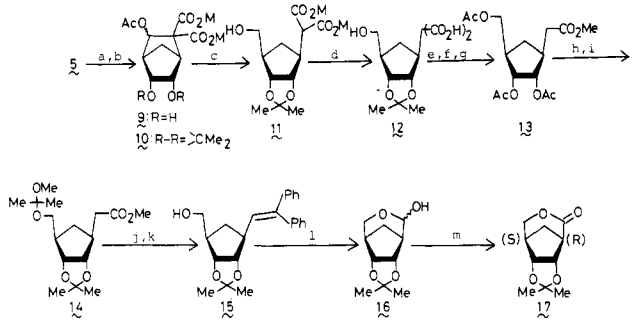
Scheme IV[a,b]



[a] (a) OsO_4, 4-methylmorpholine *N*-oxide (60 wt % solution in water), acetone–ether; (b) $Me_2C(OMe)_2$, *p*-TsOH·H_2O, acetone; (c) $NaBH_4$, NaOMe–MeOH; (d) NaOH, MeOH; (e) CH_3CO_2H, reflux; (f) $(CH_3CO)_2O$–pyridine; (g) CH_2N_2, ether; (h) NH_3–MeOH; (i) $Me_2C(OMe)_2$, *p*-TsOH·H_2O, acetone; (j) PhMgBr, THF; (k) CH_3CO_2H; (l) O_3, CH_2Cl_2, −78 °C; (m) dipyridine–chromium(VI) oxide, CH_2Cl_2. [b] M = *l*-menthyl.

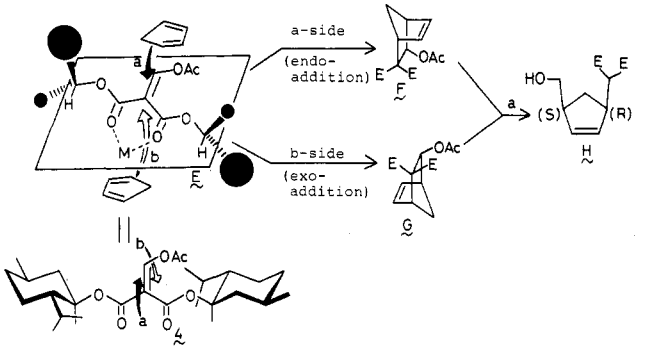
^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3 H, Me), 4.47–5.15 (m, 2 H, menthyl 1–H X 2), 8.43 (s, 1 H, olefinic H)].

Although **4** did not react with cyclopentadiene in toluene at 80 °C, addition of 0.1 molar equiv (to **4**) of $TiCl_4$ in the reaction mixture gave the 4 + 2 adduct **5** in 83% yield even at −78 °C (Scheme III). The adduct was found to be a mixture of endo and exo isomers (ca. 3/1) as judged from ^{1}H NMR spectroscopy. The mixture was then hydrogenated over Pd/C (methanol, 1 atm, room temperature) to give the dihydro derivative **6** again as a mixture of both isomers. Treatment of **6** by the retrograde aldol C–C bond fission reaction under reductive conditions (NaOMe/$NaBH_4$/MeOH, room temperature)[3] afforded the ring fission product **7** in 81% yield. Examination of the acetylated product **8** (mp 49–51 °C) by ^{1}H NMR spectroscopy using shift reagent [Eu(fod), tris[[(heptafluoro)butanoyl]pivaloylmethanato]europium] revealed its enantiomeric excess as >90%. The enantiomeric excess of the reaction was reduced to 71% when the addition was carried out at −15 °C.

The absolute configuration of the adduct **5** was determined by its transformation to the lactone **17** (Scheme IV), whose absolute structure was determined already.[4] Thus, **5** was transformed to chiral carbocyclic C-nucleoside precursor **11** [$[\alpha]^{27}_D$ −39.7° (*c* 2.6, $CHCl_3$)] by a route essentially the same as the conversion of B to D (cf. Scheme I).[1] The diacid **12** obtained by basic hydrolysis was refluxed in acetic acid to give the monoacid. After acetylation followed by methylation (CH_2N_2 in ether), the ester **13** was treated with ammonia in methanol to give a triol, which was allowed to react with 2,2-dimethoxypropane in acetone with trace of TsOH (room temperature) to give the acetonide **14** [$[\alpha]^{22}_D$ −6.9° (*c* 1.2, $CHCl_3$)]. Grignard reaction (PhMgBr–THF) followed by treatment with acetic acid then afforded **15**, which by ozonolysis followed by Collins oxidation afforded the bicyclic compound **17** [mp 141–143 °C; $[\alpha]^{26}_D$ +41° (*c* 0.19, $CHCl_3$); lit. mp 140–141.5 °C, $[\alpha]^{25}_D$ +44.4° (*c* 1.0, $CHCl_3$)].[4]

