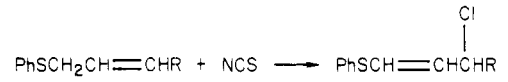
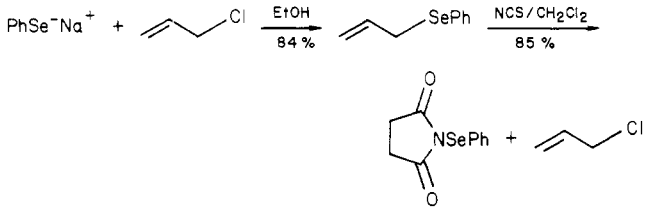
Scheme III



Scheme IV



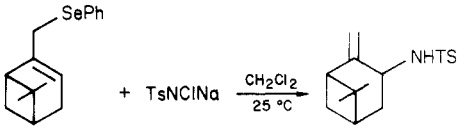
position of the double bond. A likely mechanism for this reaction is as follows: NCS reacts with the selenium moiety to give (alkylphenylsuccinimido)selenonium chlorides, which in turn undergo a 2,3-like rearrangement which leads to the allylic chlorides. It will be noticed that there is a similarity between these reactions and those of the corresponding 2,3 shifts observed for allylic phenylselenoxides.[10]

Cohen and co-workers have reported the reaction of allylic phenylsulfides with NCS shown in Scheme III. The reaction takes a completely different course than that described here for the selenium analogues.[11]

The facility of the reaction between allylic phenylselenides and NCS (e.g., reaction 3, Scheme I) suggested the efficient route to *N*-(phenylseleno)succinimide (**5**) shown in Scheme IV.[12] A number of interesting applications have been found for *N*-(thiophenyl)succinimide, and *N*-(thiophenyl)phthalimide,[13] and now that the corresponding selenium analogue is available, it seems likely that it will find uses as well.[15]

Allylic phenylselenides are potentially valuable in organic synthesis due primarily to the ease with which they undergo substitutive allylic rearrangements following oxidations at the selenium atom. We had previously established these rearrangements for oxygen[10] and carbon,[14] and the present work has extended this class of reactions to include chlorine.

Finally, we wish to describe a single experiment which demonstrates that nitrogen can also be included in this list. It was found that 10-(phenylseleno)-β-pinene (**6**) afforded 3-(*p*-toluenesulfonamido)-β-pinene (**15**) in 44% yield upon reaction with 2.5 equiv of anhydrous Chloramine-T in methylene chloride.



Acknowledgment. We are grateful to the National Science Foundation (CHE74-21260), Hoffmann-LaRoche, and Eli Lilly for financial support.

Registry No. 1, 127-91-3; 2, 71564-06-2; 3, 30897-76-8; 4, 5707-04-0; 5, 68395-72-2; 6, 71518-08-6; 7, 71518-09-7; 8, 71518-10-0; 9, 71518-11-1; 10, 42886-46-4; (*E*)-11, 71518-12-2; (*Z*)-11, 71518-13-3; 12, 71518-14-4; 13, 471-10-3; 14, 5389-87-7; 15, 57981-21-2; NCS, 128-09-6; diphenyl diselenide, 1666-13-3; allyl chloride, 107-05-1; allyl phenylselenide, 14370-82-2; TsNClNa, 127-65-1.

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Received January 3, 1979

(10) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7154. Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, 1979.

(11) Mura, A. J., Jr.; Bennett, D. A.; Cohen, T. *Tetrahedron Lett.* **1975**, 4433.

