hydrofuran. After the mixture was stirred 1 h at 0 °C, the material was taken up in ether and eluted through a silica gel column, yielding 65 mg (94%) of crude mesylate **38b**: IR ($CCl_4$) 3030 (w), 2850–3000 (s, br), 1380 (s), 1360 (s), 1190 (s) $cm^{-1}$; NMR (60 MHz, $CCl_4$) δ 0.80–2.00 (complex m, 11 H), 2.90, 3.12 (s, s, 3 H), 3.80–4.20 (m, 6 H), 5.80–6.20 (m, 2 H). Mesylate **38b** was reduced immediately without further purification.

Toward this end, to a solution of 65 mg (0.21 mmol) of the isomeric methanesulfonate esters **38b** in 0.8 mL of tetrahydrofuran was added 0.43 mL (0.43 mmol) of lithium triethylborohydride (1 M in tetrahydrofuran). The resulting solution was stirred under argon for 20 min at room temperature and then heated to reflux for 1.5 h. After the mixture was cooled to 0 °C, excess hydride was quenched by the slow addition of 1.4 mL of water, 1.4 mL of 3 N sodium hydroxide, and 1.4 mL of 30% hydrogen peroxide. The mixture was heated at reflux for 1 h, cooled, poured into 2 mL of water, and extracted into pentane. After the mixture was dried, removal of the solvent in vacuo and purification by PLC (500-μm silica gel plate, eluting with methylene chloride) yielded 17.3 mg (38%) of ene ketals **38c**, which were identical in all respects with those prepared from **11**.

**5-Methyltricyclo[4.3.2.0$^{1,6}$]undec-10-en-2-one (12α,β).** A solution containing 15 mg (0.068 mmol) of ene ketal **38c**, 13 μL of concentrated sulfuric acid in 0.7 mL of water (2% aqueous sulfuric acid), and 1 mL of acetone was stirred overnight at room temperature. The mixture was then poured into saturated sodium bicarbonate–ether, washed, and dried. After filtration through magnesium sulfate–silica and evaporation of the solvent in vacuo, **12** was isolated quantitatively as a 2:1 mixture of syn (**12β**) and anti (**12α**) isomers, respectively. Separation was effected by VPC (185 °C). Each isomer was identical with respect to IR, 250-MHz NMR, and VPC retention time with the same isomer prepared from **11**.

**Acknowledgment.** It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health (Institute of General Medical Sciences) through Grant GM 24680. In addition we thank Mr. S. T. Bella of the Rockefeller University for the microanalyses and the Middle Atlantic Regional NMR facility (Grant NIH RR542) at the University of Pennsylvania where the 220- and 360-MHz NMR spectra were recorded.

**Registry No.** (±)-**1α**, 76739-64-5; (±)-**1β**, 76739-65-6; (±)-**8α**, 76685-65-9; (±)-**8β**, 76739-60-1; (±)-**9α**, 76740-73-3; (±)-**9β**, 76685-66-0; (±)-**10**, 73537-33-4; (±)-**11**, 78676-01-4; (±)-**12α**, 80953-79-3; (±)-**12β**, 80996-28-7; (±)-**13**, 78676-00-3; (±)-**14**, 80953-80-6; **18**, 5323-87-5; **19**, 61765-62-6; **20**, 61765-54-6; (±)-**21**, 80953-81-7; **23a**, 80953-82-8; **23b**, 80953-83-9; (±)-**24** (isomer I), 80953-84-0; (±)-**24** (isomer II), 80996-29-8; (±)-**29α**, 76685-67-1; (±)-**29β**, 76739-61-2; (±)-**30α**, 76685-68-2; (±)-**30β**, 76739-62-3; (±)-**34α**, 76685-69-3; (±)-**34β**, 76739-63-4; **35**, 80953-85-1; **36**, 80953-86-2; **37a**, 80953-87-3; **37b**, 80953-88-4; (±)-**38a** (isomer I), 80953-89-5; (±)-**38a** (isomer II), 80996-30-1; (±)-**38b** (isomer I), 80953-90-8; (±)-**38b** (isomer II), 80996-31-2; (±)-**38c** (isomer I), 80953-91-9; (±)-**38c** (isomer II), 80996-32-3; (±)-**i**, 80953-93-1; isopropenyl bromide, 557-93-7; 5-methyl-10,11-dichlorotricyclo[4.3.2.0$^{1,6}$]undecan-2-one ethylene ketal, 80953-92-0; 1,2-dichloroethylene, 540-59-0.

# Stereocontrolled Total Synthesis of (±)-Pentenomycins I–III, Their Epimers, and Dehydropentenomycin I

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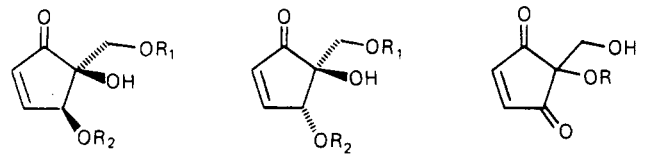
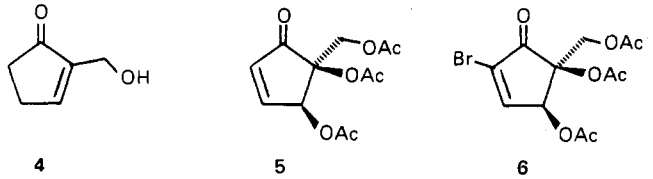
The total synthesis of (±)-pentenomycins I–III (**1a–c**), their epimers (**2a–c**) termed by us epipentenomycins (I–III), and dehydropentenomycin I (**3**), seven members of the novel cyclopentanoid class of antibiotics, has been achieved. The synthetic routes are short (ca. five to seven steps), stereocontrolled, and for the most part highly efficient. Key elements of the strategies were (i) the development of a versatile α-ketovinyl anion equivalent which permitted large-scale preparation of 2-(hydroxymethyl)-2-cyclopentenone (**4**), the common starting material for each antibiotic, (ii) the stereocontrolled cis hydroxylation of derivatives of either **4** or protected allylic alcohols derived from **4** [i.e., selective 1,2-reduction employing the method of Luche (i.e., $NaBH_4/CeCl_3{\cdot}H_2O$)], and (iii) introduction of the requisite α,β-unsaturation via $SeO_2$ oxidation.

Recently, we successfully completed the stereocontrolled total synthesis of (±)-pentenomycins I–III (**1a–c**),[2] their epimers (**2a–c**),[3] and the closely related dehydropentenomycin I (**3**),[2] seven members of the novel cyclopentanoid class of antibiotics.[4] We record here a full account of that effort. We note in advance that the synthetic stragegies are short, ranging from five to seven steps from 2-(hydroxymethyl)-2-cyclopentenone (**4**), stereocontrolled, and for the most part highly efficient. Furthermore, 2-(hydroxymethyl)-2-cyclopentenone serves as the *common synthetic precursor* for each of the pentenomycins, the latter readily available through application of a versatile latent α-ketovinyl anion equivalent recently developed in our laboratory.[5]



**1** **2** **3**

(a) $R_1 = R_2 = H$
(b) $R_1 = H$; $R_2 = Me$
(c) $R_1 = Ac$; $R_2 = H$



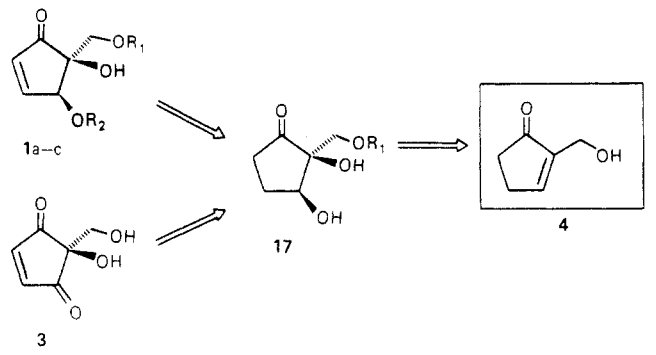
**4** **5** **6**

Pentenomycin I (**1a**), an amorphous powder, and pen-

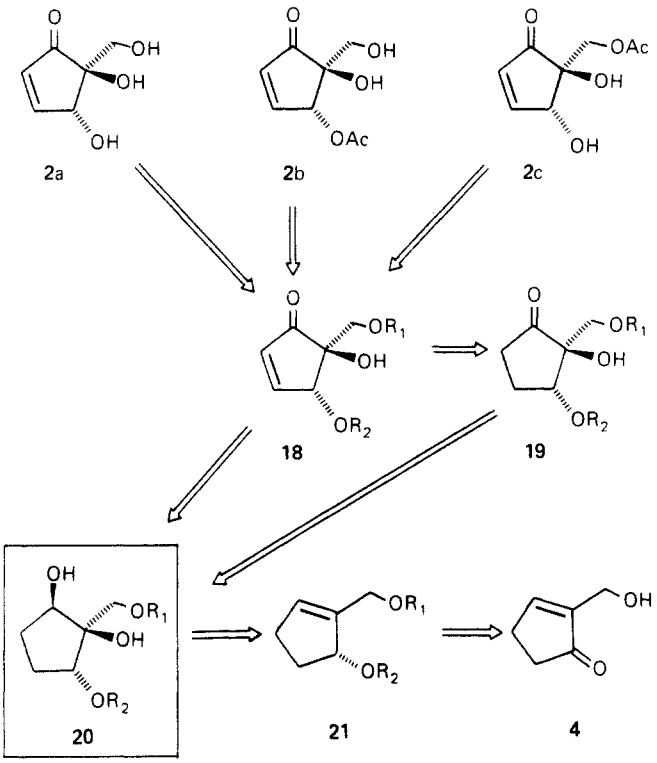
(1) Camille and Henry Dreyfus Teacher-Scholar, 1978–1983; NIH National Cancer Institute Career Development Awardee, 1980–1985.
(2) Branca, S. J.; Smith, A. B., III. *J. Am. Chem. Soc.* **1978**, *100*, 7767.
(3) Smith A. B., III; Pilla, N. N. *Tetrahedron Lett.* **1980**, 4691.
(4) For an alternate synthesis of (–)-pentenomycin I see: Verheyden, J. P. H.; Richardson, A. C.; Bhatt, R. S.; Grant, B. D.; Fitch, W. L.; Moffatt, J. G. *Pure Appl. Chem.* **1978**, *50*, 1363.
(5) Guaciaro, M. A.; Wovkulich, P. M.; Smith, A. B., III. *Tetrahedron Lett.* **1978**, 4661. Also see ref. 2.

0022-3263/82/1947-1855$01.25/0 

Scheme I




Scheme II



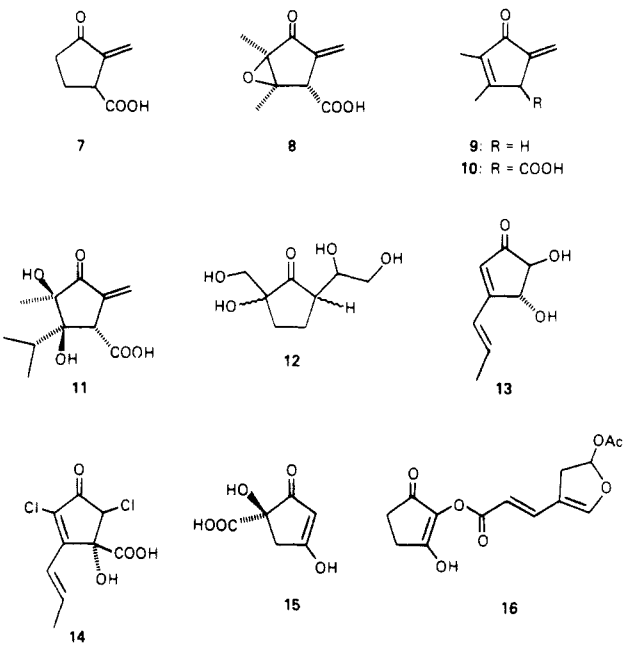

(a) $R_1 = R_2 = Si^tBuMe_2$
(b) $R_1 = Si^tBuMe_2$; $R_2$ = Ac
(c) $R_1$ = Ac; $R_2 = Si^tBuMe_2$
(d) $R_1 = Si^tBuMe_2$; $R_2$ = H
(e) $R_1$ = Ac; $R_2$ = H

tenomycin II (**1b**), a syrup, were first isolated in 1973 by Umino and co-workers from aerobically cultured broths of a mutant strain of *Streptomyces eurythermus*.[6] Structural assignments including the relative stereochemistry were derived through spectroscopic measurements, preparation of the triacetate of pentenomycin I (**5**), and X-ray crystallographic analysis of the derived bromotriacetate (**6**).[6c] The latter not only confirmed the proposed structures but also defined the absolute stereochemistry to be 4*S*,5*S*.[6c]

Three years later (1976) Shomura et al.[7] isolated pentenomycin III, also noncrystalline, from *Strepoverticillium eurocidicum* SF-1768, a strain known to produce pentenomycin II (**1b**). In the same year, three additional antibiotics (C-2254-B, AII, and AI) were isolated by the Hatano group from *Streptomyces lavendolygriseus* C-2254;[8] initially their structures were postulated to have the epimeric arrangement of hydroxyl substituents (i.e., **2a–c**). However, shortly thereafter, Hatano et al.[9] demonstrated that they were, in fact, identical with pentenomycins I–III.[10]

Finally, in 1978 Noble et al.[11] reported the isolation of **3**, a simple oxidation product of pentenomycin I, termed by us dehydropentenomycin I. Assignment of structure in this case was based solely on spectroscopic evidence.

The pentenomycins (**1a–c** and **3**) are representatives of a small but rapidly growing family of antibiotics, all of which possess a cyclopentanone or cyclopentenone ring.[12]




(6) (a) Umino, K.; Furumai, T.; Matsuzawa, N.; Awataguchi, Y.; Ito, Y.; Okuda, T. *J. Antibiot.* **1973**, *26*, 506. (b) Umino, K.; Takeda, N.; Ito, Y.; Okuda, T. *Chem. Pharm. Bull.* **1974**, *22*, 1233. (c) Date, T.; Aoe, K.; Kotera, K.; Umino, K. *Ibid.* **1974**, *22*, 1963.

(7) Shomura, T.; Hoshida, J.; Kondo, Y.; Watanabe, H.; Omoto, S.; Inouye, S.; Niida, T. *Kenkyu Nempo* **1976**, *16*, 1. Shoumura, T.; et al. (Meiji Seika). Japanese Kokai, 192 76-82, July 20, 1976.

(8) Hatano, K.; Hasegawa, T.; Izawa, M.; Asai, M.; Kwasaki, H. (Takeda Chemical Industries, Ltd.) Japanese Kokai 75 70 597, 1975; *Chem. Abstr.* **1976**, *84*, 3287.

(9) Hatano, K.; Izawa, M.; Hasegawa, T.; Tonida, S.; Asai, M.; Iwasaki, H.; Yamano, T. *J. Takeda Res. Lab.* **1979**, *38*, 22.

(10) For a synthesis of (±)-epipentenomycin I see: Shono, T.; Matsumura, Y.; Yamane, S.; Suzuki, M. *Chem. Lett.* **1980**, 1619.

(11) Noble, M.; Noble, D.; Fletton, R. A. *J. Antibiot.* **1978**, *31*, 15.

(12) Other members of the cyclopentanoid family include sarkomycin (**7**),[13b] methylenomycin A (**8**),[13] methylenomycin B (**9**),[14] deepoxy-4,5-didehydromethylenomycin A (**10**),[15] xanthocidin (**11**),[16] vertimycin (**12**),[17] terrein (**13**),[18] cryptosporiopsin (**14**),[19] kjellmanianone (**15**),[20] and reductiomycin (**16**).[21]

(13) (a) Umezawa, H.; Takeu, T., Nitta, K.; Yamamoto, T.; Yamaoka, S. *J. Antibiot., Ser. A* **1953**, *6*, 101. Umezawa, H.; Takeuchi, T.; Nitta, K.; Okami, Y.; Yamamoto, Y.; Yamaoka, S.; *Ibid.* **1953**, *6*, 153. Umezawa, H. Yamamoto, T.; Takeuchi, T.; Osato, T.; Okami, Y.; Yamamoto, S.; Yamaoka, S.; Okuda, T.; Nitta, K.; Yagishita, K.; Utahara, R.; Umezawa, S. *Antibiot. Chemother. (Washington, D.C.)* **1954**, *4*, 514 and references cited therein. (b) For synthetic approaches to Sarkomycin, see: Toki, T. *Bull. Chem. Soc. Jpn.* **1957**, *30*, 450. Toki, K. *Ibid.* **1958**, *31*, 333. Shemyakin, M. M.; Ravdel, G. A.; Chaman, Y. S.; Shvetsov, Y.; Vinogradova, T. J. *Chem. Ind. (London)* **1957**, 1320. Marx, J. N.; Minaskanian, G. *Tetrahedron Lett.* **1979**, 4175. Boeckman, R. K., Jr.; Naegely, P. C.; Arthur, S. D. *J. Org. Chem.* **1980**, *45*, 752. Smith, A. B., III; Wexler, B., unpublished results.

(14) (a) Haneishi, T.; Kitahara, N.; Takiguchi, Y.; Arai, M.; Sugawara, S. *J. Antibiot.* **1974**, *27*, 386. Haneishi, T.; Terahara, A.; Arai, M.; Hata, T.; Tamura, C. *Ibid.* **1974**, *27*, 393. (b) Haneishi, T.; Terahara, A.; Hamano, K.; Arai, M. *Ibid.* **1974**, *27*, 400. (c) Syntheses: Scarborough, R. M.; Smith, A. B., III. *J. Am. Chem. Soc.* **1977**, *99*, 7085. Jernow, J.; Tautz, W.; Rosen, P.; Blount, J. *J. Org. Chem.* **1979**, *44*, 4210. Koreeda, M.; Liang Chen, Y. P.; Akagi, H., presented at the 178th National Meeting of the American Chemical Society, Washington DC, 1979. Scarborough, R. M., Jr.; Smith, A. B., III. *J. Am. Chem. Soc.* **1980**, *102*, 3004. Takahashi, Y.; Isoke, K.; Hagiwara, H.; Kosugi, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1981**, 714. (d) Jernow, J.; Tautz, W.; Rosen, P.; Williams, T. H. *J. Org. Chem.* **1979**, *44*, 4212.

Our interest in this class, and in particular the pentenomycins, was prompted by the highly oxygenated nature of the five-membered ring, their demonstrated moderate to strong in vitro activity against a variety of both gram-positive and gram-negative bacteria including *Neisseria meningitidis* and *Neisseria gonorhoeae*, and by the potential pharmacological importance of the cyclopentenone structural unit suggested[22] to be the reactive functionality in a variety of structurally complex antitumor agents.