In our case only a catalytic amount of $TiCl_4$ is needed, whereas for the corresponding fumarate series the amount of this reagent or other Lewis acid catalysts was 1 or more molar equiv to dienophiles.[5] This shows that $TiCl_4$ does chelate with both carbonyl groups at the same time (E in Scheme V)[6] and this chelated species is the only dienophile in our reaction.[7] In order to account for remarkable diastereoselectivity in the addition step, we must assume that the C_2–C_3 moiety of cyclopentadiene is more bulky than the C_5 moiety. Then, one would expect a predominant formation of either the endo or exo isomer (F from a-side attack or **G** from b-side attack), and both of them finally afford a single enantiomer (H) through the C–C bond cleavage reaction (a).

Scheme V[a,b]



[a] (a) See Scheme I. [b] M = $TiCl_4$; E = CO_2(*l*-menthyl).

We are currently investigating the synthesis of some carbocyclic analogues of C-nucleoside using the adduct **5**[8] as well as use of the related dimenthyl methylenemalonates as the dienophiles in asymmetric Diels–Alder reactions.[9]

Acknowledgment. This research was supported in part by Grant-in-Aids from the Research Foundation for Pharmaceutical Sciences, Japan.

(3) The C–C bond fission reactions under reductive conditions of **6** and **10** can be accomplished essentially in the same manner as in the racemic series C → D. The only difference is the use of sodium methoxide instead of potassium carbonate, since the C–C bond fission reaction by use of the latter as an base proceeded much slower due to steric hindrance of the menthyl groups.

(4) Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 4044.

(5) (a) Walborsky, H. M.; Barash, L.; Davis, T. C. *Tetrahedron* **1963**, *19*, 2333. (b) Tolbert, L. M.; Ali, M. B. *J. Am. Chem. Soc.* **1984**, *106*, 3806. (c) Furuta, K.; Iwanaga, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 4507.

(6) Poll, J.; Metter, J. O.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 112.

(7) Very recently, Houk and co-workers have reported the conformational studies of chiral acrylates–Lewis acid complexes in connection with their asymmetric Diels–Alder reactions: Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14.

(8) The carbocyclic analogue of oxazinomycin recently synthesized in our laboratory exhibits interesting biological activity even in its racemic form: Katagiri, N.; Tomura, M.; Haneda, T.; Kaneko, C. *J. Chem. Soc., Chem. Commun.* **1987**, 1422.

(9) We have recently found that di-*l*-menthyl methylenemalonate also reacts with cyclopentadiene in the presence of a catalytic amount of $TiCl_4$ at −78 °C to give the Diels–Alder adduct in high diastereomeric excess. This fact shows that the presence of an acetoxy group in **4** does not play a significant role in determining the diastereoselection in the Diels–Alder reaction of **4** with cyclopentadiene.