(12) The procedure for preparation of **5** is as follows. Diphenyl diselenide (3.12 g, 10 mmol) was dissolved in 20 mL of absolute ethanol. Sodium borohydride (768 mg, 20.3 mmol) was added carefully, while stirring magnetically under nitrogen, until the bright yellow solution turned colorless. The reaction mixture was cooled in an ice bath and allyl chloride (1.68 g, 22 mmol) was added. The ice bath was removed and the reaction mixture was stirred at ambient temperature for 5 h. Extraction with hexane and distillation afforded 3.31 g (84%) of allyl phenylselenide, bp 75–76 °C (0.3 mm). It seems very likely that the standard molar scale Grignard preparation of diphenyl diselenide [Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947] could be easily modified (i.e., addition of allyl chloride to the PhSeMgBr instead of air oxidation) to produce allyl phenyl selenide directly. NCS (2.19 g, 16.4 mmol) was added to a magnetically stirred ice-cooled solution of allyl phenylselenide (3.31 g, 16.8 mmol) in 30 mL of dry methylene chloride under nitrogen atmosphere. The ice bath was removed after 30 min and the reaction mixture was stirred for an additional 1.5 h at room temperature. Concentration of the solvent to about 5 mL and addition of 17 mL of dry hexane gave 3.54 g (97% pure by NMR, but gave correct C, H analysis, mp 114–120 °C, 82% yield) of (phenylseleno)succinimide, which is sensitive to moisture but is otherwise stable: NMR (60 MHz, $CDCl_3$) δ 2.78 (4 H, s) and 7.2–7.9 (5 H, m). A signal due to the methylene protons of succinimide appears at 2.71 ppm if the product is contaminated by succinimide.

(13) Mukaiyama, T.; Kobayashi, S.; Kumamoto, T. *Tetrahedron Lett.* **1970**, 5115. Kumamoto, T.; Kobayashi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 866.

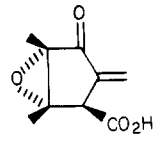
(14) Sharpless, K. B.; Gordon, K. M.; Lauer, R. F.; Patrick, D. W.; Singer, S. P.; Young, M. W. *Chem. Scr.* **1975**, *8A*, 9.

(15) (a) Dr. L. K. Truesdale (Allied Chemical Co., Morristown, N.J.) has prepared a variety of *N*-(arylseleno)succinimides using our procedure (see ref 12). He has also prepared *N*-(phenylseleno)phthalimide by the same procedure[12] except that *N*-chlorophthalimide was used in place of *N*-chlorosuccinimide. (b) For some interesting synthetic applications of both *N*-(phenylseleno)succinimide and *N*-(phenylseleno)phthalimide see Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.

Stereospecific Total Synthesis and Absolute Configuration of (+)-Methylenomycin A

Summary: Starting from 2,3-dimethyl-1-oxocyclopent-2-ene-4-carboxylic acid (**4**), a stereospecific synthesis of (+)-methylenomycin A (**1**) was accomplished and its absolute configuration was determined via X-ray crystallographic techniques.

Sir: Methylenomycin A (**1**) and B are two antibiotics recently reported by Arai and co-workers.[1] Compound



1

1 bears structural similarities to a whole family of medicinally important cyclopentanone natural products, including the pentenomycins,[2] xanthocidin,[3] and sarkomy-

(1) T. Haneishi, N. Kitahara, Y. Takiguchi, M. Arai, and S. Sugawara, *J. Antibiot.*, **27**, 386 (1974).

(2) K. Umino, N. Takeda, Y. Ito, and T. Okuda, *Chem. Pharm. Bull.*, **22**, 1233 (1974).

(3) K. Asahi, J. Nagatsu, and S. Suzuki, *J. Antibiot.*, **19**, 195 (1966); K. Asahi and S. Suzuki, *Agric. Biol. Chem.*, **34**, 325 (1970).

0022-3263/79/1944-4210$01.00/0

cin,[4] an experimental cancer drug. The relative configuration of 1 was established by an X-ray crystallographic study.[6] Methylenomycin B, however, was isolated as an unstable oil, and its proposed structure was based on spectral comparisons with methylenomycin A. The structure and synthesis of methylenomycin B are described in a following communication.[7]

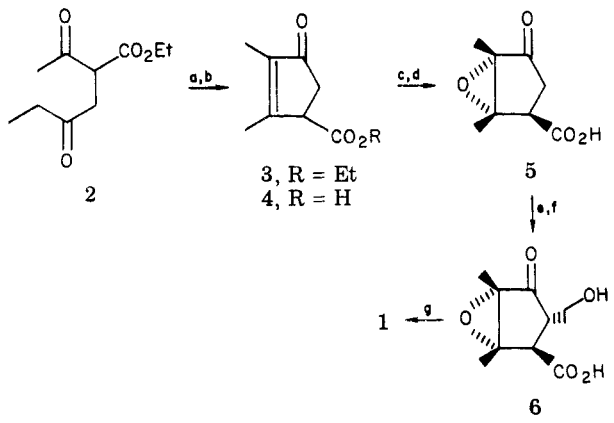
We report here a stereospecific total synthesis of (+)-methylenomycin A (**1**)[8] and the determination of its absolute configuration.