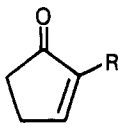
## Results

**(i) A Strategy for the Stereocontrolled Synthesis of the Pentenomycins, Their Epimers, and Dehydropentenomycin I.** From the retrosynthetic perspective, 2-(hydroxymethyl)-2-cyclopentenone (**4**) appeared to be an ideal *common* intermediate for elaboration of each member of this class. Consider first pentenomycins I–III (**1a–c**, Scheme I). By judicious selection of an appropriate primary hydroxyl substituent in conjuction with introduction of the requisite cis vicinal diol system (e.g., $OsO_4$), protection of the β-hydroxyl group to avoid potential retro-aldol processes and then dehydrogenation and deprotection as necessary appeared, at least at the outset, to be a viable strategy for the pentenomycins. Dehydropentenomycin I (**3**), on the other hand, would require oxidation of the secondary hydroxyl group in **17** prior to dehydrogenation and deprotection.

For the epimeric series a somewhat different strategy was mandated by the requisite trans disposition of the secondary and tertiary oxygen functionalities (see Scheme II). Here, diols **20a–c**, respectively, appeared to be ideal precursors from which the epimeric pentenomycins (**2a–c**) could be constructed. Central to this scenario is the stereocontrolled introduction of the vicinal *cis*-hydroxyl substituents in **20** trans to the $OR_2$ group.[23] In turn, olefin **21** in its protected form appeared to be readily available from 2-(hydroxymethyl)-2-cyclopentenone (**4**) employed in the pentenomycin strategy.

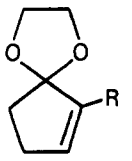
**(ii) Preparation of 2-(Hydroxymethyl)-2-cyclopentenone (4). The Initial Solution.** Although merely an olefinic positional isomer of the enolic form of 2-formyl cyclopentanone, careful examination of the literature revealed, somewhat surprisingly, no previous reports for 2-(hydroxymethyl)-2-cyclopentenone (**4**). Indeed, α-(hydroxymethyl) α,β-enones are conspicuous by their absence from the chemical literature.[24] Immediate attention was therefore turned toward the development of an efficient preparation of **4**.

At the outset, 2-carbethoxy-2-cyclopentenone (**22a**),[25]



**22**

(a) R = COOEt
(b) R = Br
(c) R = H



**23**

(a) R = COOEt
(b) R = $CH_2OH$

available via the procedure of Reich and co-workers,[26] appeared to be an ideal starting material. To our delight, albeit surprise, given the reported instability of **22a**,[25] ketalization under the usual conditions [ca. $(HOCH_2)_2$/TsOH/benzene] afforded **23a**; the maximum obtainable yield, however, was only 45%. Marked improvement in yield (i.e., 82%) could be achieved by replacement of TsOH with the less acidic furmaric acid.[27]

Selective reduction of the ester functionality of **23a** proved more difficult. Indeed, initial attempts with such metal hydrides as LAH etc.[28,29] proved unsuccessful, leading to rather complex mixtures. Diisobutylaluminum hydride (DIBAL), a reagent known[30] to be highly selective toward 1,2-reduction of α,β-unsaturated carbonyl systems, proved more useful. In particular, addition of 2 equiv of DIBAL to **23a** in toluene at −78 °C, followed by quenching the reaction with methanol, led to the desired ketal alcohol **23b** as the major component.

Since all attempts to purify ketal alcohol **23b** led to considerable hydrolysis (i.e., **4**), deketalization was effected prior to purification via treatment with a catalytic amount of aqueous oxalic acid in $CH_2Cl_2$. Purification then proved straightforward via flash chromatography,[31] affording **4** as white needles (mp 68–69 °C), the yield being 65% from ester **22a** or 40% from 2-carbethoxycyclopentanone.

**(iii) An Alternate Approach to 2-(Hydroxymethyl)-2-cyclopentenone (4). Development of a La-**

(15) Hornemann, U.; Hopwood, D. A. *Tetrahedron Lett.* **1978**, 2977. Synthesis: Boschelli, D.; Scarborough, R. M., Jr.; Smith, A. B., III. *Tetrahedron Lett.* **1981**, 19.

(16) Asahi, K.; Suzuki, S. *Agric. Biol. Chem.* **1970**, *34*, 325. Also see: Asahi, K.; Nagatsu, J.; Suzuki, S. *J. Antibiot., Ser. A* **1966**, *19*, 195. Synthesis: Boschelli, D.; Smith, A. B., III, submitted for publication.

(17) Strauss, D. "Antibiotics; Advances in Research, Production and Clinical Use", Proceedings of the Congress on Antibiotics, Praque, 1966, p 451. The stereochemistry of vertimycin has not been defined.

(18) (a) Raistrick, H.; Smith, G. *Biochem. J.* **1935**, *29*, 606. Barton, D. H. R.; Miller, E. *J. Chem. Soc.* **1955**, 1028. (b) Syntheses: Barton, D. H. R.; Hulshof, L. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, *1103*. Auerbach, J.; Weinreb, S. M. *J. Chem. Soc., Chem. Commun.* **1974**, 298.

(19) Stillwell, M.; Wood, F.; Struntz, G. *Can. J. Microbiol.* **1969**, *15*, 501. McGahren, W.; Van den Hande, J.; Mitscher, L. A. *J. Am. Chem. Soc.* **1969**, *91*, 157.

(20) Nakayama, M.; Fukuoka, Y.,; Nozaki, H.; Matsuo, A.; Hayashi, S. *Chem. Lett.* **1980**, 1243. For Syntheses see: Irie, H.; Katakawa, J.; Tomita, M.; Mizuno, Y. *Chem. Lett.* **1981**, 637. Boschelli, D.; Smith, A. B., III; Stringer, O. D.; Jenkins, R. H., Jr.; Davis, F. A. *Tetrahedron Lett.*, in press.

(21) Hirayama, K.-H.; Shimizu, K.; Shirahata, K.; Ueno, K.; Tamura, G. *Agric. Biol. Chem.* **1980**, *44*, 2083. Also see: Shimizu, K.; Tamura, A. *J. Antibiot.*, in press.

(22) Lee, K. H.; Hall, I. H.; Mar, E.-C.; Stranes, C. O.; El Gebaly, S. A.; Waddell, T. G.; Hadgraft, R. L.; Ruffner, C. G.; Weidner, I. *Science* **1977**, *196*, 533.

(23) Baran, J. S. *J. Org. Chem.* **1960**, *25*, 257.

(24) A number of natural products possessing the α-(hydroxylmethyl) α,β-unsaturation having antitumor properties are known. For example: (a) glycalase I inhibitor 2-[(crotonyloxy)methyl]-4,5,6-trihydroxycyclohex-1-en-3-one (Takeuchi, T.; Chimura, H.; Hamada, M.; Umezawa, H.; Yoshioka, O.; Oguchi, N.; Takahashi, Y.; Matsuda, A. *J. Antibiot.* **1975**, *28*, 737); (b) the sesquiterpenoid lactone alliacol A (Steglich, W. *Pure Appl. Chem.* **1981**, *53*, 1233 and references cited therein), and (c) the diterpenoids.

(25) Marx, J. N.; Cox, J. H.; Norman, L. R. *J. Org. Chem.* **1972**, *37*, 4489.

(26) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(27) De Leeuw, J. W.; De Waard, E. R.; Beetz, T.; Huisman, H. O. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 1047.

(28) Unsuccessful attempts included addition of **23a** to LAH in $Et_2O$, inverse addition of a THF solution of LAH to **23a** in THF at 0 and −10 °C (Cavill, G. W. K.; Whitfield, F. B. *Aust. J. Chem.* **1964**, *17*, 1260. Hochstein, F. A.; Brown, W. G. *J. Am. Chem. Soc.* **1948**, *70*, 3484), and treatment of **23a** in $Et_2O$ with LAH and 1 equiv of EtOH (Davidson, R. S.; Gunter, W. H. H.; Waddington-Feather, S. M.; Lythgoe, B. *J. Chem. Soc.* **1964**, 4907. Also see for a review: Malek, J.; Cerny, M. *Synthesis* **1972**, 217). In contrast, LAH added inversely in THF to methyl cyclohexenecarboxylate in THF at 0 °C was observed to give a nearly quantitative conversion to the corresponding allylic alcohol.

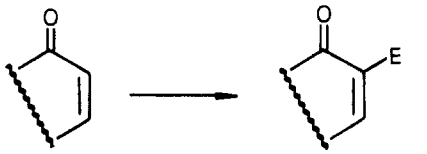
(29) (a) Brown, W. *Org. React.* **1951**, *6*, 469. (b) Dilts, J.; Ashby, E. C. *Inorg. Chem.* **1970**, *9*, 855. Lansbury, P.; MacLeay, R. *J. Am. Chem. Soc.* **1965**, *87*, 831.

(30) Wilson, K. E.; Seidner, R. T.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1970**, *213*.

(31) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

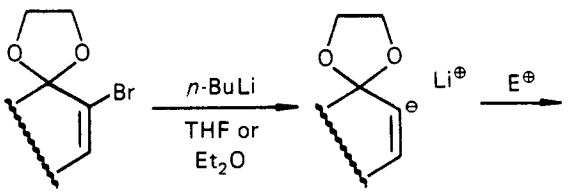
**tent α-Ketovinyl Anion Equivalent.**[5] Although the initial preparation of 2-(hydroxymethyl)-2-cyclopentenone (4) was capable of providing usable quantities (e.g., 1–2 g), the protocol was not easily amenable to large-scale (i.e., 10–20 g) preparations. This, coupled with the expense of phenylselenenyl chloride and the sometimes capricious nature of the ketalization and reduction steps necessitated development of an alternate approach.

An ideal transformation in this regard would be the construction of α-substituted enones directly from the parent enone without intervention of the thermodynamic enolate. At the time, a general solution to this recurring synthetic problem was unavailable, although Corey,[32] Fuchs,[33] and Stork[34] had independently devised a reverse polarity (umpolong) strategy for the α-alkylation and α-arylation of α,β-unsaturated ketones. Central to their approach was the generation of an effective latent equivalent for α-ketovinyl cation **24**.[35] Such a strategy however, is limited, in that it depends critically upon the availability of the requisite alkyl or aryl organometallic reagent.

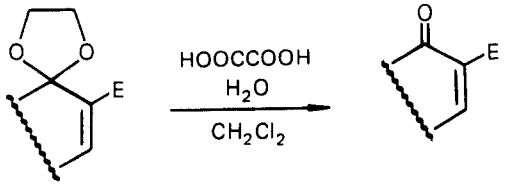


**24** α-Ketovinyl cation **25** α-Ketovinyl anion

A more versatile and possibly more direct approach would be the generation of α-ketovinyl anion **25** followed by addition of an appropriate electrophile. While such an anion, per se, is not feasible, recent studies by Ficini,[36] House,[37] and Swenton[38] suggested that α-bromo ketal **26**

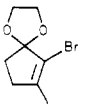
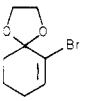



**26** **27**




**28** **29**

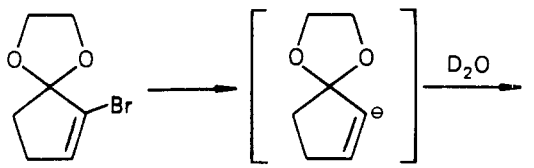
Table I. Synthesis of α-Substituted α,β-Unsaturated Ketones

| entry | substrate | electrophile ($E^+$) | solvent | overall yield from 29a–c, % | product |
|---|---|---|---|---|---|
| **29a** |  | $D_2O$ | THF | 79 | **31a** |
| | | MeI | THF/HMPA | 53 | **31b** |
| | | $n$-$C_5H_{11}I$ | $Et_2O$/HMPA | 71 | **31c** |
| | | HCHO | THF | 84 | **4** |
| | | $Me_2CO$ | THF/HMPA | 62 | **31d** |
| | | ClCOOEt | THF | 53 | **22a** |
| | | $Me_3SiCl$ | THF | 56 | **31e** |
| | | MeSSMe | THF | 73 | **31f** |
| **29b** |  | $n$-$C_5H_{11}I$ | $Et_2O$/HMPA | 60 | **31g** |
| | | ClCOOEt | THF | 62 | **31h** |
| **29c** |  | $n$-$C_5H_{11}I$ | $Et_2O$/HMPA | 69 | **31i** |
| | | ClCOOEt | THF | 81 | **31j**[a] |

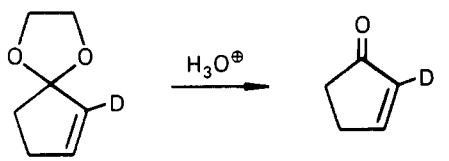
[a] Isolated as the ethylene ketal.

could serve as a viable latent equivalent for **25**, providing the following transformations proceed efficiently: (a) metalation of **26**, (b) electrophilic capture of the resultant anion **27**, and (c) hydrolysis of ketal **28**. Assuming that each step proceeds without event, the entire transformation could be effected in "one pot".

With these considerations in mind, we explored initially the metalation step.[39] Treatment of bromo ketal **29a** with




**29a**




**30a** **31a**

1.3 equiv of $n$-butyllithium in THF at −78 °C led smoothly to the corresponding anion as determined by quenching with deuterium oxide. In particular, NMR analysis (220 MHz) of both ketal **30a** and cyclopentenone, derived via mild acid hydrolysis, indicated >95% monodeuterium incorporation specifically at the α-carbon.

(32) Corey, E. J.; Melvin, L. S., Jr.; Haslanger, M. F. *Tetrahedron Lett.* **1975**, *3117*.
(33) Fuchs, P. L. *J. Org. Chem.* **1976**, *41*, 2935.
(34) Stork, G.; Ponaras, A. A. *J. Org. Chem.* **1976**, *41*, 2937.
(35) A Latent equivalent of a β-oxovinyl anion was recently reported by Okamura; see: Hammond, M. L.; Mourino, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1978**, *100*, 4907.
(36) Ficini, J.; Depezay, J. C. *Tetrahedron Lett.* **1969**, 4797.
(37) House, H. O.; McDaniel, W. C. *J. Org. Chem.* **1977**, *42*, 2155.
(38) Manning, M. J.; Raynolds, P. W.; Swenton, J. S. *J. Am. Chem. Soc.* **1976**, *98*, 5008. Also see: Raynolds, P. W.; Manning, M. J.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1977**, 499. Shih, C.; Fritzen, E. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 4467.
(39) For examples of the metalation of vinyl halides see: Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, *107*, 847. Radlick, P.; Crawford, H. T. *J. Chem. Soc., Chem. Commun.* **1974**, 127. Negishi, E. I.; Abramovitch, A.; Merill, R. E. *Ibid.* **1975**, *138*.

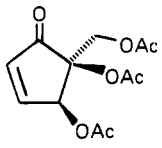
Repetition of the above experiment employing bromo ketals **29a–c** and a variety of electrophiles afforded with one exception the respective α-substituted enone derivatives **31b–j** in good to excellent yield (see Table I). Optimum results with methyl and *n*-pentyl iodide were obtained when the alkylations were carried out in ether or THF containing 10–12 equiv of HMPA as a cosolvent. Hydrolysis of the individual ketals could then be conveniently effected without purification by treatment with 2–3 equiv of oxalic acid and by employing a two-phase ($CH_2Cl_2$–$H_2O$) system. The overall efficiency for this sequence (i.e., **29** → **31**) was 51–84%. The exception was reaction of **29c** with *n*-pentyl iodide. In this case a second product, 2-*n*-butyl-2-cyclohexenone was observed after deketalization. Presumably, with the less reactive electrophile, *n*-butyl bromide produced during the metalation step[36] competes for the vinyl anion. Interestingly, in the case of **29a** only the desired 2-*n*-pentyl-2-cyclopentenone (**31c**) was observed.

The requisite bromo ketals **29a–c** were readily prepared from the corresponding parent enone in 50–73% yield via a three-step protocol: (a) bromination ($Br_2/CCl_4$), (b) dehydrobromination,[40] (c) ketalization.

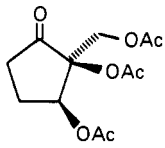
With monomeric formaldehyde as the electrophilic species, application of this reaction sequence affords 2-(hydroxymethyl)-2-cyclopentenone (**4**), the overall yield from cyclopentenone being 61%. Vis-à-vis elaboration of the pentenomycins, this alternative route to **4** is particularly attractive in that it represents a 20% increase in overall yield, can be carried out on a large scale (20–30 g), requires about half the time to execute, and is less expensive in that phenylselenenyl chloride is not required. With ample quantities of **4** in hand we return to the synthetic venture.

## Pentenomycins

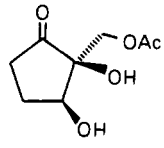
**(i) Preparation of (±)-Pentenomycin I Triacetate (5). A Successful Failure.** Not unaware of the considerable potential for problems connected with the conversion of pentenomycin I triacetate (**5**) to pentenomycin



**5**



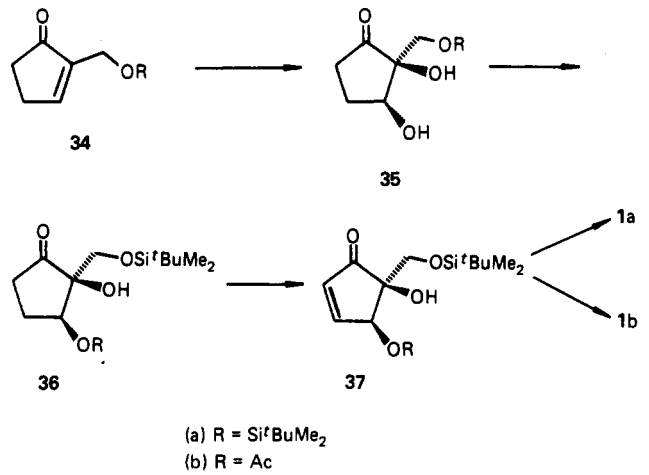
**32**



**33**

I (**1a**), our desire to establish the validity of our overall strategy, in conjunction with the availability of high-quality spectral data for both pentenomycin I triacetate (**5**)[6] and dihydropentenomycin I triacetate (**32**),[6] presuaded us to direct initial attention toward their construction. Toward this end, the acetate derived from enone **4** was treated with a stoichiometric amount of $OsO_4$;[41] reductive cleavage of the derived osmate ester with aqueous $NaHSO_3$[23] afforded, after workup, acetoxy diol **33** in 96% yield. In practice this diol, somewhat unstable upon standing, was immediately acetylated to give dihydropentenomycin I triacetate (**32**) in 77% yield (72% from enone **4**) as a white crystalline solid, mp 80.5–81.5 °C. The 60-MHz NMR of **32** was identical with that derived from dihydropentenomycin I triacetate (**32**) prepared from natural pentenomycin I (**1a**).

