex-enopyranosidulose 5, derived from glucose, reacts with butadiene in a Diels–Alder manner (eq 1) to generate two

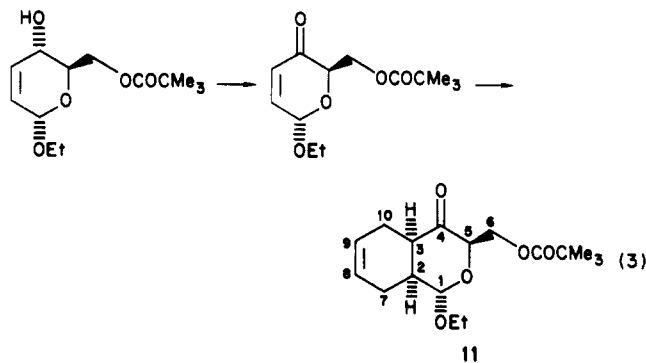


new chiral centers. Comparison of the structure of the product 6 with that of the desired 4 shows that 6 could serve as a precursor to 4 if C(1) in 6 were converted into a methyl group and C(4) oxidized to a carboxyl. However, preparation of 5 on a large scale proved unsatisfactory in our hands (see below) and so we modified the literature procedure in several minor but beneficial respects.

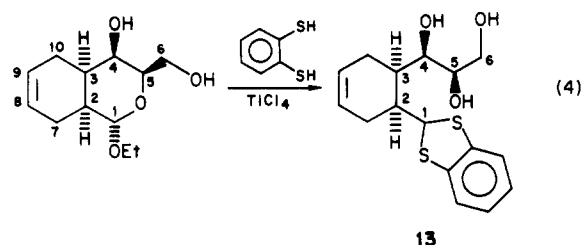
Commercial glucal triacetate (7) was converted (64%) into the diol 8.<sup>16,17</sup> We found that oxidation of the allylic



hydroxyl in 8 with manganese dioxide was an unreliable procedure that usually results in low yields. Several types<sup>18</sup> of manganese dioxide were examined as were a number of other oxidants.<sup>19</sup> None proved suitable and we decided to protect the primary hydroxyl by acylation so that only one oxidizable hydroxyl remained. Treatment of 8 at  $-5^{\circ}\text{C}$  with pivaloyl chloride in the presence of pyridine afforded 9 in 72% yield. The material was accompanied by a small amount ( $\sim 20\%$  yield) of the dipivaloate, which could be, in principle, but was not in fact, converted back into 8 for recycling. With 9 in hand, oxidation of the allylic hydroxyl (9  $\rightarrow$  10) was readily achieved (84%) with pyridinium dichromate.<sup>20</sup> The enone 10 underwent Diels–Alder reaction, catalyzed by aluminum trichloride, with butadiene to produce the desired bicyclic compound 11 (87%). This reaction is modeled on the analogous process<sup>15</sup> of eq 1 that is described in the literature; although for large-scale work (ca. 20 g of 11) extensive refinement of the reaction conditions and workup procedure were required. Comparison of the high-field  $^1\text{H}$  NMR spectrum of 11 with data for the known compound 6 showed that



our product (11) had the desired stereochemistry at the newly created asymmetric centers. Reduction to the diol 12 was accomplished efficiently (77%) with lithium aluminum hydride. The reduction ensures that there is no loss of stereochemical integrity at C(3) during the next stage (12  $\rightarrow$  13),<sup>21</sup> which involves reaction with 1,2-benzenedithiol.<sup>22</sup> In the presence of boron trifluoride



etherate, diol 12 reacts with 1,3-propanedithiol and with 1,2-ethanedithiol to give the expected dithioacetals. However, these substances do not react in a satisfactory manner with deactivated Raney nickel;<sup>23</sup> some epimerization ( $\sim 10\%$ , 400-MHz  $^1\text{H}$  NMR) occurs at C(2) (see numbering in 12 and 13), possibly through an intermediate vinyl sulfide, and partial saturation of the C(8)–C(9) double bond also occurs. Attempts to use tributyltin hydride for desulfurization were not successful.<sup>24</sup> An alternative method for cleaving an R–S single bond (R = alkyl group) is treatment of species R–SAr with an alkali metal in liquid ammonia.<sup>26,27</sup> Accordingly, the glycoside 12 was treated with benzenethiol, in the presence of boron trifluoride etherate; no dithioacetal was formed and, instead, the ethoxy group of 12 was replaced by a phenylthio unit. Clearly, introduction of a second sulfur atom at C(1) of 12 is best accomplished by an intramolecular process and this conclusion led us to use 1,2-benzenedithiol, which was readily made by a literature procedure.<sup>22</sup> Formation of the dithioacetal 13 is catalyzed by Lewis acids. Of several that were tried [ $\text{BF}_3\cdot\text{OEt}_2$ ,  $\text{AlCl}_3$ ,<sup>28</sup>  $\text{ZnCl}_2$ ,  $\text{Zn}(\text{OSO}_2\text{CF}_3)_2$ ,<sup>29</sup>

(12) Trademark of Aldrich Chemical Co., Inc.: *Aldrichimica Acta* 1983, 16, 10. Noe, C. R. *Chem. Ber.* 1982, 115, 1576, 1591, 1607.