Alkylation of ethyl acetoacetate (NaH in ethyl ether) with 1-bromo-2-butanone gave the 1,4-diketone[9] **2** [85%, bp 85–87 °C (0.3 mm)]. Treatment of **2** with NaOEt in EtOH afforded the cyclized ester **3** [37%, bp 83–84 °C (0.2 mm)] (Scheme I), which, after alkaline hydrolysis, gave (±)-**4**[10] (79%, mp 81–83 °C dec): IR ($CHCl_3$) 2730, 2640 (br), 1705, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73, 2.11 (2 s, $2CH_3$), 2.67 (d, CH_2), 3.60 (m, CH), 10.98 (s, CO_2H). Compound (±)-**4**, oxidized under alkaline conditions, gave *trans*-epoxide (±)-**5**[11] (72%, mp 125.5–127 °C): IR ($CHCl_3$) 3100 (br), 1755, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40, 1.56 (2 s, $2CH_3$), 2.26, 2.58 (2 ddd, CH_2, J = 18, 1.5, 8 Hz), 3.33 (dd, CH, J = 1.5, 8 Hz), 10.41 (br, CO_2H).

The resolution could be carried out on either unsaturated acid **4** or on the epoxy acid **5**. Thus, the addition of 0.5 equiv of (*S*)-(−)-α-methyl-*p*-nitrobenzylamine to **5** in 2-propanol afforded a dextrorotatory salt (85%, mp 138 °C dec, $[\alpha]^{25}_D$ +28°), which gave, after acidification, (+)-**5**[12] (77% from (±)-**5**, mp 52–54 °C, $[\alpha]^{22}_D$ +56°).

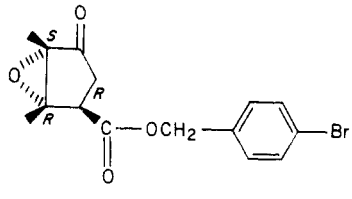
The introduction of the α-methylene functionality and thus completion of the total synthesis were achieved via the hydroxymethyl compound **6**. This was prepared by treating **5** with 2 equiv of LDA in THF/HMPA (3:1) at −40 °C and alkylating the resulting lithium enolate with gaseous formaldehyde.[13] The product (+)-**6** [30%; mp 72.5–73.5 °C;[14] $[\alpha]^{22}_D$ +28°; IR ($CHCl_3$) 3620, 3500, 2700–2500, 1750, 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42, 1.58 (2 s, $2CH_3$), 2.74 (dt, COCH, J = 7, 2.5 Hz), 3.26 (d, $CHCO_2$, J = 2.5 Hz), 3.75 (d, CH_2O, J = 7 Hz), 6.92 (br, COOH and OH)] was assigned the trans configuration between the hydroxymethyl and the carboxylic acid groups on the basis of its NMR spectrum.[15] Dehydration was achieved using dimethylformamide dineopentyl acetal[16] in DMF to afford (+)-methylenomycin A (**1**) in 77% yield after crystallization from benzene.[17] Our synthetic product[18] exhibits a melting point of 115–117 °C and a $[\alpha]^{22}_D$ +36°[19,20] which are essentially identical with those values obtained from an authentic sample kindly provided by Dr. M. Arai.[21] The NMR, IR, UV, and mass spectra of our synthetic **1** are superimposable with those published and the ^{13}C NMR spectrum (CH_2Cl_2) is consistent with the structure **1**: δ 8.1, 13.7 (2 q, $2CH_3$), 51.5 (d, CH), 65.2 (s, CO), 66.6 (s, CO), 123.3 (t, $=CH_2$), 140.3 (s, C=), 175.7 (s, CO_2), 196.6 (s, C=O).