Scheme III



(a) R = $SiBuMe_2$
(b) R = Ac

Initial attempts to introduce the requisite α,β-unsaturation included both acid- and base- (LDA) promoted α-phenylselenation.[26] Such endeavors, however, led only to recovery of starting material. The successful conversion of **32** to (±)-pentenomycin I triacetate (**4**) was accomplished by heating a solution of **32** in *t*-BuOH at reflux in the presence of excess $SeO_2$.[42] The workup, which consisted of treatment with 30% $H_2O_2$ in $CH_2Cl_2$, gave, after purification, a crystalline solid (mp 98.5–99.5 °C) having spectral properties identical in all respects with those reported for (±)-pentenomycin I triacetate (**5**).

Not unexpectedly, all attempts to remove the acetate groups by employing a wide variety of acidic and basic conditions[43] led to complex, intractable mixtures. Presumably the latter result from the variety of retro-aldol processes available to the liberated β-hydroxy ketone(s).

**(ii) Successful Conclusion to the Pentenomycin Problem. Selection of a Viable Protection Group.** From the above endeavors it was evident that a successful solution to our pentenomycin synthetic venture could be reduced to selection of an appropriate protecting group. Given the overall economy of the synthetic strategy the protecting group of choice appeared to be *tert*-butyldimethylsilyl (TBDMS).

On exploitation of the latter, the successful strategy for the pentenomycins (i.e., I–III) is as illustrated in Scheme III. Treatment of 2-(hydroxymethyl)-2-cyclopentenone (**4**) with 1.2 equiv of TBDMSCl and 2.4 equiv of imidazole in DMF[44] afforded enone **34a** in 78% yield as a crystalline solid (mp 33 °C), which in turn was cis hydroxylated with $OsO_4$.[23] Distillation afforded diol **35a** as a colorless oil in 94% yield, which in turn was converted to the disilyl derivative **36a**, again by employing TBDMSCl and imidazole (92%),[44] and then subjected to dehydrogenation via $SeO_2$. Workups, followed by chromatography, gave enone **37a** in 51% yield as white needles, mp 37 °C. That in fact enone **37a** was in hand was evident from the 220-MHz $^1H$ NMR

(40) Sato, K.; Inoue, S.; Kuranami, S.-I.; Ohashi, M. *J. Chem. Soc., Perkin Trans. 1* **1977**, *1666*. Also see: Dunn, G. L.; DiPasque, V. J.; Hoover, J. R. E. *J. Org. Chem.* **1968**, *33*, 1454. Reference 38, last reference.

(41) In a related study we have observed that cis hydroxylation of cyclopentenone systems employing a catalytic amount of $OsO_4$ and *N*-methylmorpholine *N*-oxide (NMO) as the stoichiometric oxidant leads to overoxidation: unpublished results of Diane Boschelli of this laboratory.

(42) Bernstein, S.; Littell, R. *J. Am. Chem. Soc.* **1960**, *82*, 1235. Also see: Branca, S. J.; Lock, R. L.; Smith, A. B., III. *J. Org. Chem.* **1977**, *42*, 3165.

(43) Acidic conditions included the following: 10% (v/v) aqueous HCl, THF; Amberlite CG-120 cation ($RSO_3O^-H^+$) exchange resin, MeOH. Basic conditions attempted included the following: $K_2CO_3$, MeOH; LiOH, THF; Dowex 1-X10 anion ($R_4N^+OH^-$) exchange resin, MeOH. In many cases complete loss of both olefinic and acetoxymethyl functionality was observed by $^1H$ NMR without appearance of resonances attributed to **1a**.

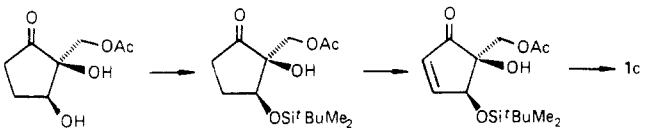
(44) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

which displayed the requisite olefinic proton resonances at $\delta$ 6.17 (d, $J$ = 7 Hz, 1 H) and 7.22 (d, $J$ = 7 Hz, 1 H).

Removal of the silyl protecting groups proved to be straightforward (e.g., aqueous THF/AcOH), affording (±)-pentenomycin I (**1a**) in 94% yield, the 60-MHz $^1$H NMR spectrum of which was identical in all respects with the published spectrum for this antibiotic.[6]

In a similar fashion, pentenomycin II (**1b**) was prepared from diol **35a** via monoacetylation and then dehydrogenation with $SeO_2$. As in the case of the pentenomycin I, precursor enone **37b** proved to be crystalline (mp 63–65 °C), the yield from **36b** being 67%. Treatment of the latter with 50% aqueous THF/AcOH at room temperature afforded (±)-pentenomycin II (**1b**) in 88% yield, having spectral properties identical in all respects with those published for this antibiotic.[6]

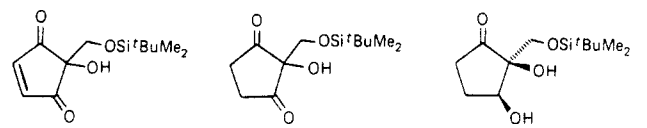
Turning finally to the synthesis of pentenomycin III (**1c**), diol acetate **35b**, prepared from **34b** (i.e., $OsO_4$), was



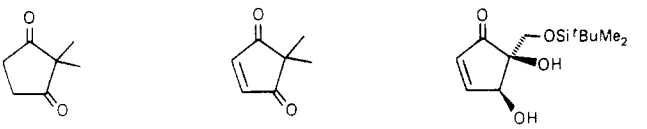

33 38 39

protected as the monosilyl ether **38** and dehydrogenated by employing $SeO_2$. In this case only a modest yield (ca. 32% based on **38**) of **39** was realized. Deprotection of the secondary hydroxy group in the usual fashion afforded (±)-pentenomycin III (**1c**, 90%) as a colorless oil possessing spectral data (IR, $^1$H NMR) identical with those reported[7] for this antibiotic.

**(iii) Preparation of Dehydropentenomycin I. New Insight vis-à-vis the Pentenomycin Synthetic Strategy.** In as much as dehydropentenomycin I (**3**) is merely a simple oxidation product of pentenomycin I (**1a**), we envisioned its preparation from diol **35a** via oxidation of the secondary hydroxyl group, dehydrogenation of the resulting cyclopentane-1,3-dione **41**, and then removal of




40 41 35a




42 43 44

the TBDMS protecting group. Precedent for the conversion of **41** to **40** appeared amply available by way of the conversion of **42** to **43**[45] developed by Agosta and Smith some years ago. However, as often happens, a seemingly trivial process proves rather difficult. Indeed, all attempts to effect oxidation of the secondary hydroxyl function of **35a** were unsuccessful.[46]

Frustrated by our inability to effect the requisite oxidation, we considered reversing the steps in order to circumvent the problem. Toward this end, treatment of diol **35a** with excess $SeO_2$ in $t$-BuOH afforded, somewhat remarkably, the desired enonediol **44** in 53% yield as white flakes, mp 80.5–81.5 °C. Oxidation of **44** was then easily effected via the Jones procedure[48] to afford **40** as beautifully crystalline yellow needles: mp 65 °C; yield 61%. Diagnostic of the assigned structure was the symmetric nature of the 220-MHz NMR spectrum (e.g., $\delta$ 7.59, s, 2 H). Deprotection in the usual fashion afforded dehydropentenomycin I (**3**) in 74% yield.

Enedione **3** prepared in this manner possessed $^1$H NMR spectral data identical in all respects with those reported for this antibiotic except for the multiplicity of the hydroxymethylene and primary hydroxyl signals. Presumably the NMR sample of synthetic **3** possessed sufficient acidic impurities to promote rapid exchange of the hydroxyl protons, thereby leading to the observed singlet for the hydroxymethylene protons and the broad absorption envelope for the hydroxyl protons. Significantly, the $^{13}$C NMR data of synthetic dehydropentenomycin I (**3**) were identical in all respects with those published for this antibiotic.[11] Finally, we note that completion of the synthesis of dehydropentenomycin I constitutes a formal proof of structure for this antibiotic.

**(vii) Return to the Synthesis of Pentenomycin I and II. Development of a More Economic Approach.** The successful construction of dehydropentenomycin I suggested a more economic preparation of pentenomycin I and II. Recall that we considered it prudent to protect the secondary hydroxyl group prior to dehydrogenation in order to prevent presumed side reactions (i.e., retro-aldol processes). The latter, however, were found not to intervene. Incorporation of this observation into the pentenomycin I and II strategies resulted, in each case, in an economy of one step. Furthermore, the overall strategies for pentenomycin I and II and dehydropentenomycin I now follow a *common path* until advanced intermediate **44**. Our concern about potential side reactions, however, was not totally without cause. Indeed, a similar economy in the pentenomycin III sequence was thwarted by our inability to dehydrogenate **33** without prior protection of the secondary hydroxyl group.

In summary, the now more direct preparation of (±)-pentenomycin I (**1a**) from **44** proceeded in 96% yield (i.e., 23–25% from 2-cyclopentenone), while treatment of diol **44** with acetic anhydride in pyridine provided the previously prepared monoacetate **37b** in 96% yield. Hydrolysis of the latter afforded pentenomycin II (**1b**), the overall yield being 22%. Finally, the synthesis of dehydropentenomycin I (**3**) via this sequence proceeded in 11% overall yield from 2-cyclopentenone. Having completed the synthesis of the pentenomycins and dehydropentenomycin I, we turned to the epimeric series.

## Epipentenomycins

**(i) Epipentenomycin Synthetic Strategy.** The central concern of any viable approach to the epimeric series of pentenomycins **1a–c** must be the trans disposition of the secondary and tertiary hydroxyl substituents. Toward this end, recall the retrosynthetic analysis illustrated in Scheme II. The cornerstone of this strategy is the expectation that vicinal cis hydroxylation of **21** with the sterically demanding $OsO_4$ would demonstrate at least modest selectivity, that is, take place predominantly trans to the secondary substituent on the cyclopentenone ring

(45) Agosta, W. C.; Smith, A. B., III. *J. Org. Chem.* **1970**, *35*, 3856.
(46) Oxidizing agents utilized included chromic acid (Jones reagent), pyridinium chlorochromate, and $Ag_2CO_3$ on Celite (Fetizon's reagent).
(47) Jackman, L. M.; Sternhell, S. "Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: New York, 1969; p 129.
(48) (a) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39. (b) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, pp 142–144.

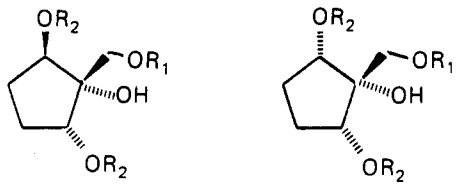
to afford advanced synthetic intermediates **20a–c**. Careful oxidation of the derived secondary hydroxyl group would then afford ketones **19a–c** which in turn would require only introduction of $\alpha,\beta$-unsaturation and deprotection to complete the specific epimer.

**(ii) Construction of Three Advanced Intermediates. Remarkable Stereoselectivity Displayed by $OsO_4$.** With epipentenomycin I (**2a**) and thereby advanced intermediate **19a** as our initial target, reduction of enone **34a** utilizing 9-borobicyclononane (9-BBN), a reagent known for high 1,2-vs. 1,4-selectivity,[49] afforded **21d** in 81% yield after the usual $H_2O_2$ workup.[50] While quite effective, workup procedures for 9-BBN reductions often prove tedious. A far more convenient procedure proved to be the $NaBH_4$–$CeCl_3$ protocol introduced recently by Luche.[51] Employing these conditions (i.e., 1.1 equiv of $NaBH_4$, 1.0 equiv of $CeCl_3 \cdot 3H_2O$, MeOH, 0 °C), we obtained alcohol **21d** in 93% yield. Significantly, the reaction was complete in less than 15 min; furthermore, isolation proved to be remarkably facile. Subsequent protection of the secondary hydroxy as the TBDMS ether afforded **21a** in 89% yield.

The stage was now set for the crucial vicinal cis hydroxylation, the cornerstone of the epipentenomycin synthetic strategy. Toward this end, olefin **21a** was treated with 1.0 equiv of $OsO_4$ in pyridine at 0 °C. After reductive cleavage of the derived osmate ester, workup and distillation afforded a *single* product in 90% yield. That indeed a single product was formed was demonstrated by the 250 MHz $^1H$ NMR. Clearly, the $OsO_4$ hydroxylation was displaying high stereoselectivity.[52]

Although it was reasonable to assume that diol **20a** possessed the structure illustrated, a rigorous structural proof was mandatory, in that the stereochemistry of this compound was crucial vis-à-vis the requisite trans relationship of the secondary and tertiary hydroxyl substituents present in epipentenomycin I.

Careful analysis of the structural features of the two possible cis diols revealed that after simple derivatization of the secondary hydroxyl substituents as the TBDMS ether, the product derived from hydroxylation syn to the secondary $OR_2$ group in **21a** would lead to symmetrical intermediate **46a** (i.e., plane of symmetry), while hydroxylation anti to $OR_2$ would afford an unsymmetrical product (i.e., **45a**). Carbon-13 NMR was thus the method of choice to establish rigorously the stereochemical consequences of the pivitol cis-hydroxylation process. That is, the maximum number of carbon resonances possible for the symmetrical intermediate **46a** is 11 whereas the unsymmetrical product **45a** could display 18 lines.




45 46

(a) $R_1 = R_2 = Si^tBuMe_2$
(b) $R_1 = Si^tBuMe_2$; $R_2$ = Ac
(c) $R_1$ = Ac; $R_2$ $Si^tBuMe_2$

In the event, derivitization of **20a** with 1.5 equiv of TBDMSCl and imidazole afforded **45a** in 84% yield, contaminated only by a small amount (ca. <5%) of the tetrasilyl ether. Removal of the latter via flash chromatography gave pure **45a** in 76% yield. Carbon-13 NMR analysis revealed 14 lines, thereby eliminating the symmetrical product. The number 14 arises from overlapping *tert*-butyl and methyl resonances of the silyl ethers. Of further significance is the fact that the two ring carbons bearing the secondary *O*-silyl groups display as distinct doublets ($\delta$ 78.51 and 74.14) in the carbon off-resonance decoupled spectrum, while the two methylene carbons appear as slightly separated triplets ($\delta$ 30.70 and 30.88). Such a spectrum is only consistent with the unsymmetrical structure.

Turning next to construction of advanced intermediate **20b** required for epipentenomycin II (**2b**) we acetylated allylic alcohol **21d**, available in 93% yield via $NaBH_4$–$CeCl_3$ reduction of **34a**, to afford **21b** in 93% yield. Focusing on the consequences of cis-hydroxylation, treatment of olefin **21b** with $OsO_4$ again yielded a single compound, **20b**. The stereochemistry in this case was established in a similar fashion via preparation of the diacetate **45b**. Consistent with the unsymmetrical nature, the 360-MHz NMR spectrum of **45b** displayed distinct singlets at $\delta$ 1.95 (3 H) and 2.00 (3 H) for the acetoxy methyl groups, while the acetoxy methine protons appeared at $\delta$ 4.90 (dd, 1 H) and 5.01 (dd, 1 H). Confirmation of this assignment was provided by the $^{13}C$ NMR spectrum. In particular, 12 resonances were observed. The maximum number of resonances possible for the symmetrical system **46b** would be 9 while the unsymmetrical diacetate could present 14 distinct lines.

In the same fashion, advanced intermediate **20c** was prepared for conversion to epipentenomycin III. Here 1,2-reduction of enone acetate **34b** ($NaBH_4$–$CeCl_3$) followed by protection of the secondary hydroxyl as the TBDMS ether and, in turn, hydroxylation ($OsO_4$) afforded **20c** in 66% overall yield. That only one product, the unsymmetric isomer, resulted (i.e., >95%) in the hydroxylation step was again demonstrated from the 360-MHz $^1H$ and 62.9-MHz $^{13}C$ NMR spectra of the derived disilyl ether **45c** (see Experimental Section).

**(iii) Conversion of Advanced Intermediates 20a–c, Respectively, to Epipentenomycins I–III. The Elusive Nature of Epipentenomycin II (2b).** With ample quantities of **20a–c** available and their stereochemistry secure, we turned to the required oxidation of the secondary hydroxyl group. After a number of unsuccessful attempts to effect the desired oxidation by employing the Jones[48] and Collins[53] protocols, success was in hand upon deployment of the Swern procedure.[54] In particular, treatment of **20a–c** with $Me_2SO$ and trifluoroacetic anhydride (or oxayl chloride) in methylene chloride at –60 °C, followed by addition of triethylamine and warming to room temperature, afforded **19a–c**, respectively, in 80%, 57%, and 61% yields.

For completion of the synthesis of the epipentenomycins, all that remained was introduction of $\alpha,\beta$-unsaturation and deprotection. Application of the $SeO_2$ dehydrogenation protocol developed for the pentenomycin series led to cyclopentenones **18a–c**. The yields, however, were only modest (i.e., 25%, 58%, and 32%, respectively).

(49) Reagents such as DIBAL led to complex mixtures.
(50) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 1197.
(51) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(52) Similar high stereoselectivity (>9:1) was observed for vicinal cis hydroxylation ($OsO_4$) with 3-substituted and 1,5-substituted cyclopentene derivatives. In each case the predominate product possessed the vicinal cis hydroxyl groups trans to the secondary substituents: unpublished results of N.N.P. of this laboratory.
(53) Collins, J. C.; Hess, W. W. *Org. Synth.* **1972**, *52*, 5.
(54) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957. Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

Final conversion of **18a** to (±)-epipentenomycin I (**2a**) was effected in 81% yield (i.e., 9% overall form cyclopentenone **34e**) via treatment with glacial acetic acid, water, and THF (3:1:1 v/v/v). That this compound was indeed epipentenomycin I was apparent from the spectroscopic properties (IR, 100-MHz NMR) as well as via comparison with pentenomycin I.[55]

Turning to epipentenomycin II, all attempts to effect selective hydrolysis of the primary silyl ether of **18b** resulted, at best, in a mixture of two compounds. One displayed all resonances expected for (±)-epipentenomycin II (**2b**), while the other appeared to be (±)-epipentenomycin III (**2c**). Indicative of the latter was the fact that the resonances for the methine ring proton had undergone an upfield shift [δ 5.87 (dd) to 4.90 (s), 1 H] while the resonance for the methylene protons had undergone the characteristic downfield shift [δ 3.70 (s) to 4.32 (AB), 2 H] that would be expected for a compound possessing a primary acetate. Interestingly, when the mixture of products was concentrated and then taken up in $CDCl_3$ as opposed to $D_2O$, the 360-MHz $^1H$ NMR indicated only one compound, that believed to be (±)-epipentenomycin III (**2c**).