(13) Cf. Gerlach, H. *Helv. Chim. Acta* 1968, 51, 1587. Jurczak, J.; Konowal, A.; Krawczyk, Z. *Synthesis* 1977, 258. Konowal, A.; Jurczak, J.; Zamojski, A. *Tetrahedron* 1976, 32, 2957.

(14) Cf. Hanessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach*, Pergamon: Oxford, 1983. See also: Mann, J.; Thomas, A. *J. Chem. Soc., Chem. Commun.* 1985, 737. Sabbioni, G.; Shea, M. L.; Jones, J. B. *J. Chem. Soc., Chem. Commun.* 1984, 236.

(15) Primeau, J. L.; Anderson, R. C.; Fraser-Reid, B. *J. Am. Chem. Soc.* 1983, 105, 5874.

(16) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* 1969, 570.

(17) Fraser-Reid, B.; McLean, A.; Usherwood, E. W.; Yunker, M. *Can. J. Chem.* 1970, 48, 2877.

(18) Fatiadi, A. J. *Synthesis* 1976, 65.

(19)  $\text{K}_2\text{Cr}_2\text{O}_7/\text{Me}_2\text{SO}$ : Santaniello, E.; Ferraboschi, P. *Synthesis* 1980, 646.  $\text{CrO}_3/\text{Et}_2\text{O}$ : Flatt, S. J.; Fleet, G. W. J.; Taylor, B. *J. Synthesis* 1979, 815.  $\text{KMnO}_4/\text{CuSO}_4$ : Menger, F. M.; Lee, C. *J. Org. Chem.* 1979, 44, 3446.  $\text{Py}_4\text{Ag}_2\text{Cr}_2\text{O}_7$ : Firouzaladi, H.; Sardarian, A.; Gharibi, H. *Synth. Commun.* 1984, 14, 89.  $(\text{Bu}_4\text{N})_2\text{Cr}_2\text{O}_7$ : Santaniello, E.; Ferraboschi, P. *Synth. Commun.* 1980, 10, 75.  $(\text{PhCH}_2\text{NEt}_3)_2\text{Cr}_2\text{O}_7$ : Huang, X.; Chan, C.-C. *Synthesis* 1982, 1091.

(20) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* 1979, 399.

(21) Reaction of 11 with 1,3-propanedithiol or with 1,2-ethanedithiol (each in the presence of boron trifluoride etherate) gave dithioacetals that were not stereochemically pure.

(22) Degani, I.; Fochi, R. *Synthesis* 1976, 471.

(23) Kyler, K. S.; Bashi-Hashemi, A.; Watt, D. S. *J. Org. Chem.* 1984, 49, 1084.

(24) Gutierrez, C. G.; Stringham, R. A.; Nitasaka, T.; Glasscock, K. G. *J. Org. Chem.* 1980, 45, 3393. We have observed (ref 25) that cleavage of C–S bonds by tin hydrides is much more difficult than cleavage of C–Se bonds.

(25) Clive, D. L. J.; Chittattu, G. J.; Farina, V.; Kiel, W. A.; Menchen, S. M.; Russell, C. G.; Singh, A.; Wong, C. K.; Curtis, N. J. *J. Am. Chem. Soc.* 1980, 102, 4438.

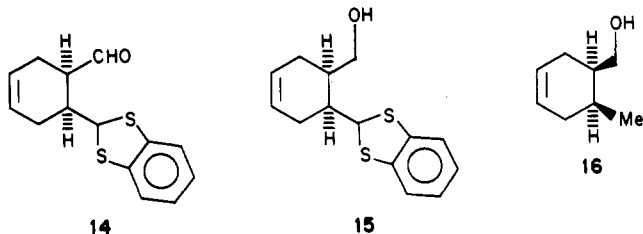
(26) For example: (a) Ireland, R. E.; Wrigley, T. I.; Young, W. G. *J. Am. Chem. Soc.* 1958, 80, 4604. (b) Degani, I.; Fochi, R. *J. Chem. Soc., Perkin Trans. 1* 1978, 1133.

(27) Cleavage of  $\text{RSR}'$  (R, R' = alkyl groups) by this method gives both  $\text{RS}^-$  and  $\text{R}'\text{S}^-$ . See, for example: Truce, W. E.; Frank, F. J. *J. Org. Chem.* 1967, 32, 1918.

(28) Ong, B. S. *Tetrahedron Lett.* 1980, 21, 4225.

TiCl<sub>4</sub><sup>30</sup>, TiCl<sub>4</sub> was best and it allowed isolation of 13 in 55% yield.

The trihydroxy dithioacetal 13 was oxidized with lead tetraacetate to the sensitive aldehyde 14, which was re-



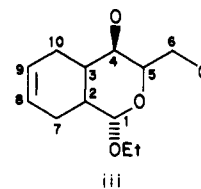
duced immediately (LiAlH<sub>4</sub>) to alcohol 15. At this stage, desulfurization (15 → 16) was easily accomplished (81% yield) with sodium in liquid ammonia.<sup>31</sup> We were not able to detect any enantiomeric impurity in our sample of 16 by examining NMR spectra (200 MHz) of its derivatives formed with (-)- $\omega$ -camphanic acid chloride<sup>13</sup> or (-)-NOE-lactol.<sup>12</sup> A racemic sample of 16<sup>32</sup> was also treated with these reagents and care was exercised in all experiments not to effect separation of diastereoisomers. The diastereoisomeric derivatives made from racemic 16 were easily distinguishable by <sup>1</sup>H NMR.

