Approach of a 1,3-diene (in a parallel plane orthogonal to the direction of σ bond formation) to the "bottom" face of the dienophile is restricted due to unfavorable H(diene)···O(CO ligand) interactions. Approach of a 1,3-diene to the "top" face appears to be more favorable. This approach of isoprene generates the proper diastereomers of **5a**.[29] Approach of isoprene from the "bottom" face of the dienophile generates the unobserved (or minor) diastereomers of **5a**. A similar "top-face" approach of DMB and MPD affords the correct diastereomers of **5b** and **5c**, also (including the relative stereochemistry at C(5) and C(16) of **5c**, see Figure 3). The unusually high stereospecificity of these Diels-Alder reactions might also be related to the rigid conformation of the BF_2 coordination to the carbonyl oxygen atom of the dienophile imposed by the chelating ferra-β-diketonato ligand.[28,30]

The formation of a mixture of endo and exo isomers of **5d** and **6d** and of predominantly the endo isomer of **7b** is not unusual. The "endo" rule is frequently violated for reactions of methyl methacrylate with cyclopentadiene under both catalyzed or noncatalyzed conditions.[31] A wide range of endo/exo isomer ratios is observed in these analogous organic reactions. Both endo and exo isomers can be formed from "top-side" approach of cyclopentadiene on the appropriate (ferra-β-diketonato)BF_2 complex.

(29) Actually, this approach of isoprene generates the mirror image of **5a** as shown in Figure 2. By using the mirror image of **5**, this approach of isoprene generates the enantiomer of **5a** shown in Figure 2. Both enantiomeric diastereomers of **5a** are present in this centrosymmetric lattice.

(30) Molecular models reveal that the observed diastereomers can be formed also from the appropriate "bottom-face" approach of the dienes to the *cisoid* conformation of the dienophiles. The relative stabilities of the *cisoid* and *transoid* conformations of the dienophiles is not known. However, the *cisoid* conformation of **5** places the C_5H_5 ligand into closer proximity to the methacryl methyl substituent than does the *transoid* conformation, so the *transoid* conformation might be expected to be more stable.

Conclusions

(Ferra-β-diketonato)BF_2 complexes having alkenyl substituents on the ferra-chelate ring react as activated dienophiles in Diels-Alder cycloaddition reactions. In this study, ten such Diels-Alder adducts have been prepared and characterized. The regioselectivity of these cycloadditions is very high and follows the regiochemistry exhibited by methyl methacrylate in analogous Diels-Alder reactions. Furthermore, due to the highly asymmetric Fe moiety within the methacrylate dienophile, diene cycloaddition occurs with unusually high stereoselectivity when diastereomeric adducts are formed. We hope to apply this stereoselectivity to the synthesis of more complex organic molecules.

Acknowledgment. We thank Drs. Thomas M. Harris and Dawood Afzal for obtaining the 400-MHz NMR spectra. C.M.L. thanks the donors of the Petroleum Research Fund, administered by the American Chemical Society, for major support of this research and the partial support of the National Science Foundation (Grant No. CHE-8106140). P.G.L. acknowledges support from NIH BRSG (Grant No. RR07089-13).

Supplementary Material Available: A complete listing of final atomic positional and thermal parameters (before rounding) and final observed and calculated structure factors for **5a** (23 pages). Ordering information is given on any current masthead page.

(31) Inukai, T.; Kojima, T. *J. Org. Chem.* **1966**, *31*, 2032-2033.

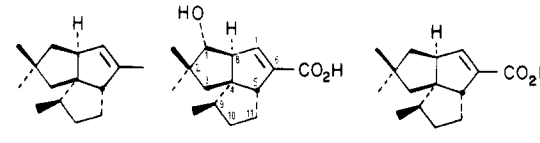
Intramolecular Photocycloadditions-Cyclobutane Fragmentation: Total Synthesis of (±)-Pentalenene, (±)-Pentalenic Acid, and (±)-Deoxypentalenic Acid

Michael T. Crimmins* and Joe A. DeLoach

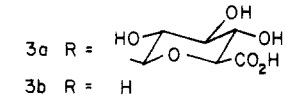
Contribution from the Kenan and Venable Laboratories of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27514. *Received July 26, 1985*