Presumably the interconversion of epipentenomycin II to III involves intramolecular migration of acetate from the secondary to the primary position via a six-membered transition state. Of possible significance is the fact that the two groups involved are cis disposed on a five-membered ring. Since primary acetates are more stable, the equilibrium is driven in that direction, the migration being accelerated in the less polar solvent, $CDCl_3$. Use of $D_2O$ evidently retards this process though hydrogen bonding with the primary hydroxyl group. Evidence in favor of the intramolecular nature of the migration derives from the fact that (±)-pentenomycin II (**1b**), in which the two groups are trans on the five-membered ring, does not display a similar propensity for rearrangement. Finally, we note that the short half-life of (±)-epipentenomycin II (**2b**) precluded its isolation in the pure state.

To prove the identity of the rearranged product, we turned to a more rational preparation of epipentenomycin III. Treatment of **18c** with glacial acetic acid, THF, and $H_2O$ in a similar fashion afforded the desired isomer, (±)-epipentenomycin III (**2c**), in 80% yield as a colorless oil. This material proved to be identical in all respects with that derived from **18b**. The overall yield of (±)-epipentenomycin III (**2c**) from 2-(hydroxymethyl)-2-cyclopentenone was 8%.

## Experimental Section

**Materials and Methods.** Vapor-phase chromatography (VPC) was performed on an Aerograph Model 920 gas chromatography employing one of the following columns: A, 25% QF-1, 10 ft × 0.375 in.; B, 1.5% OV-101, 6 ft × 0.250 in.; C, 25% Carbowax 20M, 20 ft × 0.25 in. The helium carrier gas flow rate was 60–250 mL/min, and the oven temperature ranged from 100 to 210 °C. Compounds isolated by preparative VPC were obtained as either colorless oils or white solids. Melting points were taken on a Thomas-Hoover capillary melting apparatus and are corrected. Boiling points are uncorrected. All solvents were distilled prior to use: benzene and toluene from sodium, ether and THF from sodium and benzophone, DMF from calcium hydride, ethylene glycol from magnesium sulfate, HMPA from CaH, and $Me_2SO$ from molecular sieves. Solutions were dried over $MgSO_4$. Unless specified otherwise, IR and $^1H$ NMR were obtained for $CCl_4$ solutions, the former on a Perkin-Elmer Model 337 spectrophotometer and the latter on either a Varian A-60A (60 MHz), T60A (60 MHz), HR220 (220 MHz), a Bruker WH360 (360 MHz), or a WP 250FT (250 MHz) spectrometer. $^{13}C$ NMR spectra were obtained in $CDCl_3$ or $CD_2Cl_2$ on either a JEOL PS-100 (25 MHz) or a Bruker WP-250 FT (62.9 MHz) spectrometer, and signal multiplicities were determined via off-resonance decoupling. The internal standard for $^1H$ and $^{13}C$ NMR experiments was $Me_4Si$. For those compounds containing the TBDMS protecting group, either an external reference of $Me_4Si$ or the $CHCl_3$ peak (δ 7.24) for $CDCl_3$ solutions was used. High-resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Center on a Hitachi Perkin-Elmer RMH-2 high-resolution double-focusing electron-impact spectrometer or on a VG micromass 70/70H high-resolution double-focusing electron impact–chemical ionization spectrometer, the latter using isobutane as the reagent gas, and each was interfaced with a Kratos DS-50-S data system.

Preparative thin-layer chromatography (TLC) was performed on precoated silica gel plates with fluorescent indicator supplied by Analtech, Inc. Visualization was accomplished with UV light.

**6-Carbethoxy-1,4-dioxaspiro[4.4]non-6-ene (23a).** A mixture consisting of 605.6 mg (3.93 mmol) of cyclopentenone **22a**,[26] 20 mL of benzene, 1.0 mL of ethylene glycol, and 30 mg of fumaric acid was stirred at reflux with azeotropic removal of water (Dean–Stark trap) for a period of 68 hs.[27] After cooling to room temperature, the mixture was poured onto anhydrous $K_2CO_3$, filtered, and concentrated in vacuo. Distillation [Kugelrohr, 100–110 °C (0.25 torr)] gave 637 mg (82%) of ketal **23a**. An analytical sample prepared by TLC ($CH_2Cl_2$; $R_f$ 0.55) possessed the following spectral data: IR 3070 (w), 2980 (s), 1735 (s), 1640 (m), 1230 (s), 1160 (s), 1045 (s), 1028 (s), 945 (m), 925 (m), $cm^{-1}$; NMR (60 MHz) δ 1.27 (t, $J$ = 7 Hz, 3H), 1.97–2.69 (m, 4 H), 3.73–4.50 (m, 6 H), 6.98 (t, $J$ = 2 Hz, 1 H).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.41; H, 7.19.

**6-Bromo-1,4-dioxaspiro[4.4]non-6-ene (29a).** A mixture consisting of 5.0 g (31 mmol) of 2-bromo-2-cyclopenten-1-one (**22b**),[40] 250 mL of benzene, 4.2 mL of ethylene glycol, and 25 mg of $TsOH·H_2O$ was heated at reflux with azeotropic removal of water (Dean–Stark trap) for a period of 43 h. The resulting mixture was cooled and filtered through a filter cake consisting of 5 g of $MgSO_4$ and 5 g of silica gel. The filter cake was washed with 150 mL of $CH_2Cl_2$. The filtrate and washinges were combined and concentrated in vacuo to afford 6.1 g of a mobile yellow oil. This oil on distillation [Kugelrhor, 50–52 °C (1.0 torr)] gave 5.4 g (85%) of ketal **29a** as a colorless oil possessing the following spectral data: IR 3075 (w), 2980 (m), 1635 (w), 1340 (s), 1175 (s, br), 1050 (s), 1035 (s), 945 (m), 920 (m), $cm^{-1}$; NMR (220 MHz) δ 2.16 (m, 2 H), 2.39 (m, 2 H), 3.97 (m, 2 H), 4.18 (m, 2 H), 6.16 (t, $J$ = 2 Hz, 1 H).

Anal. Calcd for $C_7H_9O_2Br$: C, 40.10; H, 4.42. Found: C, 39.99; H, 4.52.

**2-(Hydroxymethyl)-2-cyclopentenone (4). A. From Ester 22a.** A solution consisting of 1.18 g (5.95 mmol) of ester **22a** in 50 mL of toluene was cooled to −78 °C under a $N_2$ atmosphere and treated with 3.9 mL (1.3 equiv, 2.0 M) of DIBAL/PhMe. The resulting solution was stirred for 4 h at −78 °C and then treated again with 3.9 mL (1.3 equiv) of DIBAL. After an additional 3 h at −78 °C the reaction was quenched by addition of 20 mL of MeOH and gradual warming to room temperature. The resulting mixture was stirred at room temperature for 1 h and then treated with 10 mL of EtOAc and 2 mL of $H_2O$. The resulting suspension was filtered through $MgSO_4$ and concentrated in vacuo to give 389 mg of the hydroxymethyl ketal **23b**: NMR (60 MHz, $CDCl_3$) δ 1.78–2.55 (m, 4 H), 3.43 (br s, 1 H), 3.88 (s, 4 H), 4.12 (br, 2 H), 5.95 (br s, 1 H). Without further purification the ketal **23b** was

(55) Shono et al.[10] report only the olefinic resonance for the synthetic epipentenomycin I [($D_2O$) δ 6.23 (dd, $J$ = 6.0, 1.8 Hz, 1 H), 7.53 (dd, $J$ = 6.0, 2.2 Hz, 1 H)].

deketalized by addition to a mixture of 100 mL of $CH_2Cl_2$, 150 mg of oxalic acid, and 1.5 mL of $H_2O$ followed by stirring at room temperature for 3.5 h. The resulting mixture was dried over $MgSO_4$ containing ~300 mg of $K_2CO_3$, filtered, and concentrated in vacuo to give 757 mg of a dark oil. Column chromatography on silica gel [$CH_2Cl_2$/EtOAc (1:1)] gave 425 mg (65%) of crystalline hydroxymethyl enone **4**. An analytical sample (white needles, mp 68–69 °C) prepared by TLC [$CH_2Cl_2$/EtOAc (5:1), $R_f$ 0.13] possessed the following spectral data: IR ($CHCl_3$) 3620 (m), 3550–3350 (m, br), 3025 (sh), 3000 (m), 2930 (m), 1700 (sh), 1690 (s), 1645 (m), 1260 (m), 1000 (s), 910 (m) $cm^{-1}$; NMR (60 MHz, $CDCl_3$) $\delta$ 2.23–2.88 (m, 4 H), 3.42 (s, 1 H), 4.35 (m, 2 H), 7.68 (m, 1 H); NMR (220 MHz, $CDCl_3$) $\delta$ 2.46 (m, 2 H), 2.65 (m, 3 H), 4.38 (br s, 2 H), 7.71 (m, 1 H).

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.12; H, 7.07.

**B. From Ketal 29a.** A 250-mL, round-bottomed flask fitted with an additional funnel and gas inlet and outlet connections was cooled to −78 °C under $N_2$ and charged with 90 mL of THF and 13.5 mL (31 mmol) of *n*-BuLi (2.3 M). A solution consisting of 5.28 g (26 mmol) of ketal **29a** in 30 mL of THF was then added dropwise over a period of 15 min. The resulting solution was stirred for 60 min at −78 °C and then treated with anhydrous HCHO [generated by thermal depolymerization (150–158 °C, bath temperature) of 8.0 g of anhydrous paraformaldehyde (4 h)] in a stream of $N_2$ which was swept into a trap (−78 °C) prior to entering the reaction vessel. After 4 h the thermal depolymerization was complete, and the HCHO condensed in the trap was then swept into the reaction vessel by allowing the trap to warm slowly to room temperature while maintaining reaction vessel at −78 °C. After completion of the addition, the reaction was quenched by addition of 5 mL of saturated aqueous $NaH_2PO_4$ and the flask warmed to room temperature. The resulting suspension was poured into brine, extracted with $CH_2Cl_2$, washed with $H_2O$ and brine, and dried. Removal of the solvent in vacuo gave 4.12 g of the corresponding ketal alcohol which was immediately deketalized [400 mg of $(CO_2H)_2$, 2 mL of $H_2O$, 250 mL of $CH_2Cl_2$, 5 h at room temperature]. Chromatography of the resultant material on silica gel (5:1 $CH_2Cl_2$/EtOAc) gave 2.4 g (84%) of hydroxy enone **4** as a white crystalline solid (mp 68–69 °C) possessing spectral data (IR, 200-MHz NMR) identical with the corresponding data obtained for **4** prepared from ester **22a**.

**6-Bromo-7-methyl-1,4-dioxaspiro[4.4]non-6-ene (29b).** To a solution of 7.50 g (78.0 mmol) of 3-methylcyclopentenone in 60 mL of $CCl_4$ at 0 °C under $N_2$ was added 12.9 g (80.6 mmol) of bromine in 60 mL of $CCl_4$ over a 20-min period. The mixture was stirred 5 min at 0 °C, whereupon 19.6 mL (141 mmol) of triethylamine in 60 mL of $CCl_4$ was added over a 20-min period. The ice bath was removed, and the reaction mixture was stirred 1.75 h. The heterogeneous mixture was filtered with the aid of $CCl_4$, and the filtrate was washed with two 25-mL portions of 1 N HCl and one 50-mL portion of water. Drying, concentration, and distillation (short path, 0.25 mm, 65–80 °C) gave 7.64 g (56%) of 2-bromo-3-methyl-2-cyclopentenone as colorless needles: IR 1705 (s), 1620 (m) $cm^{-1}$; NMR (60 MHz) $\delta$ 2.13 (s, 3 H), 2.30–2.82 (m, 4 H). An analytical sample was prepared by two recrystallizations from ether; mp 52.5–53.5 °C.

Anal. Calcd for $C_6H_7OBr$: C, 41.11; H, 4.03. Found: C, 40.99; H, 3.98.

A mixture of 40 mL of dry benzene, 0.76 mL (13.6 mmol) of distilled ethylene glycol, 918 mg (5.24 mmol) of 2-bromo-3-methylcyclopentenone, and 32.9 mg of TsOH was heated at reflux with azeotropic removal of water (Dean–Stark trap) for 63 h. The reaction mixture was cooled to room temperature, 0.5 g of $K_2CO_3$ was added, and the mixture was filtered through a cake of silica gel on $MgSO_4$ with the aid of $CH_2Cl_2$. Concentration of the filtrate and distillation [Kugelrohr, 44–75 °C (0.1 torr)] gave 1.03 g (89%) of **29b** as white needles: mp 33–34 °C; IR 2980 (s), 2955 (m), 2900 (s) $cm^{-1}$; NMR (60 MHz) $\delta$ 1.77 (s, 3 H), 1.94–2.53 (m, 4 H), 3.87–4.07 (m, 2 H), 4.07–4.37 (m, 2 H). An analytical sample was prepared by preparative TLC (75% pentane/EtOAc) and distillation.

Anal. Calcd for $C_8H_{11}O_2Br$: C, 43.85; H, 5.06. Found: C, 43.69, H; 5.14.

**6-Bromo-1,4-dioxaspiro[4.5]dec-6-ene (29c).** To a mixture of 4.61 g (47.9 mmol) of cyclohexenone in 45 mL of $CCl_4$ at 0 °C under $N_2$ was added 7.92 g (49.5 mmol) of bromine in 30 mL of $CCl_4$ over a period of 10 min. The reaction mixture was stirred 5 min at 0 °C, whereupon 12.0 mL (86.3 mmol) of triethylamine in 30 mL of $CCl_4$ was added over a 10-min period. The ice bath was removed, and the reaction mixture was stirred 2 h and filtered with $CCl_4$. The filtrate was washed with two 15-mL portions of 1 N HCl, one 30-mL portion of water, and one 30-mL portion of brine. Drying and concentration gave a solid, which was recrystallized from ether to give 6.36 g (76%) of white needles: mp 71–72 °C (lit.[56] mp 74 °C); IR 1700 (s), 1600 (m) $cm^{-1}$; NMR (60 MHz) $\delta$ 1.83–2.90 (m, 6 H), 7.30, (t, $J$ = 3.5 Hz, 1 H).

A mixture of 2.81 g (16.0 mmol) of this enone, 115 mL of benzene, 2.32 mL (41.6 mmol) of ethylene glycol and 28 mg of TsOH was heated at reflux with azeotropic removal of water (Dean–Stark trap) for 62 h. A workup similar to that listed for **29b** followed by concentration and distillation [Kugelrohr, 72–100 °C (0.2 torr)] gave 3.03 g (87%) of **29c** as a colorless oil: IR 2955 (s), 2900 (s) $cm^{-1}$; NMR (60 MHz) $\delta$ 1.67–2.36 (m, 6 H), 3.75–4.03 (m, 2 H), 4.03–4.35 (m, 2 H), 6.17 (t, $J$ = 7 Hz, 1 H). An analytical sample was prepared by preparative TLC (80% pentane–EtOAc) and distillation [Kugelrohr, 65–75 °C (0.1 torr)].

Anal. Calcd for $C_8H_{11}O_2Br$: C, 43.85; H, 5.06. Found: C, 43.97; H, 5.13.

**General Protocol A. Lithium–Halogen Exchange and Capture by an Electrophilic Reagent.** The appropriate bromide in 5–10 mL of THF was added dropwise over 5 min to a cold (−78 °C) solution of *n*-BuLi (1.1–1.2 equiv) in 29–40 mL of THF under a $N_2$ atmosphere. The resulting solution was allowed to stir for 0.75–1.0 h and was treated with excess HMPA followed by the dropwise addition (10 min) of the appropriate electrophilic reagent in 5–10 mL of THF. The reaction was then allowed to proceed 1–5 h at −78 °C, quenched with 20% aqueous $NaH_2PO_4$, warmed to room temperature, and diluted with a 150-mL portion of $Et_2O$. The workup consisted in separation of the organic phase, washing with $H_2O$ and brine, drying, and filtration.

**2-Methyl-2-cyclopentenone (31b).**[57] Ketal **29a** (538 mg, 2.62 mmol) was reacted with MeI (13.1 mmol) in the presence of HMPA (3.41 mmol) according to general protocol A. The workup gave the corresponding methylated ketal (365 mg). Deketalization [120 mg of $(COOH)_2$, 1.2 mL of $H_2O$, 25 mL of $CH_2Cl_2$, 3 h, room temperature] followed by preparative TLC (80% pentane–EtOAc, $R_f$ 0.16–0.30) and distillation [Kugelrhor, 60–75 °C (19 torr)] afforded 255 mg (53%) of **31b** as a colorless oil: IR 1705 (s), 1640 (m) $cm^{-1}$; NMR (60 MHz) $\delta$ 1.73 (d, $J$ = 2 Hz, 3 H), 2.16–2.78 (m, 4 H), 7.10–7.31 (m, 1 H).

**2-*n*-Pentyl-2-cyclopentenone (31c).**[58] Ketal **29a** (310 mg, 1.51 mmol) was reacted in $Et_2O$ solution with *n*-pentyl iodide (4.53 mmol) and HMPA (6 mmol) according to general protocol A and gave after workup the corresponding *n*-pentyl ketal (320 mg) as an orange oil. Deketalization [200 mg of $(COOH)_2$, 2 mL of $H_2O$, 15 mL of $CH_2Cl_2$, 12 h, room temperature] followed by distillation [Kugelrohr, 50–90 °C (0.2 torr)] gave 164 mg (71%) of **31c** as a colorless oil: IR 1705 (s), 1635 (m) $cm^{-1}$; NMR (60 MHz) $\delta$ 0.89 (t, $J$ = 6 Hz, 3 H), 1.09–1.65 (m, 6 H), 1.89–2.39 (m, 4 H), 2.39–2.74 (m, 2 H), 7.11–7.30 (m, 1 H).

**2-(2-Hydroxypropan-2-yl)-2-cyclopentenone (31d).** Application of general protocol A to ketal **29a** (317 mg, 1.54 mmol) together with 3.9 mmol of HMPA and 7.7 mmol of acetone followed by quenching after 2 h at −78 °C with saturated aqueous $NH_4Cl$ and dilution with $Et_2O$ (150 mL) afforded a crude organic solution. The solution was washed with 1 N HCl, $H_2O$, and brine and dried. Concentration and preparative TLC ($CH_2Cl_2$, $R_f$ 0.15–0.20) gave 122 mg (62%) of **31d** as a colorless oil: IR 1700 (s) 1630 (m) $cm^{-1}$; NMR (60 MHz) $\delta$ 1.32 (s, 6 H), 2.25–2.72 (m, 4 H), 2.88–3.08 (m, 1 H), 7.25 (t, $J$ = 2 Hz, 1 H); mass spectrum, $m/e$ (relative intensity) 125.0609 (88, $M^+ - CH_3$), 122.0738 (10, $M^+ - H_2O$) ($M^+$ calcd for $C_8H_{12}O_2$ 140.1743).