A portion of chiral alcohol 16 was oxidized to the optically pure acid 4, needed<sup>7d</sup> for synthesis of the hexahydronaphthalene unit of compactin.

### Experimental Section

Unless otherwise stated the following particulars apply. Experiments were carried out under a slight static pressure of argon that was purified by passage through a column (3.5 × 42 cm) of R-311 catalyst<sup>33</sup> and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h (130 °C) and cooled in a desiccator over Drierite. Stirring was effected by using a dry, Teflon-coated magnetic stirring bar. Solvents were distilled before use for chromatography or extractions. Dry tetrahydrofuran (THF) and benzene were distilled from sodium benzophenone ketyl; dichloromethane and pyridine were distilled from calcium hydride. Products were isolated from solution by concentration under water pump vacuum at 40 °C (or less) on a rotary evaporator. Where compounds were isolated by simple evaporation of their solutions, the residues were kept under vacuum (<0.1 mm) until constant weight. Boiling points quoted for products distilled in a Kugelrohr apparatus refer to the oven temperature. Commercial silica (Merck 60F-254) thin-layer chromatography (TLC) plates were used. Silica gel for flash column chromatography was Merck type 60 (230–400 mesh). TLC plates were examined under UV radiation (254 nm), treated with iodine vapor, and charred on a hot plate after being sprayed with sulfuric acid (6 N in methanol). Infrared spectra were recorded on a Perkin-Elmer Model 297 spectrophotometer or a Nicolet Model 7000 FT-IR. Mass spectra were recorded on an A.E.I. MS50 mass spectrometer at an ionizing voltage of 70 eV. Optical rotations were measured at 25 °C with a Perkin-Elmer Model 141 polarimeter. The following abbreviations are used in the text: s, singlet; d, doublet; t, triplet; q, quartet. For assignment of certain NMR signals, the following numbering scheme is followed:

**Ethyl 6-O-(2,2-Dimethyl-1-oxopropyl)-2,3-dideoxy- $\alpha$ -D-glycero-hex-2-enopyranoside (9).** 2,2-Dimethylpropanoyl chloride (82 mL, 666 mmol) was added at a fast dropwise rate to a mechanically stirred and cooled (-5 °C) solution of ethyl 2,3-dideoxy- $\alpha$ -D-glycero-hex-2-enopyranoside (8)<sup>17</sup> (96 g, 551 mmol) in dry dichloromethane (100 mL) containing anhydrous pyridine (136 mL, 1.68 mol). Additional amounts [12 mL (97 mmol) and



10 mL (80 mmol)] of the acid chloride were added after 1.25 h and 2 h, respectively. After a total reaction time of 3.5 h, ice-cold water (ca. 1 L) was poured into the mixture. The organic layer was separated, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. Flash chromatography over silica gel using first 15:85 ethyl acetate-hexane (to elute the diester) and then 35:65 ethyl acetate-hexane gave 9 (102 g, 72%) as a homogeneous (TLC, silica gel, 35:65 ethyl acetate-hexane) oil: [ $\alpha$ ]<sub>D</sub> +36.23° (c 3.7, CHCl<sub>3</sub>); IR (film) 3450, 1725, 1480, 1285, 1160, 1060, 735 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  5.98 (br d, 1 H, J = 10 Hz, H-3), 5.76 (dt, 1 H, J = 2, 10 Hz, H-2), 5.00 (br s, 1 H, H-1), 4.38–4.32 (m, 2 H, H<sub>2</sub>-6), 4.00 (br m, 1 H, H-4), 3.96–3.50 (m, 3 H, H-5, OCH<sub>2</sub>CH<sub>3</sub>), 3.10 (br d, 1 H, OH), 1.42–1.18 (m, 12 H, OCH<sub>2</sub>CH<sub>3</sub>, C(CH<sub>3</sub>)<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50.32 MHz)  $\delta$  178.69 (s), 133.07 (d), 126.16 (d), 93.69 (d), 70.14 (d), 64.04 (t), 63.74 (d), 63.53 (t), 38.60 (s), 26.95 (q), 14.98 (q); exact mass, m/z 213.1126 [calcd for C<sub>11</sub>H<sub>17</sub>O<sub>4</sub> (M - OEt)<sup>+</sup>, m/z 213.1127].

The dipivaloate (38 g, 20%) had the following: IR (film) 1730, 1478, 1282, 1150, 1070, 1048, 1018, 993, 770, 732 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  5.84 (br s, 2 H, H-2, H-3), 5.28 (br dt, 1 H, J = 4, 8 Hz, H-4), 5.05 (br s, 1 H, H-1), 4.26–4.10 (m, 3 H, H-5, H<sub>2</sub>-6), 3.90 (dq, 1 H, OCH<sub>A</sub>H<sub>B</sub>CH<sub>3</sub>), 3.58 (dq, 1 H, OCH<sub>A</sub>H<sub>B</sub>CH<sub>3</sub>), 1.30–1.18 (m, 12 H, OCH<sub>2</sub>CH<sub>3</sub>, C(CH<sub>3</sub>)<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50.32 MHz) 177.85 (s), 177.44 (s), 129.25 (d), 127.69 (d), 93.98 (d), 67.29 (d), 64.90 (d), 63.88 (t), 62.98 (t), 38.64 (s), 27.01 (q), 26.86 (q), 15.05 (q); exact mass, m/z 297.1702 [calcd for C<sub>16</sub>H<sub>25</sub>O<sub>5</sub> (M - OEt)<sup>+</sup>, m/z 297.1702].