Abstract: Pentalenene, pentalenic acid, and deoxypentalenic acid, important metabolites in the biosynthesis of the pentalenolactones, have been synthesized from methyl isobutyrate through a common intermediate. The initial key step involves a novel conjugate addition-cycloacylation sequence on an acetylenic diester. The 1,6-diene which results is converted in two steps to a 1,6-diene diester which undergoes a highly stereoselective photocycloaddition to set three of the necessary stereocenters. Reductive cleavage of one cyclobutane bond produces a functionalized spirobicyclo[4.4]nonanone which is converted in three steps to dione **10**, the pivotal intermediate. Differential functionalization of this system provides efficient, stereocontrolled routes to pentalenene, pentalenic acid, and deoxypentalenic acid, all in racemic form.

Pentalenene (**1**),[1,2] pentalenic acid (**2**),[3,4] and deoxypentalenic acid glucuron (**3a**)[5] are members of a larger class of metabolites which contain the tricyclo[6.3.0.$0^{4,8}$]undecane skeleton. This



1 2



group of angularly fused triquinanes includes the sesquiterpenes isocomene (**4**),[6,7] silphinene (**5**),[8,9] and 5-oxosilphiperfolene (**6**),[10,11]

(1) Isolation: Seto, H.; Yonehara *J. Antibiot.* **1980**, *33*, 92.

(2) Synthesis: (a) Paquette, L. A.; Annis, G. D. *J. Am. Chem. Soc.* **1983**, *105*, 7358. Paquette, L. A.; Annis, G. D. *J. Am. Chem. Soc.* **1982**, *104*, 4504. (b) Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1976**, 2869. (c) Piers, E.; Karunaratne, V. *J. Chem. Soc., Chem. Commun.* **1984**, 959. (d) Pattenden, G.; Teague, S. J. *Tetrahedron Lett.* **1984**, 3021.

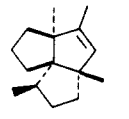
(3) Isolation: Seto, H.; Sasaki, T.; Uzawa, J.; Takeuchi, S.; Yonehara, H. *Tetrahedron Lett.* **1978**, 4411.

(4) Synthesis: (a) Crimmins, M. T.; DeLoach, J. A. *J. Org. Chem.* **1984**, *49*, 2076. (b) Sakai, K.; Ohtsuka, T.; Misumi, S.; Shirahama, H.; Matsumoto, T. *Chem. Lett.* **1981**, 355.

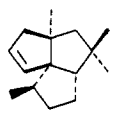
(5) Takahashi, S.; Takeuchi, M.; Arai, M.; Seto, H.; Otake, N. *J. Antibiot.* **1983**, *36*, 226.

0002-7863/86/1508-0800$01.50/0

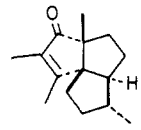
the unique diterpene laurenene (**7**),[12] (the only known naturally occurring fenestrane), and the unusual sesterterpene retigeranic acid (**8**).[13] Intensive efforts have recently been directed toward