**2-Carbethoxy-2-cyclopentenone (22a) from 29a.** Application of general protocol A to ketal **29a** (698 mg, 3.45 mmol) together with 10.4 mmol of $ClCO_2Et$ followed by workup, concentration, and preparative TLC (80% pentane–EtOAc, $R_f$ 0.26–0.46) gave

(56) Bordwell, F. G.; Wellmen, K. M. *J. Org. Chem.* **1963**, *28*, 2544.
(57) Edwards, O. E.; LeSage, M. *Can. J. Chem.* **1963**, *41*, 1592.
(58) Ravid, U.; Ikan, R. *J. Org. Chem.* **1974**, *39*, 2637.

the corresponding ester **23a** (432 mg). This experiment did not require the use of HMPA as a cosolvent. Ester **23a** was then deketalized [483 mg of $(COOH)_2$, 5 mL of $H_2O$, 5 mL of $CH_2Cl_2$, overnight at room temperature). The workup consisted of neutralization of the above mixture with saturated aqueous $NaHCO_3$ at 0 °C, separation of the organic phase, and drying. Concentration gave 291 mg (53%) of **22a** as a pale yellow oil displaying spectroscopic parameters identical with those obtained for previously prepared **22a**.[26]

**2-(Trimethylsilyl)-2-cyclopentenone (31e).**[5,40c] Application of general protocol A to ketal **29a** (492 mg 2.4 mmol) together with 9.6 mmol of $Me_3Si$ followed by workup preparative TLC (75% pentane–EtOAc, $R_f$ 0.34–0.71), and distillation [Kugelrohr, 105–125 °C (24 torr)] gave 208 mg (56%) of **31e** directly as a clear, colorless oil. The above experiment did not require the use of HMPA as a cosolvent. Spectral data for **31e** are as follows: IR 1695 (s), 1585 (m) $cm^{-1}$; NMR (60 MHz) $\delta$ 0.13 (s, 9 H), 2.00–2.40 (m, 2 H), 2.40–2.80 (m, 2 H), 7.70 (t, $J$ = 2.5 Hz, 1 H).

Anal. Calcd for $C_8H_{14}OSi$: C, 62.28; H, 9.14. Found: C, 62.00; H, 9.08.

**2-(Methylthio)-2-cyclopentenone (31f).**[59] Ketal **29a** (475 mg, 2.33 mmol) was reacted with MeSSMe (16.3 mmol) according to general protocol A. The reaction was quenched at −78 °C with saturated aqueous $NH_4Cl$, diluted with $Et_2O$ (200 mL), and worked up in the usual fashion. HMPA cosolvent was not required. Preparative TLC (75% pentane–EtOAc, $R_f$ 0.27–0.44) afforded **31f**: 197 mg (73%); IR 1710 (s), 1630 (m) $cm^{-1}$; NMR (60 MHz) $\delta$ 2.25 (s, 3 H), 2.05–2.83 (m, 4 H), 6.93 (t, $J$ = 2.5 Hz, 1 H).

**3-Methyl-2-*n*-pentyl-2-cyclopentenone (31g).** Ketal **29b** (363 mg, 1.65 mmol) was reacted with *n*-pentyl iodide (4.95 mmol) in $Et_2O$ solution containing 3.34 mmol of HMPA according to general protocol A. The reaction was quenched cold with $NaH_2PO_4$ (20% aqueous solution) and diluted with $Et_2O$ (150 mL). The organic phase was separated, washed with 1 N HCl, $H_2O$, and brine, and dried. Concentration, preparative TLC (80% pentane–EtOAc, $R_f$ 0.25–0.45), and distillation [Kugelrohr, 65–75 °C (0.1 torr)] gave 164 mg (60%) of **31g** as a clear, colorless oil identical in all respects with an authentic sample of dihydrojasmone kindly provided by Dr. W. T. Taylor of IFF.

**2-Carbethoxy-3-methyl-2-cyclopentenone (31h).** Ketal **29b** (200 mg, 0.91 mmol) was reacted with $ClCO_2Et$ (2.74 mmol) according to general protocol A. HMPA cosolvent was not required. The reaction was worked up in the usual fashion. Concentration, preparative TLC (80% pentane–EtOAc, $R_f$ 0.32–0.55), and then distillation [Kugelrohr, 110–140 °C (0.2 torr)] gave 124 mg (64%) of the corresponding ketal ester as a clear, colorless oil: IR 1715 (s), 1650 (m) $cm^{-1}$; NMR (60 MHz) $\delta$ 1.26 (t, $J$ = 5.5 Hz, 3 H), 1.81–2.57 (m, 4 H), 2.07 (s, 3 H), 4.00 (q, $J$ = 5.5 Hz, 2 H), 3.66–4.41 (m, 4 H).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 62.24; H, 7.79. Found: C, 62.09; H, 7.58.

This ketal (133 mg, 0.63 mmol) was taken up in 5 mL of dichloromethane with 2 mL of water and 146 mg (1.16 mmol) of oxalic acid. The mixture was stirred overnight at room temperature. Cooling to 0 °C, addition of 0.3 g of $K_2CO_3$, drying, concentration, and distillation (Kugelrohr, 110–140 °C (0.25 mm)] gave 103 mg (97%) of **31h** as a clear colorless oil: IR 1750 (s), 1710 (s), 1645 (m) $cm^{-1}$; NMR (60 MHz) $\delta$ 1.31 (t, $J$ = 7 Hz, 3 H), 2.28 (s, 3 H), 2.23–2.51 (m, 2 H), 2.51–2.81 (m, 2 H), 4.22 (q, $J$ = 7 Hz, 2 H).

Anal. Calcd for $C_8H_{12}O_3$: C, 64.26; H, 7.19. Found: C, 64.49; H, 7.14.

**2-*n*-Pentyl-2-cyclohexenone (31i).**[60] Ketal **29c** (300 mg, 1.36 mmol) was reacted in $Et_2O$ solution with *n*-pentyl iodide (4.1 mmol) in the presence of HMPA (13.6 mmol) according to general protocol A. The reaction was quenched at room temperature with $NaH_2PO_4$ (20% aqueous solution) and diluted with $Et_2O$ (150 mL). The organic layer was separated, washed with 1 N HCl, $H_2O$, and brine, and dried. Concentration gave 366 mg of an orange oil which was dissolved in MeOH (15 mL), treated with 1 N HCl (3 mL), and stirred at room temperature overnight. The reaction mixture was added to 50 mL of cold saturated $NaHCO_3$ and 50 mL of brine. This mixture was then extracted with ether, and the organic layers were combined and dried. Concentration and distillation [Kugelrohr, 68–80 °C (0.12 mm)] gave 154 mg (69%) of a clear colorless oil, which was shown by VPC (column C) to be a 1:1 mixture of the desired enone and 2-*n*-butyl-2-cyclohexenone.

2-*n*-Pentyl-2-cyclohexenone (**31i**): IR 1675 (s), 1510 (m) $cm^{-1}$; NMR (250 MHz, $CDCl_3$) $\delta$ 0.88 (t, $J$ = 7.5 Hz, 3 H), 1.20–1.30 (m, 6 H), 1.90–2.46 (m, 8 H), 6.20 (t, $J$ = 3.5 Hz, 1 H); mass spectrum, $m/e$ 166 ($M^+$; calcd for $C_{11}H_{18}O$ 166).

2-*n*-Butyl-2-cyclohexen-1-one: IR ($CCl_4$) 1675 (s), 1540 (m) $cm^{-1}$; NMR (250 MHz, $CDCl_3$) $\delta$ 0.90 (t, $J$ = 6.8 Hz, 3 H), 1.26–1.45 (m, 4 H), 1.92–2.48 (m, 8 H) 6.15 (t, $J$ = 3.5 Hz, 1 H); mass spectrum, $m/e$ 152 ($M^+$; calcd for $C_{10}H_{16}O$, 152).

**6-Carbethoxy-1,4-dioxaspiro[4.5]dec-6-ene (31j).** Ketal **29c** (418 mg, 1.91 mmol) was reacted with $ClCO_2Et$ (7.6 mmol) according to general protocol A. HMPA cosolvent was not required. A standard workup and preparative TLC ($CH_2Cl_2$, $R_f$ 0.15–0.35) gave 328 mg (81%) of **31j** as a colorless oil: NMR (60 MHz) $\delta$ 1.25 (t, $J$ = 7 Hz, 3 H), 1.54–2.54 (m, 6 H), 3.69–4.40 (m, 6 H), 6.95 (t, $J$ = 4 Hz, 1 H).

All attempts to effect hydrolysis of this ketal resulted in either its recovery or its destruction.

**2-(Acetoxymethyl)-2-cyclopentenone (34b).** A solution consisting of 271 mg (2.42 mmol) of enone **4** in 1.0 mL of pyridine was treated with 1.0 mL of acetic anhydride and stored overnight at 4 °C. Concentration in vacuo followed by distillation [Kugelrohr, 105–115 °C (0.05 torr)] afforded 364.6 mg (98%) of acetate **34b**. An analytical sample prepared by VPC on column B possessed the following spectral data: IR ($CHCl_3$) 3030 (m), 2940 (w), 1745 (s), 1720 (s), 1650 (m), 1375 (s), 1240 (s, br), 1028 (s), 1000 (m), 970 (m) $cm^{-1}$; NMR (220 MHz, $CDCl_3$) $\delta$ 2.10 (s, 3 H), 2.46 (m, 2 H), 2.66 (m, 2 H), 4.76 (s, 2 H), 7.60 (s, 1 H).

Anal. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 62.05; H, 6.82.

**General Protocol B. Vicinal Cis Hydroxylation Utilizing $OsO_4$.** A chilled (0–5 °C) solution (0.5 M) of the appropriate olefin in pyridine was added to a solution (0.5 M) of $OsO_4$ (1.0–1.1 equiv) in pyridine. The resulting black solution was stirred at room temperature under $N_2$ for a period of 5 h. The osmate ester was then reductively cleaved by addition of $NaHSO_3$ (1.2 g), $H_2O$ (8 mL), and pyridine (6 mL), followed by stirring at room temperature for 3 h.[23] The resulting suspension was diluted with EtOAc, filtered, and dried. Removal of the solvent in vacuo afforded the corresponding *cis*-diol.

***cis*-2,3-Dihydroxy-2-(acetoxymethyl)cyclopentanone (33).** Olefin **34b** (300 mg, 1.94 mmol) was treated with $OsO_4$ (1.0 equiv) according to general protocol B. The workup afforded 349 mg (96%) of diol **33**. An analytical sample obtained by TLC (1:1 $CH_2Cl_2$/EtOAc, $R_f$ 0.30) possessed the following spectral data: IR ($CHCl_3$) 3545 (m, br), 3025 (m), 2960 (m), 1750 (s), 1240 (s, br), 1030 (s), 965 (m) $cm^{-1}$; NMR (220 MHz, $CDCl_3$) $\delta$ 1.96–2.38, 2.08 (m, s, 5 H), 2.48 (td, $J$ = 8, 2 Hz, 2 H), 2.95 (br s, 1 H), 3.76 (br s, 1 H), 4.17 (br s, 1 H), 4.21 (AB system, $\gamma_{AB}$ = 57.8 Hz, $J_{AB}$ = 12 Hz, 2 H);[47] mass spectrum, $m/e$ 188.0684 ($M^+$; calcd for $C_8H_{12}O_5$ 188.1790).

***cis*-2,3-Diacetoxy-2-(acetoxymethyl)cyclopentanone (32).** A solution consisting of 336.7 mg (1.79 mmol) of diol **33** in 3 mL of pyridine was treated with 2.0 mL (5 equiv) of $Ac_2O$ and stirred at room temperature for 49 h under a $N_2$ atmosphere. The resulting dark solution was concentrated in vacuo and distilled [Kugelrohr, 135–145 °C (0.05 torr)], giving 375 mg (77%) of triacetate **32** as a colorless, viscous oil which crystallized on standing at room temperature. Recrystallization from diisopropyl ether gave **32** as white needles (mp 80.5–81.5 °C) possessing the following spectral data: IR ($CHCl_3$) 3030 (m), 2960 (w), 1750 (s), 1375 (s), 1240 (s, br), 1050 (s), $cm^{-1}$; NMR (220 MHz, $CDCl_3$) $\delta$ 1.59–2.69, 2.09, 2.11, 2.12 (m and 3 s, 12 H), 2.77 (m, 1 H), 4.34 (AB system, $\gamma_{AB}$ = 22.9 Hz, $J_{AB}$ = 10 Hz, 2 H),[47] 5.46 (t, $J$ = 7.5 Hz, 1 H).

The $^1H$ NMR data for synthetic **32** (Table II) is quite consistent with the corresponding data published[6] for **32** (Table II).

**General Protocol C. Dehydrogenation with $SeO_2$.** A suspension consisting of the appropriate ketone, $SeO_2$ (5 equiv), *tert*-butyl alcohol (45 mL), and benzene (5 mL) was heated at

(59) Shinobu, I., Japanese Patent; *Chem. Abstr.* **1977**, *87*, 200912.
(60) Ansell, M. F.; Kafka, T. M. *Tetrahedron* **1969**, *25*, 6025.

Table II. $^1$H NMR (60 MHz) Spectral Data Comparison between Authentic and Synthetic Pentenomycins I–III, Dehydropentenomycin I, Pentenomycin I Triacetate, and Dihydropentenouncin I Triacetate

| compd | solvent | shift,[a] δ | | | | coupling constant, Hz | | | | miscellaneous |
|---|---|---|---|---|---|---|---|---|---|---|
| | | $H_1$ | $H_2$ | $H_3$ | $H_{4,5}$ | $J_{1,2}$ | $J_{2,3}$ | $J_{1,3}$ | $J_{4,5}$ | |
| 1a (isolated) | $D_2O$ | 6.39 (dd) | 7.81 (dd) | 4.79 (dd) | 3.67 (s) | 6.0 | 3.0 | 1.5 | | |
| 1a (synthetic) | $D_2O$ | 6.30 (dd) | 7.70 (dd) | 4.68 (dd) | 3.55 (s) | 6.0 | 3.0 | 1.5 | | |
| Δδ | | 0.09 | 0.11 | 0.11 | 0.12 | | | | | |
| 1b (isolated) | $D_2O$ | 6.58 (dd) | 7.86 (dd) | 5.82 (dd) | 3.77 (s) | 6.0 | 3.0 | 1.5 | | 2.14 (s, 3 H, $CDCH_3$) |
| 1b (synthetic) | $D_2O$ | 6.47 (dd) | 7.73 (dd) | 5.72 (dd) | 3.67 (s) | 6.0 | 3.0 | 1.5 | | 2.07 (s, 3 H, $COCH_3$) |
| Δδ | | 0.11 | 0.13 | 0.10 | 0.10 | | | | | 0.07 |
| 1c (isolated) | $CDCl_3$ | 6.29 (dd) | 7.59 (dd) | 4.70 (br s) | 4.22 (d) | 6.0 | 2.3 | 1.0 | 2.0 | 2.02 ($COCH_3$) |
| 1c (synthetic) | $CDCl_3$ | 6.35 (dd) | 7.67 (dd) | 4.75 (br s) | 4.25 (d) | 6.0 | 2.3 | 1.0 | 2.0 | 2.02 ($COCH_3$) |
| Δδ | | 0.08 | 0.06 | 0.05 | 0.03 | | | | | 0.00 |
| 3 (isolated) | $(CD_3)_2CO$[c] | | 7.46 (s) | | 3.74 (d) | | | | | 4.95 (s, C-OH), 4.18 (d, $CH_2OH$) |
| 3 (synthetic) | $(CD_3)_2CO$ | | 7.43 (s) | | 3.76 (s) | | | | | 3.43–4.60 (br s, C-OH, $CH_2OH$) |
| Δδ | | | 0.03 | | 0.02 | | | | | |
| 5 (isolated) | $CDCl_3$ | 6.60 (dd) | 7.48 (dd) | 5.90 (dd) | 4.40 (s) | 6.0 | 3.0 | 1.5 | | 2.03, 2.07, 2.08 (3 s, 9 H, $COCH_3$) |
| 5 (synthetic) | $CDCl_3$ | 6.42 (dd) | 7.41 (dd) | 5.78 (dd) | 4.30 (s) | 6.0 | 3.0 | 1.5 | | 1.99, 2.03, 2.05 (3 s, 9 H, $COCH_3$) |
| Δδ | | 0.18 | 0.07 | 0.12 | 0.10 | | | | | 0.04, 0.04, 0.03 |
| 1b (isolated) | $Me_2SO$-$d_6$ | 6.45 (dd) | 7.72 (dd) | 5.78 (dd) | 3.52 (d) | 6.0 | 3.0 | 1.5 | 5.5 | 2.01 (s, 3 H, $COCH_3$) |
| 1b (synthetic) | $Me_2SO$-$d_6$ | 6.37 (dd) | 7.62 (dd) | 5.70 (dd) | 3.48 (d) | 6.0 | 3.0 | 1.5 | 5.0 | 2.00 (s, 3 H, $COCH_3$) |
| Δδ | | 0.08 | 0.10 | 0.08 | 0.04 | | | | | 0.01 |
| 32 (isolated) | $CDCl_3$ | | | 5.49 (t) | 4.31 (s) | | | | | 2.02 (s, 9 H, $COCH_3$) |
| 32 (synthetic) | $CDCl_3$[b] | | | 5.43 (t) | 4.34 (AB) | | | | | 2.06, 2.09, 2.11 (3 s, 9 H, $COCH_3$) |
| Δδ | | | | 0.06 | 0.03 | | | | | |

[a] $^1$H NMR of synthetic 1a,b in $D_2O$; $Me_4Si$ external/$CDCl_3$. [b] 220-MHz $^1$H NMR data. [c] 100-MHz $^1$H NMR data.

reflux for 140–160 h.[42] The resulting dark suspension was cooled, filtered through Celite, poured into $H_2O$, and extracted with $CH_2Cl_2$. The organic phase was separated, washed with brine, and dried. Removal of the solvent in vacuo gave the corresponding crude enone.