**Ethyl 6-O-(2,2-Dimethyl-1-oxopropyl)-2,3-dideoxy- $\alpha$ -D-glycero-hex-2-enopyranosid-4-ulose (10).** The monoester 9 (30.0 g, 116 mmol) in anhydrous dichloromethane (150 mL) was added over 20 min at room temperature to a mechanically stirred suspension of pyridinium dichromate (60.0 g, 160 mmol) in dichloromethane (300 mL). Stirring was continued for 48 h and the mixture was diluted with dry ether (300 mL). Granular chromium salts were removed by filtration through a pad of Celite and the filtrate was evaporated. Flash chromatography over silica gel using 1:3 ethyl acetate-hexane gave 10 (25.0 g, 84%) as a homogeneous (TLC, silica gel, 1:3 ethyl acetate-hexane), thick yellowish liquid: [ $\alpha$ ]<sub>D</sub> -1.09 (c 3.7, CHCl<sub>3</sub>); IR (film) 1725, 1695, 1477, 1282, 1160, 1110, 1075, 1050, 1020, 770, 760 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  6.92 (dd, 1 H, J = 4, 10 Hz, H-2), 6.16 (d, 1 H, J = 10 Hz, H-3), 5.30 (d, 1 H, J = 5 Hz, H-1), 4.72 (q, 1 H, H-5), 4.65–4.40 (m, 2 H, H<sub>2</sub>-6), 3.92 (dq, 1 H, J = 7, 9.8 Hz, OCH<sub>A</sub>H<sub>B</sub>CH<sub>3</sub>), 3.72 (dq, 1 H, J = 7, 9.8 Hz, OCH<sub>A</sub>H<sub>B</sub>CH<sub>3</sub>) 1.30 (t, 3 H, J = 7 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.21 (s, 9 H, C(CH<sub>3</sub>)<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50.32 Mz)  $\delta$  193.16 (s), 177.64 (s), 144.06 (d), 127.12 (d), 92.59 (d), 72.53 (d), 64.58 (t), 62.38 (t), 38.44 (s), 26.81 (q), 14.83 (q); exact mass, m/z 256.1302 (calcd for C<sub>13</sub>H<sub>20</sub>O<sub>5</sub>, m/z 256.1310).

**Ethyl 6-O-(2,2-Dimethyl-1-oxopropyl)-2,3-C-(2-butene-1,4-diyl)-2,3-dideoxy- $\alpha$ -D-lyxo-hexopyranosid-4-ulose (11).** Anhydrous aluminum trichloride (16.0 g, 120 mmol) was added over 30 s (via a solid addition funnel) to a magnetically stirred and cooled (cold-bath temperature = -70 °C) solution of enone 10 (20.0 g, 78 mmol) and butadiene (600 mL) in anhydrous dichloromethane (150 mL). The solution became yellow and the temperature of the cooling bath rose to -60 °C. The mixture was stirred at -60 °C for 30 min and poured into a breaker containing ice (ca. 800 g) and saturated aqueous sodium bicarbonate solution (250 mL). The mixture was stirred gently (vigorous stirring produces an emulsion) and then left for 1 h during which time the excess of butadiene evaporated. The resulting white suspension was transferred to a 2-L round-bottomed flask and kept for 30 min under water-pump vacuum on a Büchi rotary evaporator at 35 °C. At this stage, most of the organic solvent had evaporated and the aqueous suspension was extracted with ether (6 × 120 mL). The combined extracts were washed with water (3 × 200 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated to afford a pale yellow syrup. Flash chromatography over silica gel using 1:9 ethyl acetate-hexane gave 11 (21.0 g, 87%) as a homogeneous (TLC,

(29) Corey, E. J.; Shimoji, K. *Tetrahedron Lett.* 1983, 24, 169.

(30) See: Bulman-Page, P. C.; Roberts, R. A.; Paquette, L. A. *Tetrahedron Lett.* 1983, 24, 3555.

(31) Desulfurization of 13 (Na/NH<sub>3</sub>) was also possible but was less efficient than reduction of 15.

(32) Made by reduction (LiAlH<sub>4</sub>) of the corresponding methyl ester.

(33) Supplied by Chemical Dynamics Corporation, South Plainfield, NJ.