Scheme I



(a) NaOEt, EtOH; (b) 2 N NaOH; (c) 30% H_2O_2/Na_2CO_3/CH_3OH; (d) (*S*)-(−)-α-methyl-*p*-nitrobenzylamine; (e) LDA; (f) CH_2O; (g) $HCN(CH_2)_2(OC_5H_{11})_2$.

To determine the absolute configuration of (+)-**1**, we attempted to prepare the *p*-bromobenzyl ester. This met with difficulties because the product appeared to be unstable; instead, the *p*-bromobenzyl ester **7** was prepared[22] from (+)-**5**. An X-ray crystallographic study of compound **7** (mp 66–68 °C) established its absolute stereochemistry as shown. Thus (+)-methylenomycin A must have the absolute configuration depicted as **1**.



7

Crystal data: $C_{15}H_{15}BrO_4$, orthorhombic, space group $P2_12_12_1$, with a = 9.520 (1), b = 11.605 (1), c = 13.408 (1) Å, Z = 4, d_{calcd} = 1.520 g cm^{-3}. The intensity data were

(4) H. Umezawa, T. Takeuchi, and K. Nitta, *J. Antibiot., Ser. A*, 6, 101 (1953); I. Hooper, L. C. Cheney, M. J. Cron, O. B. Fardig, D. A. Johnson, F. M. Palermiti, H. Schmitz, and W. B. Wheatley, *Antibiot. Chemother.*, 5, 585 (1955).

(5) S. A. Waksman and H. A. Lechevalier, "The Actinomycetes—Antibiotics of Actinomycetes", Vol. 3, William S. Wilkins, Baltimore, Md., 1962, pp 362–364.

(6) T. Haneishi, A. Terahara, M. Arai, T. Hata, and C. Tamura, *J. Antibiot.*, 27, 393 (1974).

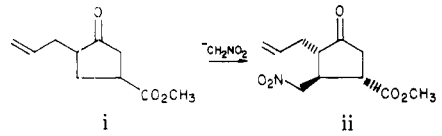
(7) J. Jernow, W. Tautz, P. Rosen, and T. H. Williams, *J. Org. Chem.*, following paper in this issue.

(8) Racemic methylenomycin A was recently synthesized: R. M. Scarborough, Jr., and A. B. Smith, III, *J. Am. Chem. Soc.*, 99, 7085 (1977).

(9) P. J. Ashworth, G. H. Whitham, and M. C. Whiting, *J. Chem. Soc.*, 4633 (1957).

(10) All yields reported here were based on analytical material purified by crystallization or distillation.

(11) A similar trans Michael addition was achieved when nitromethane was added to i:



i ii

F. Kienzle, G. W. Holland, J. L. Jernow, S. Kwoh, and P. Rosen, *J. Org. Chem.*, 38, 3440 (1973).

(12) Optical purity was determined to be of ee ≥96% by preparing an amide derivative of **5** using (*S*)-(−)-α-methyl-*p*-nitrobenzylamine and determining the relative percentage of the diastereoisomers by TLC. (*R*)-(+)-α-Methyl-*p*-nitrobenzylamine produced the corresponding amide of (−)-**5**, mp 138 °C dec, $[\alpha]^{22}_D$ −54°.

(13) P. A. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 1317 (1972).

(14) The racemic compound (±)-**6** has mp 82–84 °C.

(15) The trans vicinal proton coupling constant is ca. 2 Hz while the cis coupling constant (as in **5**) is ca. 8 Hz.

(16) A. Ruttimann, A. Wick, and A. Eschenmoser, *Helv. Chim. Acta*, 58, 1450 (1975).

(17) Methylenomycin A decomposes slightly on silica gel, but it can be purified on a Sephadex LH-20 chromatographic column (CH_3OH/EtOAc) or by sublimation.

(18) An X-ray analysis confirms the relative configuration of the synthetic material.

(19) The enantiomeric excess was estimated to be ≥96% on the basis of an NMR study of its Eu(fod)$_3$ complex.

(20) (±)-Methylenomycin A prepared by this route has mp 105–107 °C.