**(±)-Pentenomycin I Triacetate (5).** Triacetate **32** (350 mg, 1.29 mmol) was treated with $SeO_2$ (5 equiv) according to general protocol C. The workup afforded 425 mg of a red syrup which was then dissolved in 30 mL of $CH_2Cl_2$, treated with 8 mL of 30% $H_2O_2$, and stirred at room temperature for 1.5 h. The resulting solution was washed with $H_2O$ and dried. Removal of the solvent in vacuo gave 279.6 mg of a light yellow oil which after TLC (4:1 $CH_2Cl_2$/EtOAc, $R_f$ 0.41) afforded 188.4 mg (54%) of enone **5** as a white crystalline solid. Recrystallization from diisopropyl ether gave **5** as a white needlelike solid (mp 98.5–99.5 °C) possessing spectral data identical with those published:[6] IR ($CHCl_3$) 3030 (m), 2960 (w), 1750 (s, br), 1600 (w), 1375 (s), 1235 (s, br), 1052 (s) cm$^{-1}$; $^1$H NMR (60 MHz, $CDCl_3$) δ 1.99, 2.03, 2.05 (3 s, 9 H), 4.30 (s, 2 H), 5.78 (dd, $J$ = 3, 1.5 Hz, 1 H), 6.42 (dd, $J$ = 6, 1.5 Hz, 1 H), 7.41 (dd, $J$ = 6, 3 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 199.5, 135.7, 154.2, 72.0, 64.1.

**General Protocol D. Hydroxyl Protection with *tert*-Butyldimethylsilyl Chloride (TBDMSCl).**[44] A solution consisting of the appropriate alcohol, TBDMSCl (1.2–1.5 equiv), and imidazole (2.4–3.0 equiv) in DMF (8–20 mL) was stirred under $N_2$ at room temperature (unless indicated otherwise) for the appropriate amount of time. The workup consisted of depositing the reaction solution into $H_2O$ and extraction with $Et_2O$–pentane (1:1). The organic phase was separated, washed with $H_2O$ and brine, and dried. Removal of the solvent in vacuo afforded the corresponding crude silyl ether.

**2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2-cyclopentenone (34a).** Alcohol **4** (885 mg, 7.9 mmol) was treated with TBDMSCl/imidazole in DMF (20 mL) according to general protocol D. After 65 h at room temperature the reaction mixture was worked up in the usual fashion and gave 1.81 g of a yellow oil which on distillation [Kugelrohr, 70–76 °C (0.5 torr)] gave 1.38 g (78%) of **34a** as a white crystalline solid (mp 33 °C). An analytical sample obtained by VPC on column A possessed the following spectral data: IR 3060 (w), 2950 (s), 1700 (s), 1645 (w), 1390 (s), 1260 (s), 1120 (s, br), 990 (m), 835 (s, br) cm$^{-1}$; NMR (220 MHz) δ 0.07 (s, 6 H), 0.92 (s, 9 H), 2.34 (m, 2 H), 2.57 (m, 2 H), 4.25 (s, 2 H), 7.36 (s, 1 H).

Anal. Calcd for $C_{12}H_{22}O_2Si$: C, 63.67; H, 9.80. Found: C, 63.80; H, 9.63.

***cis*-2,3-Dihydroxy-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]cyclopentanone (35a).** By use of general protocol B, 779.6 mg (3.45 mmol) of enone **34a** afforded 925 mg of a crude light brown oil. This oil on distillation [Kugelrohr, 95–115 °C (0.1 torr)] gave 847 mg (94%) of diol **35a** as a colorless viscous oil. An analytical sample obtained by preparative TLC [$CH_2Cl_2$/EtOAc (10:3), $R_f$ 0.28] possessed the following spectral data: IR 3540 (s, br), 2950 (s), 2855 (s), 1750 (s), 1475 (m), 1470 (m), 1360 (m), 1260 (s), 1115 (s, br), 1090 (s, br), 840 (s, br) cm$^{-1}$; NMR (220 MHz) δ 0.01, 0.03 (2 s, 6 H), 1.30 (s, 9 H), 1.90–2.50 (m, 4 H), 3.25 (br s, 2 H), 3.59 (AB system, $\gamma_{AB}$ = 8.31 Hz, $J_{AB}$ = 10 Hz, 2 H)[47] 4.11 (m, 1 H).

Anal. Calcd for $C_{12}H_{24}O_4Si$: C, 55.35; H, 9.29 Found: C, 55.61; H, 9.05.

***t*-3-[(*tert*-Butyldimethylsilyl)oxy]-2-hydroxy-*r*-[[(*tert*-butyldimethylsilyl)oxy]methyl]cyclopentanone (36a).** Application of general protocol D to alcohol **35a** (900 mg, 3.46 mmol) gave after 45 h at room temperature and workup 1.35 g of a yellow oil. Distillation [Kugelrohr, 115–123 °C (0.075 torr)] gave 1.19 g (92%) of alcohol **36a** as a clear mobile oil. An analytical sample prepared by preparative TLC ($CH_2Cl_2$, $R_f$ 0.26) possessed the following spectral data: IR 3530 (m, br), 2955 (s), 2940 (s), 1755 (s), 1260 (s), 1095 (s, br), 1075 (s, br), 875 (s), 835 (s, br) cm$^{-1}$; NMR (220 MHz) δ 0.03, 0.05 (2 s, 6 H), 0.12, 0.13 (2 s, 6 H), 0.86 (s, 9 H), 0.93 (s, 9 H), 1.76–2.27 (m, 3 H), 2.30–2.50 (m, 1 H), 2.56 (s, 1 H), 3.54 (AB system, $\gamma_{AB}$ = 20.2 Hz, $J_{AB}$ = 10 Hz, 2 H),[47] 4.38 (t, $J$ = 7 Hz, 1 H).

Anal. Calcd for $C_{18}H_{38}O_4Si_2$: C, 57.70; H, 10.22. Found: C, 58.03; H, 10.29.

***t*-4-[(*tert*-Butyldimethylsilyl)oxy]-5-hydroxy-*r*-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-cyclopentenone (37a).** Application of general protocol C to **36a** (154 mg, 0.41 mmol) gave after 140 h at reflux and workup 164 mg of a crude, dark oil. Column chromatography on silica gel (elution with $CH_2Cl_2$) gave 78.4 mg (51%) of **37a** as a crystalline solid. An analytical sample obtained by preparative TLC ($CH_2Cl_2$, $R_f$ 0.17) gave **37a** as a white needlelike solid (mp 37 °C) possessing the following spectral data: IR 3510 (m), 2960 (s), 1735 (s), 1265 (s), 1105 (s), 1078 (s), 875 (s), 835 (s) cm$^{-1}$; NMR (220 MHz) δ −0.05, 0.00 (2 s, 6 H), 0.15, 0.16 (2 s, 6 H), 0.80, 0.94 (2 s, 18 H), 2.65 (s, 1 H), 3.61 (AB system, $\gamma_{AB}$ = 98.5 Hz, $J_{AB}$ = 10 Hz, 2 H),[47] 4.85 (s, 1 H), 6.17 (d, $J$ = 7 Hz, 1 H), 7.22 (d, $J$ = 7 Hz, 1 H).

Anal. Calcd for $C_{18}H_{36}O_4Si_2$: C, 58.02; H, 9.74. Found: C, 58.23; H, 9.85.

**Preparation of (±)-Pentenomycin I (1a) from 37a.** A solution consisting of 191.4 mg (0.52 mmol) of **37a** in 8 mL of 50% (v/v) aqueous THF was treated with 12 mL of acetic acid (glacial) and stirred at room temperature for a period of 82 h. The resulting solution was concentrated in vacuo, affording 70.7 mg (94%) of

enone **1a** as a highly viscous, colorless oil possessing the following spectral data: NMR (60 MHz, $D_2O$) $\delta$ 3.55 (s, 2 H), 4.68 (dd, $J$ = 3, 1.5 Hz, 1 H), 6.30 (dd, $J$ = 6, 1.5 Hz, 1 H), 7.70 (dd, $J$ = 6, 3 Hz, 1 H). The $^1H$ NMR data obtained for synthetic **1a** are identical with the corresponding data published for **1a** (Table II).

***t*-3-Acetoxy-2-hydroxy-*r*-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]cyclopentanone (36b).** A solution consisting of 960 mg (3.69 mmol) of **35a** in 4 mL of pyridine was treated with 50 mg (1.5 equiv) of acetic anhydride and stored at 4 °C for 10 h. The resulting mixture was poured into $H_2O$ and extracted with EtOAc. The organic phase was separated, washed with $H_2O$ and brine, and dried. Removal of the solvent in vacuo gave 1.72 g of a crude oil which on distillation [Kugelrhor, 110–120 °C (0.1 torr)] gave 1.05 g (94%) of acetate **36b** as a clear, colorless oil. An analytical sample obtained by VPC on column A possessed the following spectral data: IR 3510 (m, br), 2955 (s), 2935 (s), 1750 (s), 1240 (s, br), 1115 (s), 835 (s, br) $cm^{-1}$; NMR (220 MHz) $\delta$ 0.00, 0.02 (2 s, 6 H), 0.84 (s, 9 H), 1.91–2.48, 2.02 (m, s, 7 H), 2.91 (br s, 1 H), 3.59 (s, 2 H), 5.25 (m, 1 H).

Anal. Calcd for $C_{14}H_{26}O_4Si$: C, 55.60; H, 8.67. Found: C, 55.82; H, 8.86.

***t*-4-Acetoxy-5-hydroxy-*r*-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-cyclopentenone (37b) Prepared from Acetate 36b.** By use of general protocol C, 920 mg (3.05 mmol) of acetate **36b** gave 1.40 g of a red syrup which was first chromatographed on Florisil (elution with 10:1 $CH_2Cl_2$/EtOAc), giving 690 mg of discolored crystalline material which was then distilled [Kugelrohr, 115–125 °C (0.25 torr)] to afford 603 mg (67%) of enone **37b** as a white crystalline solid, mp 63–65 °C). An analytical sample (white flakes, mp 63.5–64.5 °C) obtained by TLC (6:1 $CHCl_3$/EtOAc, $R_f$ 0.26) possessed the following spectral data: IR ($CHCl_3$) 3580 (m), 3040 (m), 2960 (s), 2940 (s), 1740 (s), 1240 (s, br), 1125 (s, br), 1105 (s, br), 840 (s, br) $cm^{-1}$; NMR (220 MHz, $CDCl_3$) $\delta$ −0.23, 0.23 (2 s, 6 H), 0.82 (s, 9 H), 2.14 (s, 3 H), 3.13 (s, 1 H), 3.78 (s, 2 H), 5.81 (br s, 1 H), 6.43 (d, $J$ = 7 Hz, 1 H), 7.59 (d, $J$ = 7 Hz, 1 H).

Anal. Calcd for $C_{14}H_{24}O_5Si$: C, 55.97; H, 8.05. Found: C, 56.12; H, 8.23.

**(±)-Pentenomycin II (1b).** A solution consisting of 40.8 mg (0.14 mmol) of enone **37b** in 2 mL of 50% (v/v) aqueous THF was treated with 3 mL of acetic acid (glacial) and stirred at room temperature for 162 h.[44] The resulting solution was concentrated in vacuo (10 h, 0.05 torr), affording 22.3 mg (88%) of enone **1b** as a colorless, viscous oil possessing spectral data (60-MHz $^1H$ NMR) identical with the corresponding data (Table II) derived from the authentic antibiotic:[6] $^1H$ NMR (60 MHz, $D_2O$) $\delta$ 2.07 (s, 3 H), 3.67 (s, 2 H), 5.72 (dd, $J$ = 3, 1.5 Hz, 1 H), 6.47 (dd, $J$ = 6, 1.5 Hz, 1 H), 7.73 (dd, $J$ = 6, 3 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 204.9 (s), 134.8 (d), 157.3 (d), 73.5 (d), 75.7 (s), 64.9 (t).

***t*-3-[(*tert*-Butyldimethylsilyl)oxy]-2-hydroxy-*r*-2-(acetoxymethyl)cyclopentanone (38).** Application of general protocol D to diol **35b** gave after 112 h at room temperature and workup a pale yellow oil. Distillation [Kugelrohr, 85–100 °C (0.4 torr)] afforded 550 mg (88%) silyl ether **38** as a colorless oil, possessing the following spectral data: IR ($CCl_4$) 3500 (w, br), 2950 (s), 1750 (s), 1250 (s), 1230 (s), 1130 (s), 1100 (s), 1040 (m), 830 (s) $cm^{-1}$; NMR (60 MHz, $CDCl_3$) $\delta$ 0.08 (s, 6 H), 0.85 (s, 9 H), 2.00 (s, 3 H), 2.00–2.48 (m, 4 H), 3.00 (br s, 1 H), 4.10–4.30 (m, 3 H).

Anal. Calcd for $C_{14}H_{26}O_5Si$: C, 55.60; H, 8.66. Found: C, 55.71; H, 8.83.

***t*-4-[(*tert*-Butyldimethylsilyl)oxy]-5-hydroxy-*r*-5-(acetoxymethyl)-2-cyclopentenone (39).** Application of general protocol C to ketone **38** (155 mg, 0.51 mmol) gave after workup a red syrup. Preparative TLC (95:5 $CH_2Cl_2/Et_2O$, $R_f$ 0.45] afforded 55 mg (36%) of a colorless oil possessing the following spectral data: IR 3550 (m), 3440 (m, br), 2950 (s), 2870 (s), 1735 (s), 1220 (s), 1130 (s), 840 (s) $cm^{-1}$; NMR (60 MHz, $CDCl_3$) $\delta$ 0.13 (s, 6 H), 0.85 (s, 9 H), 1.98 (s, 3 H), 3.43 (br s, 1 H), 4.18 (s, 2 H), 4.73 (dd, $J$ = 1.2, 2.3 Hz, 1 H), 6.28 (dd, $J$ = 1.2, 6.0 Hz, 1 H), 7.38 (dd, $J$ = 2.3, 6.0 Hz, 1 H).

Anal. Calcd for $C_{14}H_{24}O_5Si$: C, 55.97; H, 8.15. Found: C, 56.06; H, 8.05.

**(±)-Pentenomycin III (1c).** A solution consisting of 119 mg (0.4 mmol) of enone **39** in 3 mL glacial acetic acid, 1 mL of THF, and 1 mL of $H_2O$ was stirred at room temperature for 10 days.[44]

**Table III. $^{13}C$ NMR Spectral Data Comparison for Authentic and Synthetic Dehydropentenomycin I**

| compd | solvent | shift, $\delta$ (from $Me_4Si$) C-1, C-4 | C-2, C-3 | C-5 | C-6 |
|---|---|---|---|---|---|
| 3 (isolated) | $Me_2SO$-$d_6$ | 205.2 | 149.9 | 74.0 | 62.9 |
| 3 (synthetic) | $Me_2SO$-$d_6$ | 205.2 | 149.9 | 74.0 | 63.0 |

Removal of the solvent in vacuo and preparative TLC [$CH_2Cl_2/Et_2O$ (40:60); $R_f$ 0.53] afforded (±)-pentenomycin III (**1c**) as a colorless oil possessing spectral data identical with those reported for authentic **1c** (Table II): IR ($CHCl_3$) 3445 (m, br), 3040 (w), 2940 (w), 1730 (s), 1600 (w), 1230 (s), 1050 (s), 870 (w) $cm^{-1}$; NMR (60 MHz, $CDCl_3$) $\delta$ 2.02 (s, 3 H), 3.85 (br s, 1 H), 4.25 (d, $J$ = 2.0 Hz, 2 H), 4.75 (m, 1 H), 6.35 (dd, $J$ = 1.0, 6.0 Hz, 1 H), 7.67 (dd, $J$ = 2.3, 6.0 Hz, 1 H).

***cis*-4,5-Dihydroxy-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-cyclopentenone (44).** By use of general protocol C, 285.2 mg (1.10 mmol) of diol **35a** afforded 338 mg of a red syrup. The reaction product was then dissolved in 25 mL of $CH_2Cl_2$, treated with 5 mL of 30% $H_2O_2$, and stirred at room temperature for 60 min. The resulting mixture was washed with $H_2O$ and dried. Removal of the solvent in vacuo gave 171.4 mg of a light brown crystalline solid which after TLC (10:3 $CH_2Cl_2$/EtOAc, $R_f$ 0.30) afforded 147.2 mg (53%) of enone **44** as white flakes (mp 80.5–81.5 °C) possessing the following spectral data: IR ($CHCl_3$) 3550 (s, br), 3450 (sh, br), 3025 (w), 2870 (s), 1730 (s), 1600 (w), 1262 (s), 1105 (s, br), 840 (s, br) $cm^{-1}$. NMR (220 MHz, $CDCl_3$) $\delta$ 0.25, 0.29 (2 s, 6 H), 1.08 (s, 9 H), 3.80, 3.98 (br s, AB system, $\gamma_{AB}$ = 25.6 Hz, $J_{AB}$ = 10 Hz, 4 H),[47] 5.03 (s, 1 H), 6.56 (br d, $J \approx 6$ Hz, 1 H), 7.91 (m, 1 H).

Anal. Calcd for $C_{12}H_{22}O_4Si$: C, 55.78; H, 8.58. Found: C, 55.47; H, 8.68.

**2-Hydroxy-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-cyclopent-4-ene-1,3-dione (40).** A solution consisting of 128 mg (0.5 mmol) of diol **44** in 20 mL of acetone was chilled to −10 °C and then treated with 280 μL (1.5 equiv, 2.7 M) of $CrO_3/H_2SO_4$. The resulting suspension was stirred for 60 min, treated with 30 mg of $Na_2SO_3$, poured into brine, and extracted with $CH_2Cl_2$. The organic phase was separated and dried. Removal of the solvent in vacuo gave 109 mg of crystalline material which after TLC (10:1 $CH_2Cl_2$/EtOAc, $R_f$ 0.32) gave 78.5 mg (61%) of **40** as yellow needles (mp 65 °C) possessing the following spectral data: IR ($CHCl_3$) 3560 (m), 3040 (m), 2955 (s), 2935 (s), 1755 (m), 1720 (s), 1265 (s), 1115 (s, br), 835 (s) $cm^{-1}$; NMR (220 MHz, $CDCl_3$) $\delta$ 0.14 (s, 6 H), 0.95 (s, 9 H), 3.72 (br s, 1 H), 4.02 (s, 2 H), 7.59 (s, 2 H).

Anal. Calcd for $C_{12}H_{20}O_4Si$: C, 56.22; H, 7.86. Found: C, 56.11; H, 7.90.

**Dehydropentenomycin I (3).** A solution consisting of 100 mg (9.39 mmol) of **40** in 6 mL of 50% (v/v) aqueous THF was treated with 9 mL of glacial acetic acid and stirred at room temperature for a period of 168 h. The resulting solution was concentrated in vacuo, affording 86.4 mg of a crude, viscous, yellow oil. Purification by preparative TLC (EtOAc, $R_f$ 0.40) gave 40.9 mg 73.8%) of enone **3** as a viscous yellow oil possessing the following spectral data: IR (Nujol) 3550–3250 (s, br), 1750 (s), 1600 (m), $cm^{-1}$; $^1H$ NMR (60 MHz, acetone-$d_6$) $\delta$ 3.43–4.60, 3.76 (br s, s, 4 H), 7.43 (s, 2 H); $^1H$ NMR (220 MHz, acetone-$d_6$) $\delta$ 2.60–5.6, 3.76 (br s, s, 4 H), 7.42 (s, 2 H): $^{13}C$ NMR ($Me_2SO$-$d_6$) 205.2, 149.9, 74.0, 63.0.