3:7 ethyl acetate-hexane), pale yellow liquid:  $[\alpha]_D^{25} +139.28^\circ$  (c 7.9,  $\text{CHCl}_3$ ); IR (film) 1730, 1479, 1282, 1165, 1140, 1065, 1030, 985, 770,  $677\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  5.61 (br s, 2 H, H-8, H-9), 4.76 (d, 1 H,  $J = 2.5\text{ Hz}$ , H-1), 4.37 (br s, 3 H, H<sub>2</sub>-6, H-5), 3.90 (dq, 1 H,  $\text{OCH}_A\text{H}_B\text{CH}_3$ ), 3.68 (dq, 1 H,  $\text{OCH}_A\text{H}_B\text{CH}_3$ ), 3.16 (br m, 1 H), 2.70 (br d, 1 H,  $J = 15.6\text{ Hz}$ ), 2.50 (m, 1 H), 2.22-1.98 (m, 3 H), 1.30 (t, 3 H,  $J = 7\text{ Hz}$ ,  $\text{OCH}_2\text{CH}_3$ ), 1.20 (s, 9 H,  $\text{C}(\text{CH}_3)_3$ );  $^{13}\text{C NMR}$  ( $\text{C}_6\text{D}_6$ , 200 MHz)  $\delta$  5.52 (m, 2 H, H-8, H-9), 4.57 (m, 2 H, H<sub>2</sub>-6), 4.44 (d, 1 H,  $J = 2\text{ Hz}$ , H-1), 4.06 (1 H, dd, H-5), 3.63 (dq, 1 H,  $J = 7, 9.2\text{ Hz}$ ,  $\text{OCH}_A\text{H}_B\text{CH}_3$ ), 3.28 (dq, 1 H,  $J = 7, 9.2\text{ Hz}$ ,  $\text{OCH}_A\text{H}_B\text{CH}_3$ ), 2.90-2.63 (m, 2 H), 2.23-1.60 (m, 4 H), 1.20 (s, 9 H,  $\text{C}(\text{CH}_3)_3$ ), 1.10 (t, 3 H,  $J = 7\text{ Hz}$ ,  $\text{OCH}_2\text{CH}_3$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 50.32 MHz) 205.90 (s), 177.65 (s), 124.94 (d), 124.09 (d), 99.36 (d), 73.05 (d), 63.29 (t), 62.27 (t), 42.04 (d), 38.91 (d), 38.51 (s), 26.98 (q), 25.19 (t), 22.02 (t), 14.97 (q); exact mass,  $m/z$  310.1774 (calcd for  $\text{C}_{17}\text{H}_{26}\text{O}_5$ ,  $m/z$  310.1780).

**Ethyl 2,3-C-(2-Butene-1,4-diyl)-2,3-dideoxy- $\alpha$ -D-talopyranoside (12).**<sup>15</sup> The keto ester 11 (106 g, 342 mmol) in THF (360 mL) was added at 0 °C over 30 min to a mechanically stirred suspension of lithium aluminum hydride (13 g, 343 mmol) in THF (800 mL). The ice-salt cooling bath was removed and stirring was continued for 1 h. At this stage no starting material remained (TLC) and excess reagent was destroyed by slow addition (vigorous stirring) of saturated aqueous ammonium chloride solution. Then ethyl acetate (500 mL) was added followed by enough Celite to make the precipitated aluminum hydroxide filterable. (This stage is reached when all solids sink to the bottom of the flask if the stirrer is stopped.) Stirring was continued for 4 h and the mixture was filtered through a pad of Celite. Evaporation of the filtrate afforded a colorless liquid (54.6 g). A further quantity (21.8 g) of the product was obtained by stirring the filter cake with more ethyl acetate for 18 h. The crude diol (76.4 g) was purified by flash chromatography over silica gel using 7:3 ethyl acetate-hexane. The diol 12<sup>15</sup> (70.0 g, 90%) was obtained as a homogeneous (TLC, silica gel, 7:3 ethyl acetate-hexane) oil:  $[\alpha]_D^{25} +134.6^\circ$  (c 3.6,  $\text{CHCl}_3$ ) [lit.<sup>15</sup>  $+126^\circ$  (c 2.56,  $\text{CHCl}_3$ )]; IR (film) 3420, 1132, 1060, 1010, 975, 900, 830, 790, 750,  $665\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  5.80 (br s, 2 H, H-8, H-9), 4.73 (s, 1 H, H-1), 4.00-3.68 (m, 5 H, H-4, H-5, H<sub>2</sub>-6,  $-\text{OCH}_A\text{H}_B\text{CH}_3$ ), 3.56 (dq, 1 H,  $J = 7, 9.5\text{ Hz}$ ,  $-\text{OCH}_A\text{H}_B\text{CH}_3$ ), 3.05 (m, 1 H, OH), 2.78 (m, 1 H, OH), 2.60-2.00 (m, 6 H, H-2, H-3, H<sub>2</sub>-7, H<sub>2</sub>-10), 1.22 (t, 3 H,  $J = 7\text{ Hz}$ ,  $-\text{OCH}_2\text{CH}_3$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 50.32 MHz)  $\delta$  126.59 (d), 125.89 (d), 100.31 (d), 71.64 (d), 70.77 (d), 62.83 (t), 62.20 (t), 34.03 (d), 29.90 (d), 27.48 (t), 26.59 (t), 14.69 (q).