4

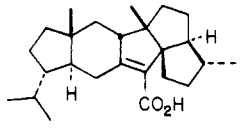


5

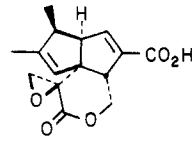


6

7



8

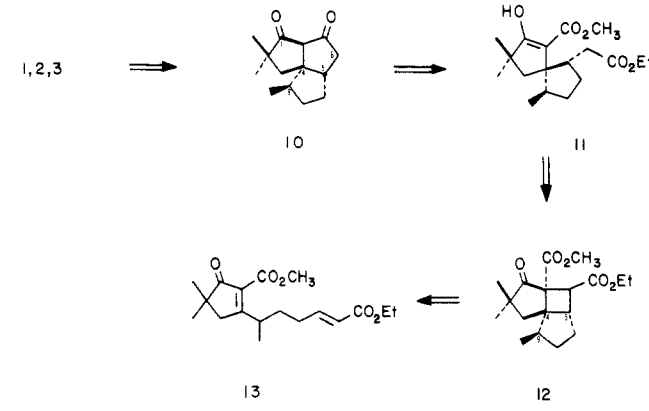


9

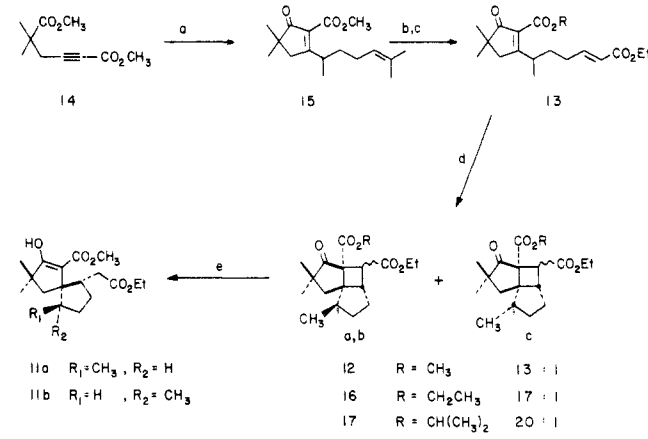
the synthesis of these structurally intriguing molecules.[14] Additional interest in **1**, **2**, and **3a** has resulted from the demonstrated role of pentalenene (**1**) and pentalenic acid (**2**) in the biosynthesis of the antibiotic pentalenolactone (**9**)[15] and the biogenetic relationship of pentalenene to other humulene-derived sesquiterpenes.[16] Deoxypentalenic acid glucuron (**3a**), which has displayed antitumor activity against sarcoma 180 in mice,[5] is in all probability biosynthetically related to **1**, **2**, and **9**, although this has not been explicitly demonstrated.

Due to the obvious structural similarities of **1**, **2**, and **3b** it seemed attractive to approach their syntheses through a common intermediate. Dione **10** was deemed an appropriate pivotal intermediate by virtue of the oxygen function at C-1 and the flexibility of substituent introduction at C-6. Spirocyclic diester **11** was chosen as the precursor for dione **10** since it could be

Scheme I



Scheme II[a]



[a] (a) $(CH_3)_2C{=}CHCH_2CH_2CH(CH_3)MgCl$, TMEDA, THF, CuI, −78 °C to 25 °C, 48%. (b) O_3, −78 °C, CH_2Cl_2. (c) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, reflux, 91%, two steps. (d) *hν*, uranium filter, hexane, 73%. (e) Li, NH_3, THF, −78 °C, 90%.

obtained by the reductive cleavage of tricyclic cyclobutane diester **12**, the product of an intramolecular [2 + 2] photocycloaddition of diene **13**. Thus, the stereocenters at C-4, C-5, and C-9 would be established through the intramolecular photocycloaddition of **13**.

Construction of Diene 13. The plan for the construction of diester **13** centered around a new conjugate addition–cycloacylation strategy previously established in this laboratory.[17] Addition of organocopper reagents to acetylenic diester **14** results in cycloacylation to produce the highly functionalized cyclopentenones **15**. Ester **14** was prepared in two steps in high yield from methyl isobutyrate. Alkylation[18] of the lithium enolate of methyl isobutyrate with propargyl bromide followed by carbomethoxylation of the resultant terminal acetylene by the method of Tsuji[19] provided **14** in 58% overall yield. Treatment of diester **14** with the Grignard reagent derived from 6-chloro-2-methyl-2-heptene[20] in the presence of added tetramethylethylenediamine (TMEDA) and copper(I) iodide resulted in conjugate addition and subsequent cyclization of the intermediate vinyl copper reagent to produce 48% of diene **15**. Conversion of diene **15** to diene ester **13** was readily accomplished by selective ozonolysis of the more electron-rich trisubstituted olefin to yield aldehyde **16**, which was immediately condensed with (carbethoxymethylene)triphenylphosphorane to provide 91% yield of **13** after flash chromatography.

(6) Isolation: (a) Zalkow, L. H.; Harris, R. N., III; Van Derveer, D.; Bertrand, J. A. *J. Chem. Soc., Chem. Commun.* **1977**, 456. (b) Zalkow, L. H.; Harris, R. N., III; Burke, N. I. *J. Nat. Prod.* **1979**, *42*, 96. (c) Bohlmann, F.; LeVan, N.; Pickhardt, J. *Chem. Ber.* **1977**, *110*, 3777.