(21) We wish to thank Dr. M. Arai for this generous sample; we found it to give a melting point of 115–117 °C and $[\alpha]^{22}_D$ +37°.

(22) The ester formation was achieved via the Cs salt of (+)-**5**, an extremely mild method: S. S. Wang, B. F. Gisin, D. P. Winter, R. Makofske, I. D. Kulesha, C. Tzougraki, and J. Meienhofer, *J. Org. Chem.*, 42, 1286 (1977).

measured on a Hilger-Watts diffractometer using Ni-filtered Cu Kα radiation. The reflection data were corrected for absorption [μ = 42.7 cm^{-1}]. Of the 1177 independent reflections for $\theta < 57°$, 1086 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was resolved by Patterson and Fourier methods and was refined by full-matrix least squares to $R = 0.036$ and $wR = 0.044$ (nonhydrogen atoms anisotropic, hydrogen atoms isotropic and not refined).

The absolute configuration was determined by carrying out two refinements, one using the correct value of the imaginary part of the anomalous dispersion corrected for bromine ($\Delta f''$) and the other with the sign of $\Delta f''$ reversed (equivalent to refining the antipode). The weighted discrepancy indices at the end of the two refinements were 0.0436 and 0.0540 for $\Delta f''$ and $-\Delta f''$, respectively. Thus, according to the test described by Hamilton,[23] the absolute configuration is established at better than the 0.995 confidence level.

Acknowledgment. The authors wish to thank Dr. E. P. Oliveto for his interest and stimulating discussions of this work. We also with to thank Drs. W. Benz, V. Toome, and T. Williams and Mr. S. Traiman for mass, UV, NMR, and IR spectra, respectively, as well as Dr. F. Scheidl for the microanalyses.

Registry No. (±)-1, 64911-60-0; (+)-1, 52775-76-5; (±)-2, 71749-31-0; (±)-3, 71749-32-1; (±)-4, 71749-33-2; (±)-5, 71749-34-3; (+)-5, 71773-00-7; (−)-5 (*R*)-(+)-α-methyl-*p*-nitrobenzylamine salt, 71773-02-9; (+)-5 (*S*)-(−)-α-methyl-*p*-nitrobenzylamine salt, 71806-47-8; (±)-6, 71749-35-4; (+)-6, 71773-03-0; 7, 71749-36-5.

Supplementary Material Available: Experimental Section providing preparation details for the compounds in the text (6 pages). Ordering information is given on any current masthead page.

(23) W. C. Hamilton, *Acta Crystallogr.*, 18, 506 (1960).

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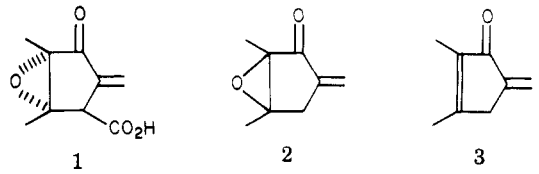
Methylenomycin B: Revised Structure and Total Syntheses

Summary: Starting from 2,3-dimethylcyclopent-2-en-1-one (4), it has been shown that methylenomycin B is not the epoxide 2 as reported, but rather 2,3-dimethyl-5-methylenecyclopent-2-en-1-one (3).

Sir: In the previous communication, we describe the total synthesis of methylenomycin A (1).[1] The related antibiotic methylenomycin B was isolated as an unstable oil, and on the basis of spectral evidence[2] was assigned structure 2. However, analysis of these spectral data did not lend support to the assigned structure,[3] and indeed led us to propose compound 3 as the material isolated as methylenomycin B. To confirm this, both compounds 2 and 3 were synthesized.