**( $\alpha$ R, $\beta$ R,1R,6S)- $\alpha,\beta$ -Dihydroxy-6-(1,3-benzodithiol-2-yl)-3-cyclohexenepropanol (13).** Benzene-1,2-dithiol<sup>22</sup> (7.00 g, 49.2 mmol) and then anhydrous dichloromethane (300 mL) were added to diol 12 (10.0 g, 43.8 mmol) under an argon atmosphere. The mixture was cooled to -70 °C and titanium tetrachloride<sup>30</sup> (20 mL, 182 mmol, from a fresh bottle) was added over 30 min with vigorous stirring. Stirring was continued for an additional 45 min and the reaction was quenched by addition of crushed ice (ca. 200 g) and water (200 mL). The mixture was stirred for a further 15 min. The organic layer was separated, washed with water (2  $\times$  100 mL), dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. The residual thick liquid was dissolved in ethyl acetate (300 mL) and washed by gentle swirling with 10% w/v aqueous sodium hydroxide (3  $\times$  75 mL) and then with water (3  $\times$  100 mL). (Vigorous shaking will result in emulsions that are difficult to crack.) The organic layer was dried and evaporated. Flash chromatography of the crude product over silica gel using 20:1 methanol-dichloromethane gave the triol 13 (8.29 g, 58%) as a homogeneous (TLC, silica gel, ethyl acetate) gummy foam:  $[\alpha]_D^{25} -2.2^\circ$  (c 0.82,  $\text{CHCl}_3$ ); IR (cast from  $\text{CHCl}_3$ ) 3400, 1445, 1432, 1119, 1050, 975, 945, 910, 870, 742,  $660\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  7.20 (m, 2 H, Ar H), 7.04 (m, 2 H, Ar H), 5.80-5.50 (m, 2 H, H-3, H-4), 5.44 (d, 1 H,  $J = 11\text{ Hz}$ , SCHS), 3.96-3.60 (m, 4 H,  $\text{CH}(\text{OH})\text{CH}(\text{OH})\text{CH}_2\text{OH}$ ), 3.08-2.00 (m, 8 H, H-1, H<sub>2</sub>-2, H<sub>2</sub>-5, H-6, three OH);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 50.32 MHz)  $\delta$  137.85 (s), 137.59 (s), 126.46 (d), 125.29 (d), 125.26 (d), 124.93 (d), 122.37 (d), 122.28 (d), 72.00 (d), 71.09 (d), 66.07 (t), 59.10 (d), 43.32 (d), 36.73 (d), 28.23 (t), 27.77 (t); exact mass,  $m/z$  324.0859 (calcd for  $\text{C}_{16}\text{H}_{20}\text{S}_2\text{O}_3$ ,  $m/z$  324.0854). Anal. Calcd for  $\text{C}_{16}\text{H}_{20}\text{O}_3\text{S}_2$ : C, 59.23; H, 6.21; S, 19.76. Found: C, 59.39; H, 6.39; S, 19.57.

For further characterization, a portion of the triol was acetylated (pyridine, acetic anhydride, DMAP, room temperature, 12 h). The

triacetate had the following: IR (cast from  $\text{CHCl}_3$ ) 1742, 1441, 1431, 1370, 1245, 1216, 1045,  $742\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  7.2 (m, 2 H, Ar H), 7.03 (m, 2 H, Ar H), 5.70 (m, 2 H, H-3, H-4), 5.32 (m, 2 H,  $\text{CHOAc}$ , SCHS), 4.85 (br d, 1 H,  $J = 8.8\text{ Hz}$ ,  $\text{CHOAc}$ ), 4.30 (dd, 1 H,  $J = 11, 4.4\text{ Hz}$ ,  $-\text{CH}_A\text{H}_B\text{OAc}$ ), 3.95 (dd, 1 H,  $J = 11, 7.2\text{ Hz}$ ,  $-\text{CH}_A\text{H}_B\text{OAc}$ ), 2.8-1.8 (m, including 3 singlets at 2.20, 2.16, and 2.05, 15 H); exact mass,  $m/z$  450.1161 (calcd for  $\text{C}_{22}\text{H}_{26}\text{O}_6\text{S}_2$ ,  $m/z$  450.1170).

**(1R,6S)-6-(1,3-Benzodithiol-2-yl)-3-cyclohexenecarbaldehyde (14).** Note: Aldehyde 14 is unstable: the reaction mixture should be worked up quickly and the product reduced immediately. Commercial lead tetraacetate (29.0 g, 65 mmol) was added in portions to a magnetically stirred and cooled (cooling bath filled with ice-cold water) solution of triol 13 (10.0 g, 31 mmol) in anhydrous benzene (300 mL). The mixture was stirred for 30 min after the end of the addition and the excess of reagent was destroyed by addition of sufficient ethylene glycol to produce two phases. The benzene layer was separated, washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. Flash chromatography of the residue over silica gel using 12:88 ethyl acetate-hexane gave aldehyde 14 (5.30 g, 65%) as an almost colorless oil. The material, which contained only trace impurities (TLC, silica gel, 12:88 ethyl acetate-hexane) had the following: FT-IR (cast from  $\text{CHCl}_3$ ) 1715, 1650, 1562, 1445, 1422, 1260, 1115, 930, 800, 742, 672,  $660\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  9.72 (br s, 1 H,  $-\text{CHO}$ ), 7.24 (m, 2 H, Ar H), 7.06 (m, 2 H, Ar H), 5.74 (br s, 2 H, H-3, H-4), 5.13 (d, 1 H,  $J = 10.4\text{ Hz}$ , SCHS), 3.06-2.92 (m, 1 H), 2.60-2.06 (m, 5 H, i.a. H<sub>2</sub>-2, H<sub>2</sub>-5); exact mass,  $m/z$  262.0481 (calcd for  $\text{C}_{14}\text{H}_{14}\text{OS}_2$ ,  $m/z$  262.0486).