(7) Synthesis: (a) Paquette, L. A.; Han, Y. K. *J. Org. Chem.* **1979**, *44*, 4014; *J. Am. Chem. Soc.* **1981**, *103*, 1835. (b) Oppolzer, W.; Bättig, K.; Hudlicky, T. *Helv. Chim. Acta* **1979**, *62*, 1493; *Tetrahedron* **1981**, *37*, 4359. (c) Pirrung, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 7130; **1981**, *103*, 82. (d) Dauben, W. G.; Walker, D. M. *J. Org. Chem.* **1981**, *46*, 1103. (e) Wender, P. A.; Dreyer, G. B. *Tetrahedron* **1981**, *37*, 4445. (f) Tobe, Y.; Yamashita, T.; Kakiuchi, K.; Odaira, Y. *J. Chem. Soc., Chem. Commun.* **1985**, 898.

(8) Isolation: Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259.

(9) Synthesis: (a) Paquette, L. A.; Leone-Bay, A. *J. Am. Chem. Soc.* **1983**, *105*, 7352; *J. Org. Chem.* **1982**, *47*, 4173. (b) Tsunoda, T.; Kodama, M.; Ito, S. *Tetrahedron Lett.* **1983**, 83. (c) Wender, P. A.; Ternansky, R. J. *Tetrahedron Lett.* **1985**, *26*, 2625. (d) Sternbach, D. D.; Hughes, J. W.; Burdi, D. F.; Banks, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 2149. (e) Crimmins, T. T.; Mascarella, S. W., manuscript submitted.

(10) Isolation: (a) Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259. (b) Bohlmann, F.; Suding, H.; Cuatrecasas, J.; Robinson, H.; King, R. M. *Phytochemistry* **1980**, *19*, 2399.

(11) Synthesis: (a) Paquette, L. A.; Roberts, R. A.; Dritna, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 6690. (b) Wender, P. A., private communication.

(12) Corbett, R. E.; Lauren, D. R.; Weavers, R. T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1774. Corbett, R. E.; Couldwell, C. M.; Lauren, D. R.; Weavers, R. T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1791.

(13) Isolation: Kaneda, M.; Takahashi, R.; Iitaka, Y.; Shibata, S. *Acta Crystallogr., Sect. B* **1974**, *B30*, 358. Synthesis: Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339.

(14) Reviews: Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41; **1984**, *119*, 1.

(15) For a discussion and further references, see ref **2a**.

(16) (a) Cane, D. E.; Nachbour, R. B. *J. Am. Chem. Soc.* **1978**, *100*, 3208. (b) Hanson, J. R.; Marten, T.; Nyfeler, R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 876. (c) Dugan, J. J.; deMayo, P.; Nisbet, M.; Robinson, J. R.; Anchel, M. *J. Am. Chem. Soc.* **1966**, *88*, 2838. (d) Feline, T. C.; Mellows, G.; Jones, R. B.; Phillips, L. *J. Chem. Soc., Chem. Commun.* **1974**, 63. (e) Tanabe, M.; Suzuki, K.; Jankowski, W. C. *Tetrahedron Lett.* **1974**, 2271.

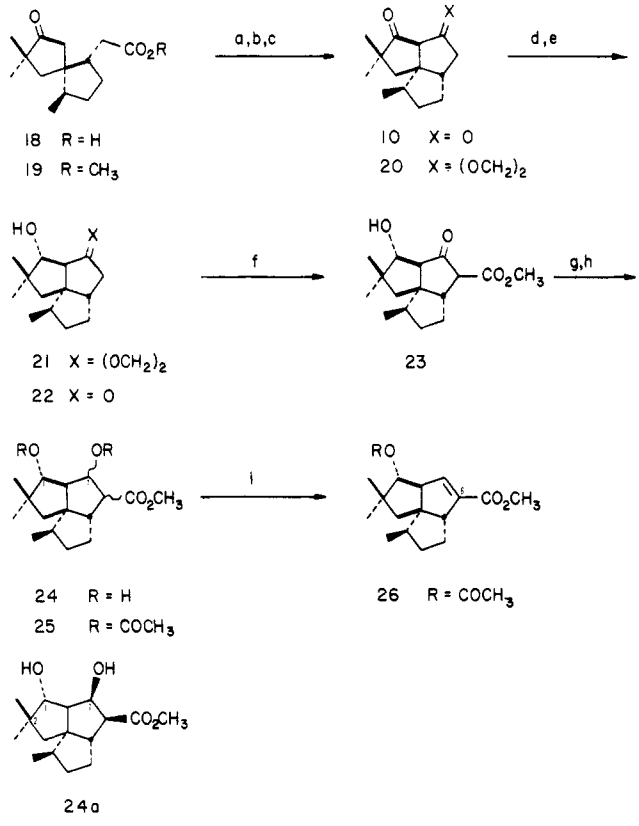
(17) Crimmins, M. T.; Mascarella, S. W.; DeLoach, J. A. *J. Org. Chem.* **1984**, *49*, 3033.