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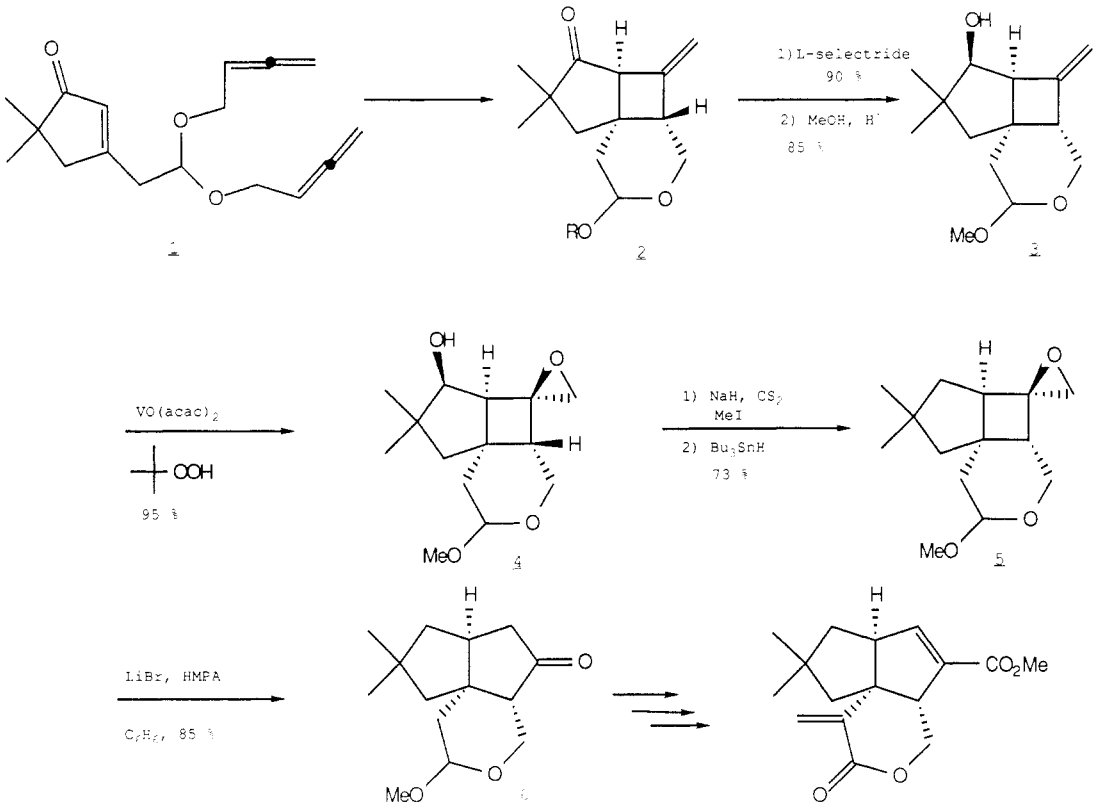
Total Synthesis of Pentalenolactone G Methyl Ester

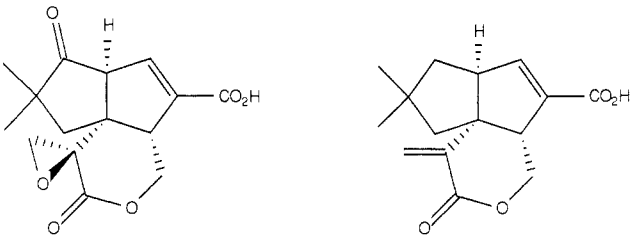
Summary: The total synthesis of pentalenolactone G has been achieved by a general synthetic approach featuring an intramolecular [2 + 2] photocycloaddition as the key tactic.

Sir: The family of humulene-derived natural products produced by *Streptomyces arenae* known as the penta-

Scheme I



lenolactones has grown since the initial isolation of pentalenolactone in 1957[1] to include more than half a dozen members.[2] Prompted by studies revealing their biological activity as antibiotics and antitumor agents,[1] irreversible enzyme inactivators,[3] and inhibitors of DNA viruses,[4] both synthesis[5] and biosynthesis[6] of the pentalenolactones have been active areas of investigation. Despite a decade of work in a number of groups, no general synthetic approach has emerged. In particular, maintaining a high state of oxidation in each of the three rings presents a formidable challenge. We demonstrate here a general approach to the pentalenolactones that has resulted in a formal synthesis of pentalenolactone E and the total synthesis of pentalenolactone G. It relies on our previously reported methodology[7] for the construction of lactone rings using the intramolecular photochemical cycloaddition of enone–acetals.



Pentalenolactone G Pentalenolactone E

Compound **2** can be prepared in six steps and 20% overall yield[7] from isobutyric acid, methallyl chloride, and propargyl alcohol. The key step in this sequence is the intramolecular [2 + 2] reaction of **1**. Because of the constraint of the forming tetrahydropyran ring, the trans stereochemical relationship between the two ring junction hydrogens is enforced in this reaction.[8] It also serves to construct the quaternary carbon. Acetal **2** is obtained as a mixture of anomers. Stereocontrolled reduction yields a single, endo alcohol, and the allenic glycoside, a remnant of the photocycloaddition, is exchanged for methyl. Treatment of the alcohol with 1 mol % toluenesulfonic acid in methanol (25 °C, 4 h) produces a kinetically controlled 9:1 mixture of isomers **3** that can be separated chromatographically. Subsequent operations used a single stereoisomer of **3**, although its complete stereostructure remains unknown. Directed epoxidation according to the Sharpless protocol[9] (benzene, $VO(acac)_2$, *t*-BuOOH, 4 h)

(1) Koe, B. K.; Sobin, B. A.; Celmer, W. D. *Antibiot. Ann.* **1975**, 672.