The spectral data obtained for synthetic **3** were identical with the corresponding data obtained for the isolated antibiotic (Tables III and IV).

**Pentenomycin I (1a) Prepared from Enone 44.** A solution consisting of 29.8 mg (0.12 mmol) of enone **44** in 2 mL of 50% (v/v) aqueous THF of treated with 3 mL of acetic acid (glacial) and stirred at room temperature for a period of 80 h. Concentration in vacuo (10 h, 0.1 torr) gave 16.0 mg (96%) of enone **1a** as a highly viscous, colorless oil possessing spectral data (60-MHz $^1H$ NMR) identical with those derived from the natural antibiotic (see Table II).

**Compound 37b Prepared from Diol 44.** A solution consisting of 27.9 mg (0.11 mmol) of diol **44** in 80 μL of pyridine was treated with 11 μL (1.2 equiv) of $Ac_2O$ and stored at 4 °C for 24 h. The resulting solution was concentrated in vacuo followed by distil-

Table IV. $^1$H NMR (60 MHz) Spectral Comparison of Synthetic Pentenomycins I-III with Epipentenomycins I-III, Respectively

| compd | solvent | shift, δ (from $Me_4Si$[a]) | | | | J, Hz | | | | miscellaneous |
|---|---|---|---|---|---|---|---|---|---|---|
| | | $H_1$ | $H_2$ | $H_3$ | $H_{4,5}$ | $J_{1,2}$ | $J_{2,3}$ | $J_{1,3}$ | $J_{4,5}$ | |
| 1a (synthetic) | $D_2O$ | 6.30 (dd) | 7.70 (dd) | 4.68 (dd) | 3.55 (s) | 6.0 | 3.0 | 1.5 | | |
| 2a (synthetic) | $D_2O$ | 6.58 (dd) | 7.90 (dd) | 5.00 (t) | 3.88 (d) | 6.5 | 2.0 | 2.0 | 2.0 | |
| 1b (synthetic) | $D_2O$ | 6.47 (dd) | 7.73 (dd) | 5.72 (dd) | 3.67 (s) | 6.0 | 3.0 | 1.5 | | 2.07 (s, 3 H, $COCH_3$) |
| 2b (synthetic) | $D_2O$ | 6.55 (dd) | 7.77 (dd) | 5.87 (dd) | 3.70 (s) | 6.0 | 1.5 | 2.0 | | 2.15 (s, 3 H, $COCH_3$) |
| 1c (synthetic) | $CDCl_3$ | 6.35 (dd) | 7.67 (dd) | 4.75 (s) | 4.25 (d) | 6.0 | 2.3 | 1.0 | 2.0 | 2.02 (s, 3 H, $COCH_3$) |
| 2c (synthetic) | $CDCl_3$ | 6.33 (dd) | 7.52 (dd) | 4.90 (s) | 4.32 (AB) | 6.8 | 1.7 | 1.7 | 12.0 | 2.06 (s, 3 H, $COCH_3$) |

[a] $Me_4Si$ was external for $D_2O$ experiments.

lation [Kugelrohr, 110–140 °C (0.25 torr)] to afford 31.2 mg (96%) of enone acetate **37b** as a white crystalline solid (mp 65 °C) possessing spectral data identical with those obtained previously.

**Preparation of 2-[[(*tert*-Butyldimethylsilyl)oxy]-methyl]-3-hydroxycyclopentene (21d). A. Reduction of 34a with 9-BBN.**[50] A solution consisting of 303 mg (1.34 mmol) of enone **34a** in 3 mL of THF was chilled to 0–5 °C (ice bath). To this mixture was added, over 10 min, 2.8 mL (0.5 M, 1.40 mmol) of 9-BBN in THF. The resulting solution was stirred under $N_2$ for 4 h at 0–5 °C, followed by 2 h at room temperature, after which 0.5 mL of MeOH was added to destroy any excess 9-BBN. For oxidation of the boronic acid derived, 0.8 mL of 2 N NaOH (1.6 mmol) was added followed by 0.5 mL of 30% $H_2O_2$ (4.80 mmol). This was stirred for 1 h at 60 °C. The aqueous layer was then saturated with $K_2CO_3$ and the organic layer separated. The aqueous phase was extracted with $Et_2O$, and the combined organic layers were washed with $H_2O$ and dried. Removal of the solvent in vacuo afforded 278 mg of pale yellow oil, which upon distillation [Kugelrohr, 60–70 °C (0.5 torr)] gave 248 mg (81%) of **21d** as a colorless oil. An analytical sample obtained by preparative TLC (9:1 $CH_2Cl_2/Et_2O$, $R_f$ 0.52) possessed the following spectral data: IR ($CHCl_3$) 3550 (m, br), 2950 (s), 2935 (s), 1260 (s), 1140 (s, br), 1100 (s, br), 1060 (s), 905 (s), 835 (s), $cm^{-1}$; NMR (360 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.88 (s, 9 H), 1.70–1.81 (m, 1 H), 2.13–2.77 (m, 2 H), 2.41–2.51 (m, 1 H), 2.67 (br s, 1 H), 4.32 (s, 2 H), 4.77 (br s, 1 H), 5.71 (br s, 1 H).

Anal. Calcd for $C_{12}H_{24}O_2Si$: C, 63.10; H, 10.59. Found: C, 63.05; H, 10.74.

**B. Reduction of 34a with $NaBH_4$ and $CeCl_3 \cdot H_2O$.**[51] A solution consisting of 1.02 g (4.4 mmol) of **34a** dissolved in 12 mL (4.80 mmol) of 0.4 M $CeCl_3 \cdot H_2O$ in MeOH was treated portionwise of 171 mg (4.50 mmol) of $NaBH_4$ at room temperature. The resulting milky solution was stirred an additional 10 min and then quenched with 10 mL of $H_2O$. The aqueous layer was extracted with $Et_2O$, and the combined organic layers were washed with brine and concentrated in vacuo to yield 1.02 g of pale yellow oil. Kugelrohr distillation afforded 940 mg (93%) of a colorless mobile oil identical in all respects with **21d**, described above.

**2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-3-[(*tert*-butyldimethylsilyl)oxy]cyclopentene (21a).** Application of general protocol D to alcohol **21d** (1.02 g, 4.43 mmol) afforded after 72 h at 45 °C (oil bath) and workup 1.46 g of a yellow oil. Distillation [Kugelrohr, 90–100 °C (0.25 torr)] gave 1.35 g (85%) of **21a** as a colorless oil. An analytical sample obtained via preparative TLC (95:5 $CH_2Cl_2/Et_2$, $R_f$ 0.86) possessed the following spectral data: IR ($CHCl_3$) 2955 (s), 2935 (s), 1255 (s), 1075 (s), 940 (m), 835 (s) $cm^{-1}$; NMR (60 MHz, $CDCl_3$) δ 0.02 (s, 12 H), 0.85 (s, 18 H), 1.42–1.60 (m, 4 H), 4.23 (m, 2 H), 4.82 (br s, 1 H), 5.80 (m, 1 H).

Anal. Calcd for $C_{18}H_{38}O_2Si_2$: C, 63.09; H, 11.18. Found: C, 63.03; H, 11.36.

***c*-2-[(*tert*-Butyldimethylsilyl)oxy]-*t*-5-hydroxy-*r*-1-[[(*tert*-butyldimethylsilyl)oxy]methyl]cyclopentan-1-ol (20a).** By use of general protocol B, 340 mg (1.0 mmol) of olefin **21a** gave 384 mg of yellow oil. Kugelrohr distillation [93–100 °C (0.3 torr)] gave 336 mg (90%) of diol **20a** as a colorless oil. An analytical sample obtained by preparative TLC (9:1 $CH_2Cl_2/Et_2O$, $R_f$ 0.51) possessed the following spectral data: IR ($CHCl_3$) 3550 (m, br), 2950 (s), 2935 (s), 1260 (s), 1090 (s, br), 905 (m), 840 (s) $cm^{-1}$; NMR (250 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.10 (s, 6 H), 9.88 (s, 9 H), 9.94 (s, 9 H), 1.30–1.48 (m, 1 H), 1.50–1.7 (m, 1 H), 2.00–2.14 (m, 2 H), 2.52–2.70 (br s, 1 H), 2.96–3.10 (br s, 1 H), 3.88 (AB q, $J_{AB}$ = 10.0 Hz, 2 H), 3.96–4.14 (m, 2 H).

Anal. Calcd for $C_{18}H_{40}O_4Si_2$: C, 57.40; H, 10.70. Found: C, 57.55; H, 10.65.

***c*-2,*t*-5-Bis[(*tert*-butyldimethylsilyl)oxy]-*r*-1-[[(*tert*-butyldimethylsilyl)oxy]methyl]cyclopentan-1-ol (45a).** Application of general protocol D to diol **20a** (182 mg, 0.48 mmol) gave after 96 h at 35 °C and workup a yellow oil. Distillation [Kugelrohr, 95–105 °C (0.3 torr)] afforded 218 mg (84%) of a colorless oil. Flash chromatography[31] (silica gel, 40:60 $CH_2Cl_2$/pentane, $R_f$ 0.47) afforded 197 mg (76%) of trisilyl ether **45a** as an analytically pure sample possessing the following spectral data: IR ($CCl_4$) 3525 (w, br), 2955 (s), 2945 (s), 1255 (s), 1095 (s), 860 (m), 830 (s) $cm^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.06 (s, 6 H), 0.07 (s, 6 H), 0.87 (s, 9 H), 0.89 (s, 18 H), 1.30–1.58 (m, 2 H), 1.84–2.08 (m, 2 H), 2.97 (br s, 1 H), 3.61 (AB q, $J_{AB}$ = 8.4 Hz, 2 H), 3.98 (t, J = 5.1 Hz, 1 H), 4.05 (t, J = 6.3 Hz, 1 H); $^{13}$C NMR (62.9 MHz, $CD_2Cl_2$) δ −4.91 (q), −4.61 (q), −4.43 (q), −4.07 (q), 18.26 (s), 18.81 (s), 25.97 (q), 26.27 (q), 30.70 (t), 30.88 (t), 65.28 (t), 74.14 (d), 78.51 (d), 80.75 (s).

Anal. Calcd for $C_{23}H_{54}O_4Si_3$: C, 58.72; H, 11.09. Found: C, 58.42; H, 11.36.

**2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-3-acetoxycyclopentene (21b).** A solution consisting of 940 mg (4.08 mmol) of **21d** in 3 mL of pyridine was treated with 2 mL of acetic anhydride and stirred overnight at room temperature. Removal of the solvents in vacuo followed by Kugelrohr distillation [94–112 °C (0.2 torr)] afforded 1.03 g (93%) of **21b** as a colorless mobile oil. An analytical sample obtained via preparative TLC (95:5 $CH_2Cl_2/Et_2O$, $R_f$ 0.74) possessed the following spectral data: IR ($CHCl_3$) 2955 (s), 2930 (s), 1720 (s), 1250 (s), 1090 (s), 830 (s) $cm^{-1}$; NMR (60 MHz, $CDCl_3$) δ −0.07 (s, 6 H), 0.88 (s, 9 H), 1.53–2.58 (m, 4 H), 2.03 (s, 3 H), 4.26 (d, J = 4.5 Hz, 2 H), 5.77 (m, 1 H), 6.00 (m, 1 H).

Anal. Calcd for $C_{14}H_{26}O_3Si$: C, 62.18; H, 9.69. Found: C, 62.42; H, 9.59.

***c*-2-Acetoxy-*t*-5-hydroxy-*r*-1-[[(*tert*-butyldimethylsilyl)oxy]methyl]cyclopentan-1-ol (20b).** Application of general protocol B to olefin **21b** (304 mg, 1.00 mmol) gave a crude red oil. Distillation [Kugelrohr, 100–108 °C (0.15 torr)] afforded 216 mg (63%) white crystals, mp 63.4–66.0 °C. An analytical sample obtained from recrystallization ($Et_2O$/pentane) possessed the following spectral data: IR ($CHCl_3$) 3540 (m, br), 2950 (s), 2925 (s), 1725 (s), 1260 (s), 1095 (s), 840 (s) $cm^{-1}$; NMR (360 MHz, $CDCl_3$) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.90 (s, 9 H), 1.44–1.74 (m, 2 H), 2.04 (s, 3 H), 2.04–2.16 (m, 1 H), 2.26–2.38 (m, 1 H), 2.59 (d, J = 6.1 Hz, 1 H), 3.29 (s, 1 H), 3.71 (AB q, $J_{AB}$ = 10.4 Hz, 2 H), 4.02 (dd, J = 6.9, 13.1 Hz, 1 H), 5.00 (dd, J = 4.2, 7.1 Hz, 1 H).

Anal. Calcd for $C_{14}H_{28}O_5Si$: C, 55.23; H, 9.27. Found: C, 55.23; H, 9.04.

***c*-2,*t*-5-Diacetoxy-*r*-1-[[(*tert*-butyldimethylsilyl)oxy]-methyl]cyclopentan-1-ol (45b).** A solution of diol **20b** (152 mg, 0.5 mmol) in 2 mL of pyridine was treated with 70 μL of acetic anhydride (1.5 equiv) and stored at 4 °C for 45 h. The solvents were removed in vacuo, and the resulting colorless oil was distilled [Kugelrohr, 113–120 °C (0.25 torr)] to afford 161 mg of colorless, mobile oil containing some triacetate. This was purified via preparative TLC (9:1 $CH_2Cl_2/Et_2O$, $R_f$ 0.58) to afford 90 mg (53%) analytically pure **45b**, possessing the following spectral data: IR ($CHCl_3$) 3550 (m, br), 2955 (s), 2940 (s), 1725 (s), 1375 (s), 1235 (s), 1090 (s), 830 (s) $cm^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) δ 0.02 (s, 6 H), 0.82 (s, 9 H), 1.38–1.50 (m, 1 H), 1.64–1.76 (m, 1 H), 1.95 (s, 3 H), 2.00 (s, 3 H), 2.06–2.18 (m, 1 H), 2.22–2.34 (m, 1 H), 2.88

(br s, 1 H), 3.59 (AB q, $J_{AB}$ = 10.8 Hz, 2 H), 4.90 (dd, $J$ = 6.4, 3.3 Hz, 1 H), 5.01 (dd, apparent t, $J$ = 7.6 Hz, 1 H); $^{13}C$ NMR (25 MHz, $CD_2Cl_2$) $\delta$ −6.50 (q), 17.92 (s), 20.48 (q), 25.36 (q), 26.58 (t), 27.07 (t), 63.89 (t), 75.04 (d), 78.21 (d), 80.23 (s), 169.35 (s), 169.83 (s).

Anal. Calcd for $C_{16}H_{30}O_6Si$: C, 55.46; H, 8.73. Found: C, 55.39; H, 8.64.

**2-(Acetoxymethyl)-3-hydroxycyclopent-1-ene (21e).** A chilled (0–5 °C) solution consisting of 1.22 g (7.91 mmol) of enone **34b** in 19.8 mL (1.0 equiv of 0.4 M $CeCl_3 \cdot 6H_2O$ in MeOH was treated portionwise with 321 mg (1.1 equiv of $NaBH_4$.[51] After the mixture was stirred an additional 10 min at 0–5 °C, 20 mL of $H_2O$ was added. The solution was extracted with $Et_2O$, the combined organic layer was washed with brine and dried, and then the solvent was removed in vacuo to afford a yellow oil, which was distilled [Kugelrohr, 90–100 °C (0.25 torr)] to yield 942 mg (75%) of **21e** as a colorless oil, possessing the following spectral data: IR ($CHCl_3$) 3600 (m), 3500 (m, br), 3025 (w), 3000 (m), 2940 (m), 1725 (s), 1375 (s), 1250 (s), 1050 (s), 1030 (s), 970 (m), 835 (m), $cm^{-1}$; NMR (60 MHz, $CDCl_3$) $\delta$ 1.58–2.67 (m, 4 H), 2.05 (s, 3 H), 3.15 (br s, 1 H), 2.24 (br s, 2 H), 5.88 (m, 1 H).

Anal. Calcd for $C_8H_{12}O_3$: C, 66.15; H, 7.74. Found: C, 66.32; H, 7.69.

**2-(Acetoxymethyl)-3-[(*tert*-butyldimethylsilyl)oxy]-cyclopent-1-ene (21c).** Application of general protocol D to alcohol **21e** gave after 48 h at room temperature and workup a yellow oil. Distillation [Kugelrohr, 98–107 °C (0.2 torr)] afforded 743 mg (85%) of **21c** as a colorless mobile oil. An analytical sample obtained by preparative TLC ($CH_2Cl_2$, $R_f$ 0.69) possessed the following spectral data: IR ($CHCl_3$) 2955 (s), 2940 (s), 1735 (s), 1255 (s), 1080 (s), 890 (m), 840 (s) $cm^{-1}$; NMR (360 MHz, $CDCl_3$) $\delta$ 0.08 (s, 6 H), 0.90 (s, 9 H), 1.68–1.78 (m, 1 H), 2.06 (s, 3 H), 2.06–2.18 (m, 2 H), 2.38–2.52 (m, 1 H), 4.64 (AB q, $J_{AB}$ = 12.2 Hz, 2 H), 4.86 (dd, apparent t, $J$ = 5.8 Hz, 1 H), 5.80 (br s, 1 H).

Anal. Calcd for $C_{14}H_{26}O_3Si$: C, 62.18; H, 9.69. Found: C, 62.20; H, 9.70.

***c*-2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-*t*-5-hydroxy-*r*-1-(acetoxymethyl)cyclopentan-1-ol (20c).** Application of general protocol B to **21c** (828 mg, 3.06 mmol) gave a yellow oil. This product, which was not stable to distillation, was purified by using flash chroamtography[31] (silica gel, 7:3 $CH_2Cl_2/Et_2O$) to afford 722 mg (78%) of diol **20c** as a colorless, mobile oil. An analytical sample obtained by preparative TLC (6:4 $CH_2Cl_2/Et_2O$, $R_f$ 0.52) possessed the following spectral data: IR ($CHCl_3$) 3500 (m, br), 2950 (s), 2860 (m), 1720 (s), 1455 (m), 1365 (m), 1250 (s), 1220 (m), 1130 (m), 1050 (s, br), 900 (w), 835 (s) $cm^{-1}$; NMR (60 MHz, $CDCl_3$) $\delta$ 0.01 (s, 6 H), 0.83 (s, 9 H), 1.27–2.37 (m, 4 H), 2.08 (s, 3 H), 3.18 (br s, 2 H), 3.93–4.22 (m, 4 H), 4.25 (s, 2 H).