(18) Gregge, R. J.; Hermann, J. L.; Lee, C. S.; Richman, J. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2425.

(19) Tsuji, J.; Takahashi, M.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 849.

(20) Fetizon, M.; Lazare, S.; Pascard, C.; Prange, T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1407.

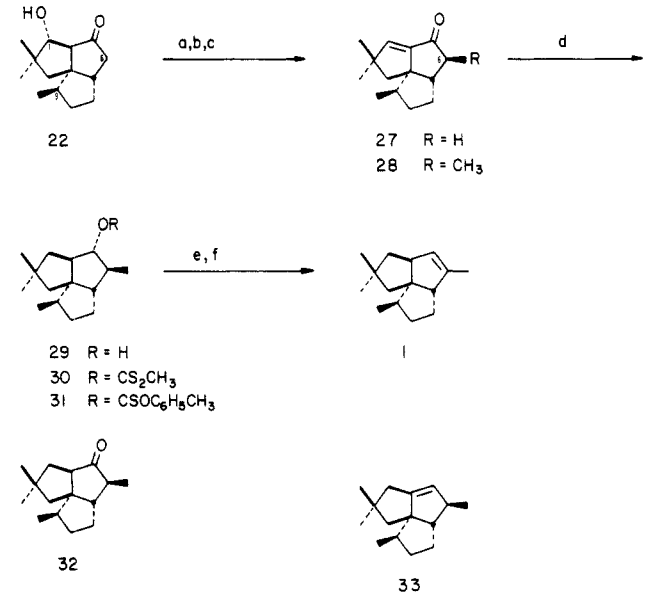
Scheme III[a]



[a] (a) MeOH, H_2SO_4, reflux, 99%. (b) *t*-BuOK, C_6H_6, 80 °C, 90%. (c) $(CH_2OH)_2$, C_6H_6, *p*-TSA, 80 °C. (d) Li, NH_3, MeOH. (e) 10% HCl, acetone, 81%, three steps. (f) LDA; CO_2; H^+, CH_2N_2, 90%. (g) $NaBH_4$, 100%. (h) Ac_2O, Et_3N. (i) DBU, C_6H_6, 67%, two steps.

Photocyclization of Diene 13. With diene **13** in hand the stage was set to carry out the key photocycloaddition reaction.[21] Initially, irradiation of a solution of **13** in hexane through a pyrex filter ($\lambda > 290$ nm) resulted in production of a secondary cleavage product which has not yet been characterized. However, irradiation of diene **13** through a uranium glass filter ($\lambda > 350$ nm) resulted in smooth cycloaddition to produce 73% yield of photoadducts **12** as a 10:3:1 (**12a**:**12b**:**12c**) mixture. Reductive cleavage[22] of the cyclobutane ring of **12** was accomplished by treatment with lithium in liquid ammonia (−78 °C) to produce 90% of β-keto ester **11a,b** in a ratio of 13:1 (**11a**:**11b**) diastereomeric at C-9. Therefore, the major isomers **12a,b** obtained from the photocycloaddition must have the same relative stereochemistry at C-9 and be isomeric at the carbon bearing the carbethoxy group. The stereoselectivity[23] in the photocycloaddition can be improved by increasing the size of the vinyl substituent on the cyclopentenone from $-CO_2CH_3$ (13:1, **12a**:**b**) to $-CO_2CH_2CH_3$ (17:1, **16a**:**b**) to $-CO_2$-*i*-Pr (>20:1, **17a**:**b**). These observations are consistent with Oppolzer's[23a] hypothesis that the secondary methyl experiences a steric interaction with the vinyl substituent during the final bond closure of the cyclobutane and that cycloreversion of the initially formed biradical is responsible for the observed selectivity. However, on the basis of recent results by Becker,[24] which indicate that at least in some systems cycloreversion is not observed, mechanisms which do not involve cycloreversion cannot be excluded. Experiments designed to resolve this issue are currently in progress. That this approach provides excellent stereocontrol of the C-9 secondary methyl is noteworthy since control of C-9 stereochemistry has proven particularly problematic in other approaches to these systems.[2a,c]