(2) Pentalenolactone: Martin, D.; Slomp, G.; Mizsak, S.; Duchamp, D.; Chidester, C. *Tetrahedron Lett.* **1970**, 4901. E: Cane, D. E.; Rossi, T. *Ibid.* **1979**, 2973. F: Tillman, A. M.; Cane, D. E. *J. Antibiot.* **1983**, *36*, 170. G: Seto, H.; Noguchi, H.; Sankawa, U.; Iitaka, Y. *J. Antibiot.* **1984**, *37*, 816. Seto, H.; Sasaki, T.; Yonehara, H.; Uzawa, J. *Tetrahedron Lett.* **1978**, 923. H and pentalenic acid: Seto, H.; Sasaki, T.; Uzawa, J.; Takeuchi, S.; Yonehara, H. *Ibid.* **1978**, 4411. P: Takahashi, S.; Takeuchi, M.; Arai, M.; Seto, H.; Otake, N. *J. Antibiot.* **1983**, *36*, 226.

(3) Duszenko, M.; Balla, H.; Mecke, D. *Biochem. Biophys. Acta* **1982**, *714*, 344. Mann, K.; Mecke, D. *Nature (London)* **1982**, *282*, 535.

(4) Nakagawa, A.; Tomoda, H.; Hao, M. V.; Okano, K.; Iwai, Y.; Omura, S. *J. Antibiot.* **1985**, *38*, 1114.

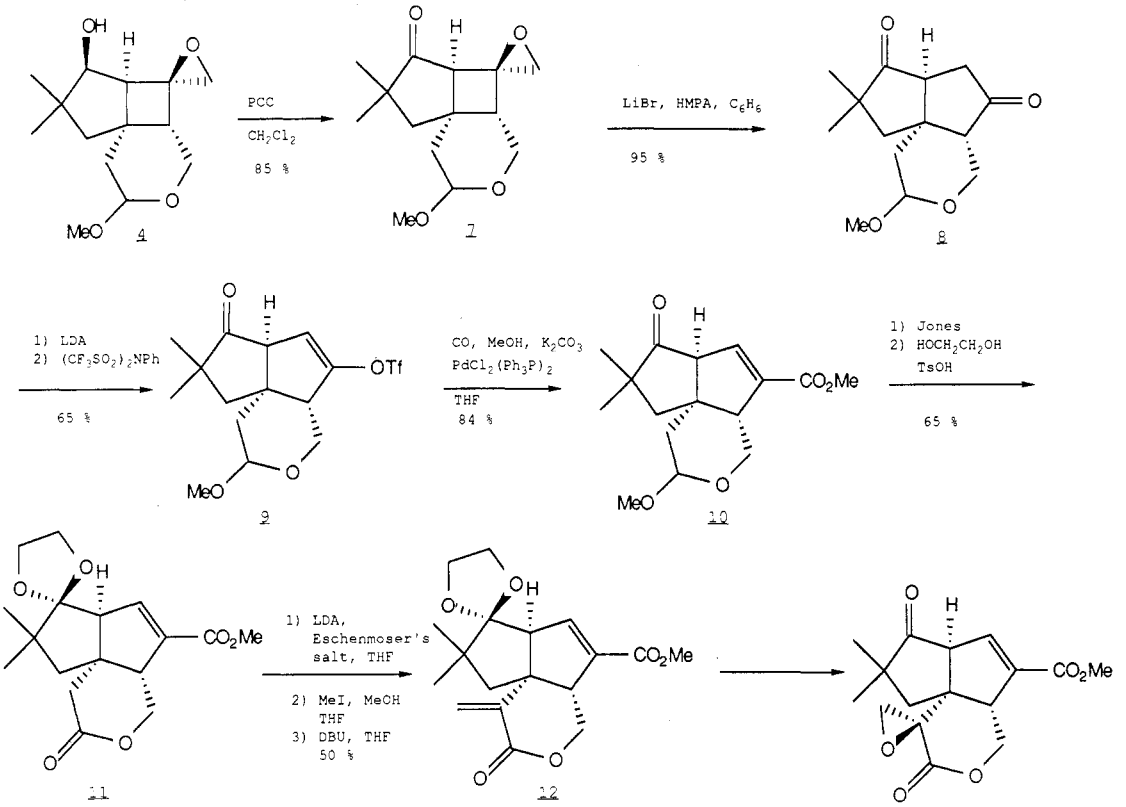
(5) Pentalenolactone: Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. F. *J. Am. Chem. Soc.* **1978**, *100*, 6536; **1979**, *101*, 7020. Parsons, W. H.; Schlessinger, R. H.; Quesada, M. L. *Ibid.* **1980**, *102*, 889. Pentalenolactone E, F: Ohtsuka, T.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1983**, *21*, 3851. Paquette, L. A.; Annis, G. D.; Schostarez, H. *J. Am. Chem. Soc.* **1981**, *103*, 6526. Cane, D. E.; Thomas, P. J. *Ibid.* **1984**, *106*, 5295. Taber, D. F.; Schuchardt, J. L. *Ibid.* **1985**, *107*, 5289. Pentalenic acid: Sakai, K.; Ohtsuka, T.; Misumi, T.; Shirahama, H., Matsumoto, T. *Chem. Lett.* **1981**, 355. Crimmins, M. T.; DeLoach, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 800.