**(1R,6S)-6-(1,3-Benzodithiol-2-yl)-3-cyclohexenemethanol (15).** Aldehyde 14 (45.0 g, 172 mmol) in anhydrous THF (150 mL) was added over 30 min to a mechanically stirred and cooled (ca. 0 °C) slurry of lithium aluminum hydride (3.00 g, 79 mmol) in THF (300 mL). The ice-bath was removed and stirring was continued for 1 h. At this stage no starting material remained (TLC) and excess reagent was destroyed by slow addition (vigorous stirring) of ice-cold, saturated aqueous ammonium chloride solution. Then ethyl acetate (500 mL) was added followed by enough Celite to make the precipitated aluminum hydroxide filterable. (This stage is reached when all solids sink to the bottom of the flask if the stirrer is stopped.) Stirring was continued for 2 h and the mixture was filtered through a pad of Celite. The solids were washed with ethyl acetate (400 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel using 1:3 ethyl acetate-hexane gave 15 (43.5 g, 96%) as a homogeneous (TLC, silica gel, 3:7 ethyl acetate-hexane) oil:  $[\alpha]_D^{25} +14.36^\circ$  (c 1.4,  $\text{CHCl}_3$ ); IR (film) 3350, 1650, 1565, 1445, 1260, 1120, 1035, 745, 680,  $670\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  7.22 (m, 2 H, Ar H), 7.00 (m, 2 H, Ar H), 5.64 (br s, 2 H, H-3, H-4), 5.16 (d, 1 H,  $J = 11\text{ Hz}$ , SCHS), 3.76 (dd, 1 H,  $-\text{CH}_A\text{H}_B\text{OH}$ ), 3.59 (dd, 1 H,  $-\text{CH}_A\text{H}_B\text{OH}$ ), 2.56-1.76 (m, 7 H, H-1, H<sub>2</sub>-2, H<sub>2</sub>-5, H-6, OH);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 50.32 MHz)  $\delta$  137.61 (s), 137.50 (s), 125.27 (d), 122.33 (d), 122.28 (d), 61.83 (t), 59.05 (d), 42.96 (d), 36.53 (d), 28.38 (t), 27.08 (t); exact mass,  $m/z$  264.0644 (calcd for  $\text{C}_{14}\text{H}_{16}\text{OS}_2$ ,  $m/z$  264.0643). Anal. Calcd for  $\text{C}_{14}\text{H}_{16}\text{OS}_2$ : C, 63.60; H, 6.10; S, 24.25. Found: C, 63.54; H, 6.25; S, 24.07.

**(1R,6S)-6-Methyl-3-cyclohexenemethanol (16).** The apparatus consisted of a three-necked, 1-L round-bottomed flask fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a Dewar condenser filled with dry ice-acetone. The flask was immersed in a dry ice-acetone bath and charged with anhydrous ammonia (600 mL, run directly from a tank). The ammonia was stirred vigorously and the alcohol 15 (8.00 g, 30 mmol) in anhydrous THF (100 mL) was added quickly from the addition funnel. The cooling bath was removed and sodium (3.00 g, 130 mmol, cut into small pieces) was added. The suspension was allowed to decolorize before each fresh piece of sodium was introduced and an ethanol bath was occasionally placed beneath the reaction vessel to ensure vigorous boiling of the ammonia. When the blue color persisted for 25 min the desulfurization was judged to be complete. The stirrer was stopped and the ammonia was allowed to evaporate overnight. Saturated aqueous ammonium chloride (200 mL) containing a little crushed ice (ca. 100 g) was added cautiously to the solid residue with gentle stirring. The mixture was diluted with water (300 mL) and extracted with ether (4  $\times$  75 mL). The extract was washed with 10% w/v

aqueous sodium hydroxide (3 × 50 mL) and with water (5 × 70 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated at 1 atm using a simple Claisen head and an oil bath. The residual liquid was distilled under water-pump vacuum to give 16 (3.10 g, 81%) as a colorless, homogeneous (TLC, silica gel, 3:7 ethyl acetate-hexane) liquid: bp 108–110 °C (water-pump), [α]<sub>D</sub> -23.84° (c 2.2, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) δ 5.60 (m, 2 H, H-3, H-4), 3.58 (m, 2 H, -CH<sub>2</sub>OH), 2.34–1.50 (m, 7 H, H-1, H<sub>2</sub>-2, H<sub>2</sub>-5, H-6, OH), 0.89 (d, 3 H, J = 6.8 Hz, CH<sub>3</sub>); exact mass, *m/z* 126.1044 (calcd for C<sub>8</sub>H<sub>14</sub>O, *m/z* 126.1044). NMR measurements on derivatives<sup>12,13</sup> (see text) showed the material to be optically pure.

(1*R*,6*S*)-6-Methyl-3-cyclohexenecarboxylic Acid (4). Jones reagent<sup>34</sup> was added dropwise to a stirred and cooled (0 °C) solution of alcohol 16 (126.3 mg, 1.00 mmol) in acetone (3 mL). Each drop of reagent was added only after the yellow color of the reaction mixture had changed to green and sufficient reagent was introduced to produce a persistent (30 min) yellow coloration. Excess reagent was then destroyed with 2-propanol and the reaction mixture was diluted with diethyl ether (40 mL) and water (20 mL). The green precipitate initially present dissolved. The phases were separated and the aqueous layer was extracted with diethyl ether (20 mL). The combined extracts were washed with 10% w/v aqueous sodium hydroxide (1 × 40 mL, 1 × 20 mL).

(34) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; p 142.