Anal. Calcd for $C_{14}H_{28}O_5Si$: C, 55.23; H, 9.27. Found: C, 55.10; H, 9.34.

***c*-2,*t*-5-Bis[(*tert*-butyldimethylsilyl)oxy]-*r*-1-(acetoxymethyl)cyclopentan-1-ol (45c).** Application of general protocol D to diol **20c** (178 mg, 0.58 mmol) gave after 48 h at 45 °C and workup a yellow oil. Flash chromatography[31] (8:2 $CH_2Cl_2$/pentane) afforded 162 mg (66%) of disilyl ether **45c** as a colorless oil. An analytical sample obtained via preparative TLC ($CH_2Cl_2$, $R_f$ 0.45) possessed the following spectral data: IR ($CHCl_3$) 3550 (m, br), 2950 (s), 2930 (s), 1725 (s), 1610 (w), 1260 (s), 1075 (s), 960 (m), 940 (m), 900 (m), 860 (s), 835 (s) $cm^{-1}$; $^1H$ NMR (60 MHz, $CDCl_3$) $\delta$ 0.07 (s, 6 H), 0.10 (s, 6 H), 0.87 (s, 9 H), 0.92 (s, 9 H), 1.33–2.33 (m, 4 H), 2.07 (s, 3 H), 3.07 (br s, 1 H), 3.92–4.22 (m, 2 H), 4.13 (s, 2 H); $^{13}C$ NMR (25 MHz, $CDCl_3$) $\delta$ −5.03 (q), −4.98 (q), −4.94 (q), $\delta$ −4.63 (q), 17.68 (s), 20.73 (q), 25.48 (q), 30.66 (t), 65.96 (t), 74.25 (d), 77.12 (d), 80.10 (s), 170.83 (s).

Anal. Calcd for $C_{20}H_{42}O_5Si_2$: C, 57.37; H, 10.11. Found: C, 57.22; H, 10.12.

***c*-3-[(*tert*-Butyldimethylsilyl)oxy]-2-hydroxy-*r*-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-cyclopentanone (19a).** To a solution consisting of 660 μL of $Me_2SO$ (7.0 equiv) in 5 mL of $CH_2Cl_2$ at −78 °C was added slowly with stirring 600 μL of trifluoroacetic anhydride (3.5 equiv) in 4 mL of $CH_2Cl_2$.[54] After the resulting milky solution had been stirred at −78 °C for 1 h, 500 mg (1.33 mmol) of diol **20a** in 5 mL of $CH_2Cl_2$ was added dropwise, keeping the temperature of the solution below −60 °C. This mixture was stirred 1 h at −78 °C whereupon 660 μL (3.5 equiv) of triethylamine in 3 mL of $CH_2Cl_2$ was added, and the solution allowed to slowly warm to room temperature over 2.5 h. The resulting clear yellow solution was added to 20 mL of $Et_2O$, and the organic layer was washed with 2% HCl, 3% $Na_2CO_3$, and $H_2O$ and then dried. The solvents were removed in vacuo to yield a yellow oil, which was distilled [Kugelrohr, 90–98 °C (0.2 torr)] to afford 395 mg (80%) of **19a** as a colorless oil. An analytical sample obtained via preparative TLC (9:1 $CH_2Cl_2/Et_2O$, $R_f$ 0.40) possessed the following spectral data: IR ($CHCl_3$) 3560 (w, br), 2970 (s), 2945 (s), 1760 (s), 1270 (s), 1140 (s), 1090 (s), 830 (s) $cm^{-1}$; NMR (360 MHz, $CDCl_3$) $\delta$ 0.04 (s, 3 H), 0.06 (s, 3 H), 0.20 (s, 3 H), 0.21 (s, 3 H), 0.88 (s, 9 H), 0.92 (s, 9 H), 1.90–2.04 (m, 1 H), 2.10–2.32 (m, 2 H), 2.40–2.54 (m, 1 H), 2.98 (br s, 1 H), 3.77 (AB q, $J_{AB}$ = 10.2 Hz, 2 H), 4.18 (dd, apparent t, $J$ = 7.0, 7.9 Hz, 1 H).

Anal. Calcd for $C_{18}H_{38}O_4Si_2$: C, 57.70; H, 10.22. Found: C, 57.33; H, 10.35.

***c*-3-Acetoxy-2-hydroxy-*r*-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-cyclopentanone (19b).** To a solution consisting of 84 μL of oxalyl chloride (1.2 equiv) in 2 mL of $CH_2Cl_2$ at −78 °C was added dropwise 145 μL of $Me_2SO$ (2.4 equiv) in 0.5 mL of $CH_2Cl_2$, keeping the temperature below −60 °C. After the mixture was stirred for 2 min, 256 mg of diol **20b** (0.84 mmol) in 1 mL of $CH_2Cl_2$ was added slowly, again keeping the temperature below −60 °C. After the mixture was stirred 15 min at −78 °C, 588 μL (5.0 equiv) of triethylamine was added dropwise, and the resulting mixture was stirred 5 min at −78 °C and then allowed to warm slowly to room temperature.[54] The resulting yellow solution was added to 4 mL of $H_2O$, the layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine and dried, and the solvent was removed in vacuo to afford a brown oil which was purified by preparative TLC (9:1 $CH_2Cl_2/Et_2O$, $R_f$ 0.40) to afford 142 mg (57%) of a colorless oil possessing the following spectral data: IR ($CHCl_3$) 3545 (m, br), 2955 (s), 2940 (s), 1750 (s), 1255 (s), 1110 (s), 840 (s) $cm^{-1}$; NMR (60 MHz, $CDCl_3$) $\delta$ 0.00 (s, 6 H), 0.77 (s, 9 H), 2.02 (s, 3 H), 2.13–2.53 (m, 4 H), 3.25 (br s, 1 H), 3.68 (AB q, $J_{AB}$ = 10.0 Hz, 2 H), 5.12 (t, $J$ = 7.0 Hz, 1 H).

Anal. Calcd for $C_{14}H_{28}O_5Si$: C, 55.60; H, 8.66. Found: C, 55.50; H, 8.79.

***c*-3-[(*tert*-Butyldimethylsilyl)oxy]-2-hydroxy-*r*-2-(acetoxymethyl)-1-cyclopentanone (19c).** To a solution consisting of 205 μL of oxalyl chloride (1.2 equiv) in 4 mL of $CH_2Cl_2$ at −78 °C was added dropwise 345 μL of $Me_2SO$ (2.4 equiv) in 1.5 mL of $CH_2Cl_2$, keeping the temperature below −60 °C. The resulting milky solution was stirred for 2 min at −78 °C, and then 614 mg (2.02 mmol) of diol **20c** in 2 mL of $CH_2Cl_2$ was added dropwise at a rate such that the temperature did not exceed −60 °C. After the mixture was stirred an additional 15 min at −78 °C, 1.3 mL of triethylamine was added dropwise. The solution was stirred for 5 min at −78 °C, the cold bath removed, and the reaction mixture allowed to warm slowly to room temperature.[54] The resulting clear yellow solution was poured into $H_2O$, the layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine and dried, and the solvent was removed in vacuo to afford a yellow oily solid. This was purified by flash chromatography[31] (silica gel, 95:5 $CH_2Cl_2/Et_2O$) to yield a white solid which was recrystallized from pentane to afford 370 mg (61%) of **19c** as white plates (mp 70.5–72.0 °C), possessing the following spectral data: IR ($CHCl_3$) 3550 (m, br), 2955 (s), 2930 (s), 1740 (s), 1240 (s), 1145 (s), 935 (m), 835 (s) $cm^{-1}$; NMR (60 MHz, $CDCl_3$) $\delta$ 0.15 (s, 6 H), 0.95 (s, 9 H), 2.10 (s, 3 H), 2.10–2.77 (m, 4 H), 3.37 (br s, 1 H), 4.38 (AB q, $J_{AB}$ = 12.0 Hz, 2 H), 4.20 (t, $J$ = 7.0 Hz, 1 H).

Anal. Calcd for $C_{14}H_{26}O_5Si$: C, 55.60; H, 8.66. Found: C, 55.74; H, 8.63.

***c*-5-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-*t*-5-hydroxy-*r*-4-[(*tert*-butyldimethylsilyl)oxy]-2-cyclopentenone (18a).** Application of general protocol C to ketone **19a** (85 mg, 0.23 mmol) gave a red syrup. Preparative TLC (94:6 $CH_2Cl_2/Et_2O$, $R_f$ 0.64) yielded 22 mg (25%) of pale yellow oil, which crystallized on standing to afford pale yellow needles, mp 48.5–50.0 °C. this analytically pure sample possessed the following spectral data: IR ($CHCl_3$) 3545 (w, br), 2955 (s), 2940 (s), 1720 (s), 1255 (s), 1215 (s), 1140 (s), 1065 (m), 990 (m), 920 (m), 850 (s, br), $cm^{-1}$; NMR (250 MHz, $CDCl_3$) $\delta$ 0.00 (s, 6 H), 0.14 (s, 3 H), 0.15 (s, 3 H), 0.85 (s, 9 H), 0.91 (s, 9 H), 3.29 (AB q, $J_{AB}$ = 15.1 Hz, 2 H), 4.77 (br

s, 1 H), 6.22 (dd, $J$ = 6.1, 1.5 Hz, 1 H), 7.27 (dd, $J$ = 1.5, 6.3 Hz, 1 H).

Anal. Calcd for $C_{17}H_{36}O_4Si_2$: C, 58.02; H, 9.74. Found: C, 57.97; H, 9.64.

***c*-5-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-*t*-5-hydroxy-*r*-4-acetoxy-2-cyclopentenone (18b).** Application of general protocol C to ketone **19b** (47 mg, 0.16 mmol) gave a red syrup. This was purified via preparative TLC (9:1 $CH_2Cl_2/Et_2O$, $R_f$ 0.38) to afford 26 mg (58%) of **18b** as a colorless oil possessing the following spectral data: IR ($CHCl_3$) 3540 (m, br), 3450 (m, br), 2960 (s), 2935 (s), 1725 (s), 1235 (s), 1140 (s), 990 (w), 860 (s), 835 (m) $cm^{-1}$; NMR (360 MHz, $CDCl_3$) $\delta$ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.83 (s, 9 H), 2.12 (s, 3 H), 3.37 (br s, 1 H), 3.68 (AB q, $J_{AB}$ = 9.9 Hz, 2 H), 5.74 (dd, apparent t, $J$ = 1.5, 1.3 Hz, 2 H), 6.37 (dd, $J$ = 1.5, 6.1 Hz, 1 H), 7.46 (dd, $J$ = 1.8, 6.1 Hz, 1 H).

Anal. Calcd for $C_{14}H_{24}O_5Si$: C, 55.97; H, 8.05. Found: C, 56.06; H, 8.02.

***c*-5-(Acetoxymethyl)-*t*-5-hydroxy-*r*-4-[(*tert*-butyldimethylsilyl)oxy]-2-cyclopentenone (18c).** Application of general protocol C to ketone **19c** (55 mg, 0.18 mmol) gave a red syrup. The latter was purified via preparative TLC (9:1 $CH_2Cl_2/Et_2O$, $R_f$ 0.42) to afford 17 mg (32%) of enone **18c** as pale yellow needles. An analytical sample was obtained via recrystallization (pentane, −20 °C; mp 77.5–79.0 °C) and possessed the following spectral data: IR 3550 (m), 3450 (m, br), 2950 (s), 2940 (s), 2870 (s), 1735 (s), 1470 (s), 1375 (s), 1120 (s), 1040 (m), 920 (w), 840 (s) $cm^{-1}$; NMR (250 MHz, $CDCl_3$) $\delta$ 0.15 (s, 6 H), 0.91 (s, 9 H), 2.04 (s, 3 H), 3.32 (br s, 1 H), 4.24 (AB q, $J_{AB}$ = 12.3 Hz, 2 H), 4.78 (dd, apparent t, $J$ = 1.5, 1.8 Hz, 1 H), 6.26 (dd, $J$ = 1.5, 6.3 Hz, 1 H), 7.32 (dd, $J$ = 1.8, 6.3 Hz, 1 H).

Anal. Calcd for $C_{14}H_{24}O_5Si$: C, 55.97; H, 8.05. Found: C, 55.62; H, 7.95.

**(±)-Epipentenomycin I (2a).** A solution consisting of 81 mg (0.21 mmol) of enone **18a** in 3 mL of acetic acid, 1 mL of $H_2O$, and 1 mL of THF was stirred at room temperature for 8 days.[44] Removal of solvents in vacuo afforded a yellow oil which was purified via preparative TLC (EtOAc, $R_f$ 0.17) to yield 25 mg (81%) of a colorless oil possessing the following spectral data: IR (neat) 3330 (s, br), 2950 (w), 2910 (w), 1700 (s), 1650 (m), 1125 (m), 1060 (m) $cm^{-1}$; NMR (Table IV; 60 MHz, $D_2O$) $\delta$ 3.88 (d, $J$ = 2 Hz, 2 H), 5.00 (dd, apparent t, $J$ = 2.0 Hz, 1 H), 6.58 (dd, $J$ = 2.0, 6.5 Hz, 1 H), 7.90 (dd, $J$ = 2.0, 6.5 Hz, 1 H); Chemical ionization mass spectrum: M+1, 145.0497; (Calcd for $C_6H_8O_4$) 145.0500.

**(±)-Epipentenomycin III (2c).** A solution consisting of 75 mg (0.25 mmol) of enone **18c**,[44] 3 mL of HOAc, 1 mL of $H_2O$, and 1 mL of THF was stirred at room temperature for 10 days. Removal of the solvents in vacuo afforded 55 mg of an orange oil. Purification via preparative TLC (EtOAc, $R_f$ 0.35) afforded 37 mg (80%) of **2c** as a colorless oil possessing the following spectral data: IR 3500 (m, br), 3000 (m), 2960 (s), 1730 (s), 1725 (s), 1260 (s), 1235 (s), 1000 (s), 950 (s), 820 (m) $cm^{-1}$; NMR (250 MHz, $CDCl_3$) $\delta$ 2.06 (s, 3 H), 4.32 (AB q, $J_{AB}$ = 12.0 Hz, 2 H), 4.90 (br s, 1 H), 6.33 (dd, $J$ = 1.7, 6.8 Hz, 1 H), 7.52 (dd, $J$ = 1.7, 6.8 Hz, 1 H); chemical-ionization mass spectrum, $m/e$ 187.0593 (M + 1; calcd for $C_8H_{10}O_5$ 187.0606).

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**Registry No.** (±)-**1a**, 68907-79-9; (±)-**1b**, 68907-80-2; (±)-**1c**, 81024-51-3; (±)-**2a**, 77480-52-5; (±)-**2b**, 77480-53-6; (±)-**2c**, 77480-54-7; (±)-**3**, 66655-93-4; **4**, 68882-71-3; **5**, 81024-52-4; (±)-**18a**, 77419-55-7; (±)-**18b**, 77419-59-1; (±)-**18c**, 80963-20-8; (±)-**19a**, 77429-47-1; (±)-**19b**, 80963-21-9; (±)-**19c**, 80963-22-0; (±)-**20a**, 77419-53-5; (±)-**20b**, 77419-57-9; (±)-**20c**, 77419-61-5; (±)-**21a**, 77419-52-4; (±)-**21b**, 77419-56-8; (±)-**21c**, 77419-60-4; (±)-**21d**, 77419-51-3; (±)-**21e**, 80963-23-1; **22a**, 57020-97-0; **22b**, 10481-34-2; **23a**, 80963-24-2; **23b**, 80963-19-5; **29a**, 68241-78-1; **29b**, 70156-97-7; **29c**, 70156-98-8; **31a**, 70156-99-9; **31b**, 1120-73-6; **31b** ketal, 23153-76-6; **31c**, 25564-22-1; **31c** ketal, 80963-25-3; **31d**, 70157-00-5; **31e**, 70157-01-6; **31f**, 60887-85-6; **31g**, 1128-08-1; **31h**, 70157-02-7; **31h** ketal, 80963-26-4; **31i**, 25435-63-6; **31i** ketal, 80963-27-5; **31j**, 80963-28-6; (±)-**32**, 81024-53-5; (±)-**33**, 80963-29-7; **34a**, 68882-72-4; **34b**, 76047-51-3; (±)-**35a**, 68882-73-5; (±)-**36a**, 80963-30-0; (±)-**36b**, 80963-31-1; (±)-**37a**, 80963-32-2; (±)-**37b**, 68882-75-7; (±)-**38**, 80963-33-3; (±)-**39**, 80963-34-4; (±)-**40**, 68882-76-8; (±)-**44**, 68882-74-6; (±)-**45a**, 77419-54-6; (±)-**45b**, 77419-58-0; (±)-**45c**, 80963-35-5; 3-methylcyclopentenone, 2758-18-1; 2-bromo-3-methyl-2-cyclopentenone, 80963-36-6; cyclohexenone, 930-68-7; 2-bromocyclohexenone, 50870-61-6; 2-*n*-butyl-2-cyclohexenone, 34737-39-8.

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# On the Existence of Stable Structural Isomers of Ketene. A Theoretical Study of the $C_2H_2O$ Potential Energy Surface

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Ab initio molecular orbital theory has been used to study in detail the $C_2H_2O$ potential energy surface. Equilibrium structures and transition structures have been explicitly identified by using gradient techniques and the split-valence 4-31G basis set. Improved relative energies have been obtained by using the split-valence plus dp-polarization 6-31G** basis set with electron correlation incorporated at the levels of second-order (MP2) and third-order (MP3) Møller–Plesset perturbation theory. Zero-point vibrational effects have also been taken into account. Three structures are predicted to be stable, observable species; these are the well-known ketene and the as yet unobserved hydroxyacetylene (ethynol) and oxiranylidene. Of the remaining structures studied, oxirene is found to lie in a shallow potential well with a small barrier to rearrangement to ketene. Two carbenoid species, formylmethylene and hydroxyvinylidene, are predicted to rearrange without activation energy to ketene and hydroxyacetylene, respectively.

Although a considerable number of possible isomeric $C_2H_2O$ structures may be contemplated (Figure 1), only one of these, ketene (1), has been observed experimentally. It is of interest to examine whether any of the other $C_2H_2O$ isomers are likely to be stable observable species, and to this end we have undertaken an ab initio molecular orbital study of the $C_2H_2O$ potential energy surface. The structures examined include ketene (1), hydroxyacetylene

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