(6) Cane, D. E.; Rossi, T.; Tillman, A. M.; Pachlatko, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 1838. Cane, D. E.; Tillman, A. M. *Ibid.* **1983**, *105*, 122.

(7) Pirrung, M. C.; Thomson, S. A. *Tetrahedron Lett.* **1986**, *27*, 2703.

(8) This stereochemical assignment is based on the lack of W-coupling or an NOE between these methine hydrogens and the calculated (MM2) energy difference between the cis and trans bicyclo[4.2.0] ring junctions of 12 kcal mol^{-1}. Furthermore, only cis ring junctions previously have been observed in bicyclo[4.2.0] systems generated by intramolecular [2 + 2]'s: Winkler, J. D., personal communication. Dauben, W. G.; Shapiro, G.; Luders, L. *Tetrahedron Lett.* **1985**, *26*, 1429.

Scheme II



delivers exclusively the syn epoxy alcohol **4**. Deoxygenation using Barton's xanthate method[10] (1. NaH, CS_2, MeI, THF; 2. Bu_3SnH, toluene, reflux) yields **5** in a quite acceptable 53% overall yield from **2** (Scheme I).

The plan now called for a ring expansion process. Previous work[11] suggested that the oxaspiro[2.3]hexane system should be rearranged to a 3-oxobicyclo[3.3.0]octane. Indeed, treatment of epoxide **5** with LiBr (1 equiv) and HMPA (1 equiv) in refluxing benzene for 1 h provides ketone **6** in greater than 95% isomeric purity. This compound proved identical (^1H NMR, ^{13}C NMR spectral data) with one of the acetal isomers prepared and separated by Cane in the course of his pentalenolactone E and F syntheses. Since he has converted this compound by Paquette's route to pentalenolactone E methyl ester, the attainment of **6** constitutes a formal synthesis of pentalenolactone E and serves to confirm the assignment of regiochemistry in the ring expansion process.

A true advance in the synthesis of the pentalenolactones requires the maintenance of oxygenation in each ring. Intermediate **4** proved best for this purpose. Its oxidation by pyridinium chlorochromate produces **7**, whose rearrangement to **8** (>20:1 isomeric ratio) proved exceptionally facile. In only 5 min at 25 °C, the reaction is complete.[12]

While **8** is analogous to an intermediate in the Paquette–Cane syntheses, the methodology they used to convert the ketone to the cyclopentene-carboxylate proceeds with low selectivity and yield. A new procedure to accomplish this transformation was needed (Scheme II).