The alkaline solution was washed with diethyl ether (1 × 20 mL), acidified with 1 N HCl, and extracted with diethyl ether (2 × 40 mL). This last ethereal extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated (water-pump vacuum, 20 °C). Kugelrohr distillation [70–75 °C, 0.05 mm] of the residue gave 4 (84.3 mg, 60%) as a colorless liquid [α]<sub>D</sub> -31.77° (c 1.98, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) δ 12 (br, 1 H, COOH), 5.66 (br s, 2 H, H-3, H-4), 2.80–2.66 (m, 1 H, H-6), 2.50–2.12 (m, 4 H, H<sub>2</sub>-2, H<sub>2</sub>-5), 2.02–1.82 (m, 1 H, H-1), 0.98 (d, 3 H, J = 7.2 Hz, CH<sub>3</sub>); exact mass, *m/z* 140.0836 (calcd for C<sub>8</sub>H<sub>12</sub>O<sub>2</sub>, *m/z* 140.0837). Anal. Calcd for C<sub>8</sub>H<sub>12</sub>O<sub>2</sub>: C, 68.55; H, 8.63. Found: C, 69.04; H, 8.71. Examination of the derived methyl ester (diazomethane) by VPC (Carbowax 20M on Chromosorb W, 6 ft, 190 °C) showed the mixture to be free of trans isomer.

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**Registry No.** 1 (R = H), 73573-88-3; 4, 102629-35-6; 8, 23339-15-3; 8 (dipivolate), 102586-32-3; 9, 102574-24-3; 10, 102574-25-4; 11, 102574-26-5; 12, 86646-59-5; 13, 102574-27-6; 14, 102574-28-7; 15, 102574-29-8; 16, 102629-34-5; 2,2-dimethylpropanoyl chloride, 3282-30-2; butadiene, 106-99-0; benzene-1,2-dithiol, 17534-15-5.

## Homochiral Ketals in Organic Synthesis. Enantioselective Synthesis of (*R*)-Muscone

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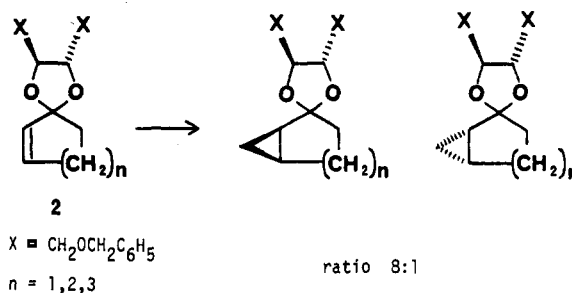
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An efficient, enantioselective preparation of (*R*)-muscone employing a diastereoselective Simmons-Smith cyclopropanation is described. Cyclopropanation is directed via chelation control by a homochiral ketal protecting group derived from unnatural tartaric acid. The overall yield of (*R*)-muscone (>95% *R*) from commercially available cyclopentadecanone is 60% over seven steps.

(*R*)-Muscone (1) (Scheme I) is an odoriferous principle isolated from the male musk deer *Moschus moschiferus*. Since the natural supply is severely limited, a number of muscone syntheses have appeared in the literature<sup>1</sup> and several have addressed the problem of enantioselectivity.<sup>2</sup> However, each of the published enantioselective syntheses suffers from one or more of the following: excessive length, low chemical and optical yields, and scarcity of starting materials.

Recently we reported a novel diastereoselective cyclopropanation process involving homochiral ketals 2.<sup>3</sup> Good diastereoselectivity was observed for conformationally restricted small ring systems, while lower diastereoselec-



tivity was observed for acyclic systems.<sup>4</sup> Intuitively, larger rings (e.g., 2, *n* = 11) might be expected to display intermediate diastereoselectivity. However, recent work by Still and Novack has dramatically shown that diastereoselectivity can be observed in conformationally biased large ring systems.<sup>5</sup> Since a number of natural products, including muscone, contain large rings, we decided to test the ap-

(1) For recent syntheses of (±)-muscone, see: (a) Cantoni, G.; Galli, C.; Mandolini, L. *J. Org. Chem.* 1980, 45, 1906–1908. (b) Fliri, H. G.; Scholz, D.; Stutz, A. *Montash Chem.* 1979, 110, 245–247 and references cited therein.

(2) For enantioselective syntheses of muscone, see: (a) Stallberg-Stenhagen, S. *Arkiv. Kemi* 1951, 3, 517–524. (b) Mamdapur, V. R.; Pai, P. P.; Chakravarti, K. K.; Nayak, U. G.; Bhattacharyya, S. C. *Tetrahedron* 1964, 20, 2601–2604. (c) Branca, Q.; Fischli, A. *Helv. Chim. Acta* 1977, 925–944. (d) Utimoto, K.; Tanaka, M.; Kitai, M.; Nozaki, H. *Tetrahedron Lett.* 1978, 2301–2304. (e) Abad, A.; Arno, M.; Pardo, A.; Pedro, J. R.; Seoane, E. *Chem. Ind. (London)* 1985, 29–30.

(3) Mash, E. A.; Nelson, K. A. *J. Am. Chem. Soc.* 1985, 107, 8256–8258.

(4) However, Arai, et al. have described conditions under which related acyclic acetals are cyclopropanated with good diastereoselectivity. See: Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* 1985, 107, 8254–8256.

(5) Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* 1984, 106, 1148–1149. For additional examples of diastereoselective additions to large ring systems, see references cited therein.