Scheme IV[a]



[a] (a) MsCl, CH_2Cl_2, Et_3n. (b) DBU, CH_2Cl_2, 65%, five steps. (c) LDA, CH_3I, 0 °C, 85%. (d) Li, NH_3, MeOH, 82%. (e) *p*-$CH_3C_6H_4OCSCl$, C_5H_5N. (f) 200 °C, 20 mm, 60%, two steps.

Initial attempts to complete the triquinane skeleton by a Dieckmann condensation on **11** directly, as well as numerous efforts to protect the ketone of **11** and carry out a subsequent Dieckmann cyclization, failed completely.

Closure of the remaining five-membered ring to generate the triquinane skeleton was ultimately accomplished in three high yield steps from β-keto ester **11**. Hydrolysis–decarboxylation of β-keto ester **11** in aqueous hydrochloric–acetic acid[25] produced crystalline acid **18** in quantitative yield. Esterification of the carboxylic acid in methanol and trimethyl orthoformate with catalytic *p*-toluenesulfonic acid yielded keto ester **19** in 99% yield. This keto ester was cyclized to dione **10** in 90% yield by the action of potassium *tert*-butoxide in refluxing benzene.[26] The crystalline dione thus produced in 10 steps from methyl isobutyrate was a single pure isomer after one recrystallization. The cis stereochemistry of the ring juncture formed in this cyclization is a result of both kinetic and thermodynamic control.

Conversion of Dione 10 to Pentalenic Acid (2). Completion of pentalenic acid first required differentiation of the two carbonyl groups. This was readily accomplished, since the different steric environments of the two carbonyls allowed selective ketalization to yield ketal **20** even in the presence of excess ethylene glycol. Hydride reductions of **20** gave predominantly the undesired β-alcohol, while reduction with lithium–ammonia produced the necessary α-alcohol **21** accompanied by only traces of the alternate isomer. Hydrolysis of the ketal provided keto alcohol **22** in 81% yield from dione **10**.

Direct carboxylation of hydroxy ketone **22** was carried out with excess (4 equiv) LDA and CO_2 followed by protonation of the carboxylate and esterification with diazomethane at −78 °C yielding 91% of keto ester **23**.[27] Exposure of **23** to sodium

(21) For a review of some work in this area, see: Oppolzer, W. *Acc. Chem. Res.* **1982**, *15*, 135.

(22) (a) Coates, R. M.; Senter, P. D.; Baker, W. R. *J. Org. Chem.* **1982**, *47*, 3597. (b) Gassman, P. G.; Crearey, X. *J. Chem. Soc., Chem. Commun.* **1972**, 1214.

(23) For similar photocycloadditions of cyclohexenones, see: (a) Oppolzer, W.; Zutterman, F.; Battig, K. *Helv. Chim. Acta* **1983**, *66*, 522. (b) Hoye, T. R.; Martin, S. J.; Peck, D. R. *J. Org. Chem.* **1982**, *47*, 331. (c) Fetizon, M.; Khac Manh, D. D.; Ecoto, J.; Colin, H.; Diez-Mala, J. *J. Chem. Soc., Chem. Commun.* **1981**, 953. (d) Oppolzer, W.; Gorrichon, L.; Bird, T. G. C. *Helv. Chim. Acta* **1981**, *64*, 186. Birch, A. M.; Pattenden, G. *J. Chem. Soc., Chem. Commun.* **1980**, 1195.