1 2 3

Starting with ketone 4 (prepared from methylmagnesium iodide and the *N*-pyrrolidine enamine of 3-methyl-1,2-cyclopentanedione),[4] alkaline hydrogen peroxide treatment produced epoxide 5 [47%,[5] bp 80–81 °C (20 mm)] (Scheme I). The introduction of the α-methylene function was carried out via the hydroxymethyl compound 6, which was prepared by the procedure of Grieco and Hiroi[6] (50%, LDA and gaseous CH_2O). An analytical sample of 6, purified via chromatography, appeared to be homogeneous: IR ($CHCl_3$) 3630, 3550 (br), 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.36 (s, CH_3), 1.51 (s, CH_3) 1.83, 2.28[7] (2 dd, J = 7, 3 Hz, ring CH_2), 2.45 (m, CH, OH), 3.75 (m, CH_2O–); MS m/e 156 (M^+); GC–MS (Me_3Si derivative) m/e 228 (M^+). For the total synthesis of 2, crude 6 was subjected to dehydration (DCC, CuCl). After column chromatography on neutral silica gel followed by distillation [molecular, bath temperature 35 °C (0.2 mm)], compound 2 was isolated in an overall yield of 15% from 5:[8] IR (neat) 1735, 1650 cm^{-1}; UV λ_{max} (CH_3OH) 228–229 nm (ε 7050); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, CH_3), 1.54 (s, CH_3), 2.75 (tq, ring CH_2, J = 2.5 and 18 Hz), 5.39, 6.13 (2 t, CH_2=, J = 2.5 Hz); MS m/e 138 (M^+). Although these data are in agreement with structure 2, they are distinct from those published for methylenomycin B[2]. This confirmed our earlier suspicion of the erroneous structure assignment.

The preparation of 3, our proposed alternate structure for methylenomycin B, started with enone 4 (Scheme II). It was transformed as described previously for compound 6 into compound 7 [bp 80–82 °C (0.2 mm)] in 53% yield: IR ($CHCl_3$) 1675, 1635 cm^{-1}; UV λ_{max} (CH_3OH) 236 nm (ε 12720); ^{1}H NMR ($CDCl_3$) δ 1.69 (s, CH_3), 2.06 (s, CH_3), 2.3–2.9 (m, ring CH_2CH), 2.99 (br s, OH), 3.80 (m, CH_2O); MS m/e 140 (M^+). The structure of 7 was confirmed by an X-ray analysis of its *p*-bromobenzoate ester (mp 91–93 °C). Compound 7 was smoothly transformed (DCC, CuCl) into 3, which after distillation [molecular, bath temperature 37 °C (0.3 mm)] was obtained in 80% yield: IR (neat) 1690, 1662, 1630 cm^{-1}; UV λ_{max} (CH_3OH) 242 (ε 10000); 260–266 nm (sh, ε 7900); ^{1}H NMR ($CDCl_3$) δ 1.78 (br s, CH_3), 2.07 (br s, CH_3), 3.08 (br s, ring CH_2), 5.34, 6.04 (2 t, CH_2=); MS m/e 122 (M^+). A comparison of the IR, UV,

(1) J. Jernow, W. Tautz, P. Rosen, and J. F. Blount, *J. Org. Chem.*, preceding paper in this issue.
(2) T. Haneishi, N. Kitahara, Y. Takiguchi, M. Arai, and S. Sugawara, *J. Antibiot.*, 27, 386 (1974); T. Haneishi, A. Terahara, M. Arai, T. Hata, and C. Tamura, *ibid.*, 27, 393 (1974).
(3) Despite the fact that methylenomycin B was reported to have a microanalysis of $C_8H_{10}O_2$, with m/e 138 (M^+) and a zero optical rotation.
(4) According to the method of Dahill for the preparation of 2-*n*-amyl-3-methylcyclopent-2-en-1-one: R. T. Dahill, Jr., *J. Org. Chem.*, 31, 2694 (1966).
(5) Because of the alkali sensitivity of 5, this reaction has to be terminated when the rate of destruction overtook the production of 5.
(6) P. A. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 1317 (1972).
(7) In a cyclopentane system, an epoxide deshields the cis vicinal proton. The C(4) proton which absorbs at δ 2.28 (downfield) is therefore cis to the epoxide. It must be, at the same time, trans to the C(5)-H as deduced from the small J = 3 Hz, and in contrast to J = 7 Hz for the C(4) proton, which absorbs at δ 1.83, indicating cis relationship to the C(5)-H. Therefore, the hydroxymethyl group at C(5) must be cis to the epoxide in the analytical sample of 6.
(8) All yields were based on analytical samples purified by distillation, crystallization, or sublimation.

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