Stille[14] has reported several examples of the palladium-catalyzed coupling and carbonylative coupling of vinyl triflates with organotins. It was no great insight to imagine the reaction of a putative intermediate in the Stille work, an enoyl–palladium(II) complex, with methanol in place of the organotin. The required triflate was obtained from **8** by a selective enolization (LDA, THF, −78 °C) and trapping (*N*-phenyltrifluoromethanesulfonimide).[15] On treatment with bis(triphenylphosphine)palladium chloride (10 mol %) and potassium carbonate (3 equiv) in 30:1 THF/MeOH under a stream of carbon monoxide, **9** is converted to the desired cyclopentenecarboxylate **10** (55% from **8**). Subsequently, the conversion of vinyl triflates to esters and amides under somewhat different conditions has been reported by an Italian group.[16]

It now remained to introduce the spiroepoxymethylene unit. For this purpose, lactone **11** was obtained (80%) by Jones oxidation (25 °C, 18 h, slow addition to **10**) and a fairly difficult ketalization (toluenesulfonic acid, benzene, 5 equiv of ethylene glycol, removal of azeotrope by distillation). Danishefsky's procedure[17] for introduction of the α-methylene group using Eschenmoser's salt (1. LDA, THF, −78 °C, 1.25 h; 2. 3 equiv of $CH_2N(CH_3)_2I$; 3. MeI, MeOH, THF, 18 h; 4. DBU, THF) affords **12** in 50% yield.

(9) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.
(10) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
(11) Morton, D. R.; Brokaw, F. C. *J. Org. Chem.* **1979**, *44*, 2880. Hart, T. W.; Comte, M.-T. *Tetrahedron Lett.* **1985**, *26*, 2713.
(12) Also studied in the rearrangement process were **4**, its trimethylsilyl ether, and the epoxide epimer of **5**. Precedents[13] suggest the opposite regiochemistry should be found when a group capable of chelation is present. The product ratios (3-oxobicyclo[3.3.0] to 2-oxo) are 1:2, 5:1, and 1:20, respectively. The rationale for these observations will be discussed in the full paper.
(13) Tobe, Y.; Yamashita, S.; Yamashita, T.; Kakiuchi, K.; Odaira, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1259. Tobe, Y.; Kishida, T.; Yamashita, T.; Kakiuchi, K. *Chem. Lett.* **1985**, 1437. Tobe, Y.; Yamashita, T.; Kakiuchi, K.; Odaira, Y. *J. Chem. Soc., Chem. Commun.* **1985**, 898.
(14) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. Crisp, G. T.; Scott, W. J.; Stille, J. K. *Ibid.* **1984**, *106*, 7500. Scott, W. J.; Crisp, G. T.; Stille, J. K. *Ibid.* **1984**, *106*, 4630. Goure, W. F.; Wright, M. E.; Davis, P. D.; Labadie, S. S.; Stille, J. K. *Ibid.* **1984**, *106*, 6417.
(15) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, 979.
(16) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.
(17) Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P. F. *J. Am. Chem. Soc.* **1976**, *98*, 6715. Roberts, J. C.; Borromeo, P. S.; Poulter, C. D. *Tetrahedron Lett.* **1977**, 1621.

This method is superior to others attempted or reported in previous pentalenolactone syntheses. Reaction at the hindered neopentyl carbon is difficult indeed. In refluxing THF/aqueous 5% HCl, ketal **12** is hydrolyzed in 85% yield.

The introduction of the epoxide moiety with the correct stereochemistry seems trivial. Danishefsky was able to accomplish this task for pentalenolactone by reduction to the lactol, directed epoxidation, and Jones oxidation (23% overall). Since pentalenolactone G has the same epoxide stereochemistry, a similar sequence was contemplated. However, it has recently been proven that pentalenolactone F, the epoxymethylene analogue of E and available from it by a similar directed epoxidation sequence, has the epoxide stereochemistry *opposite* that of pentalenolactone and pentalenolactones G and H.[18] Given two such contrary precedents, it should hardly be surprising that application of the same sequence to **12** leads to a 1.5:1 mixture of pentalenolactone G methyl ester and its epoxide epimer (total yield 25%). These are easily separated on silica gel chromatography (3:1 ether/hexane), with the more mobile isomer possessing spectral properties identical with material obtained by Prof. Seto.

(18) Cane, D. E., private communication of X-ray results with Williard, P. G. and Shong, J. K. This was also postulated by Seto.[2]

In conclusion, we have demonstrated a synthetic strategy that provides entry to pentalenolactones E and G, and by virtue of previous work,[19] to F, H, and pentalenolactone itself. A general solution to the pentalenolactone challenge is in hand.

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(19) Ohtsuka, T.; Shirahama, H.; Matsumoto, T. *Chem. Lett.* **1984**, 1923.

(20) Research Fellow of the Alfred P. Sloan Foundation, 1986–88. Presidential Young Investigator, 1985–89.

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