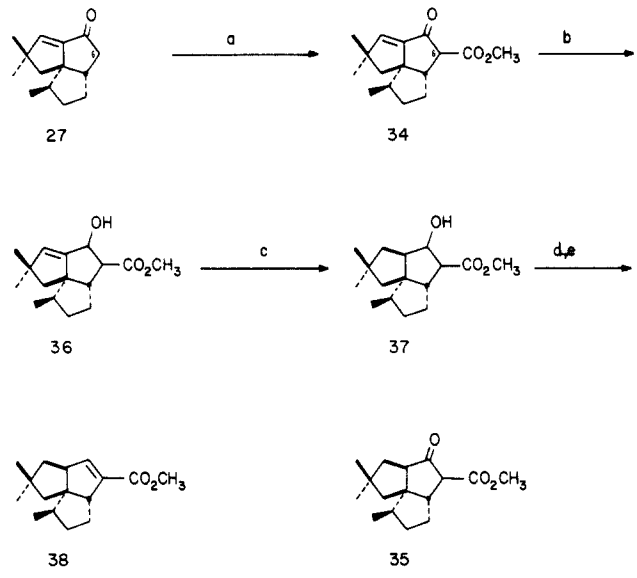
(24) Becker, D.; Nagler, M.; Hirsh, S.; Ramun, J. *J. Chem. Soc., Chem. Commun.* **1983**, 371.

(25) Oehldrich, J.; Cook, J. M.; Weiss, U. *Tetrahedron Lett.* **1976**, 4549.

(26) Quesada, M. L.; Schlessinger, R. H.; Parsons, W. H. *J. Org. Chem.* **1978**, *43*, 3968.

(27) Parsons, W. H.; Schlessinger, R. H.; Quesada, M. L. *J. Am. Chem. Soc.* **1980**, *102*, 889.

Scheme V[a]



[a] (a) LDA, CO_2, H^+, CH_2N_2, 62%. (b) $NaBH_4$, MeOH, 99%. (c) H_2, Pd/C, EtOH, 100%. (d) MsCl, Et_3N, CH_2Cl_2. (e) DBU, CH_2Cl_2, 56%, two steps.

borohydride in methanol generated a diastereomeric mixture of diols **24** in 100% yield. Initial attempts to take advantage of the hindered nature of the C-1 hydroxyl to selectively mesylate or tosylate the C-7 alcohol gave mixtures of monosulfonates and the disulfonate. This result was somewhat surprising at first because of the earlier ketalization result, but further inspection of models indicated that the major isomer **24a** has the C-7 hydroxyl sandwiched between the carbomethoxyl and the cis C-2 methyl. Fortunately, the C-6,7 double bond could be introduced by an alternative sequence. Treatment of diols **24** with excess acetic anhydride and catalytic 4-(dimethylamino)pyridine[28] gave the diacetate **25**, which upon treatment with DBU in refluxing benzene provided methyl pentalenate acetate **26** in 67% yield. No evidence for the diene could be detected, presumably due to the high degree of strain which would be introduced by a second elimination. Finally, concomitant hydrolysis of the acetate and methyl esters with aqueous potassium hydroxide produced an 87% yield of pentalenic acid (**2**). Spectra (250-MHz ^1H NMR and IR) of the methyl ester of synthetic **1** were identical with those of authentic natural samples.[3,29]

Synthesis of Pentalenene (1) from Keto Alcohol 22. Preparation of pentalenene (**1**) from ketal **20** required removal of the C-1 carbonyl and introduction of the C-6 methyl. Attempted Wolff–Kishner reduction of the ketone of **20** was totally unsuccessful due to the extremely hindered nature of the carbonyl. Alternatively, mesylation of hydroxy ketone **22** followed by treatment with DBU in dichloromethane produced crystalline enone **27** in 65% yield from dione **10** (five steps).

Introduction of the remaining methyl group was achieved by alkylation of the lithium enolate (LDA, −78 to 0 °C) with methyl iodide to produce ketone **28** as a single stereoisomer in 85% yield. The stereochemistry was determined by conversion to ketone **32** which has been prepared from hydroboration of pentalenene.[1] Addition of enone **28** to a solution of lithium–ammonia–methanol resulted in reduction of the double bond and the carbonyl function to produce the thermodynamic cis-fused triquinane alcohol **29** in 82% yield. Various attempts to directly dehydrate **29** to pentalenene ($SOCl_2$, pyridine; $POCl_3$, pyridine, benzene) or to eliminate the mesylate of **29** (*t*-BuOK, Me_2SO; DBU, benzene) produced either intractable mixtures or recovery of starting material. However, pyrolysis (200 °C, 25 mm) of the xanthate **30** cleanly produced pentalenene in modest yield. Subsequently, it was found that pyrolysis of the *p*-cresol thiocarbonate proceeded more efficiently to yield 60% of pure pentalenene (**1**).[30] None of the alternative olefin isomer **33** could be detected, presumably due to the higher thermodynamic stability of **2** as a result of ring strain in **33**.[31] Synthetic pentalenene **2** was spectrally identical with authentic spectra provided by Professor Paquette.[1]

Preparation of Deoxypentalenic Acid from Enone 27. Completion of deoxypentalenic acid (**3b**) closely followed the late stages of the pentalenene synthesis but necessitated the introduction of a carboxyl group at C-6 instead of a methyl. Carboxylation of **27** as in the pentalenic acid route produced β-keto ester **34** in 62% yield. Catalytic hydrogenation of **34** provided β-keto ester **35**, which was unusually resistant to reduction with sodium borohydride in a variety of solvents. This was attributed to its high enol content and ease of deprotonation. Thus, it seemed plausible to reverse the order of the two reduction steps. In the event, sodium borohydride reduction of ketone **34** proceeded smoothly to give 99% of allylic alcohol **36**, which could be quantitatively hydrogenated (Pt; EtOH) to alcohol **37**. Mesylation of the alcohol and elimination with DBU in dichloromethane yielded methyl deoxypentalenate (**38**) in 56% yield. Deoxypentalenic acid (**3b**) was obtained in 100% yield by hydrolysis of **38** in aqueous KOH.

In conclusion, the total syntheses of pentalenene, pentalenic acid, and deoxypentalenic acid have been achieved through a common intermediate with excellent stereoselectivity. The crucial role which intramolecular photocycloadditions have played in the stereoselection in these syntheses is certainly worthy of note.

Experimental Section

Materials and Methods. Tetrahydrofuran (THF) and diethyl ether were dried by distillation from sodium benzophenone ketyl immediately prior to use. Dichloromethane, triethylamine, pyridine, tetramethylethylenediamine (TMEDA), and hexamethylphosphoramide (HMPA) were dried by distillation from calcium hydride immediately prior to use.

Infrared spectra were recorded on a Beckman IR 4210. Nuclear magnetic resonance spectra (NMR) were recorded either at 100 MHz on a Varian XL-100 or at 250 MHz on a Bruker WM-250 spectrometer.

Microanalyses were performed by Galbraith Labs. Melting points and boiling points are uncorrected.

Dimethyl 5,5-Dimethylhex-2-ynedioate (14). A solution of *n*-butyllithium (83 mL of a 2.6 M solution, 0.216 mol) in hexane was added dropwise to a cooled (0 °C) stirred solution of diisopropylamine (30.2 mL, 0.216 mol) in 200 mL of dry tetrahydrofuran. The solution was stirred 10 min and cooled to −78 °C, whereupon a solution of methyl isobutyrate (20.0 g, 0.196 mol) in 20 mL of tetrahydrofuran was added dropwise. The solution was stirred for 1 h at −78 °C, and a solution of propargyl bromide (24 mL; 80% by weight, 0.216 mol) in 37 mL of HMPA was added dropwise. After stirring for 1 h at −78 °C the mixture was quenched with saturated ammonium chloride and warmed to room temperature. The THF was removed in vacuo. The residue was dissolved in ether, washed 4 times with water, dried, concentrated, and distilled at reduced pressure to provide 21.79 g (80%) of a clear liquid: bp 48–50 °C (12 mm); 100-MHz ^1H NMR ($CDCl_3$, δ) 1.22 (s, 6 H), 1.88 (t, J = 3 Hz, 1 H), 2.34 (d, J = 3 Hz, 2 H), 3.58 (s, 3 H).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.63; H, 8.79.

A mixture (initially heterogeneous) of the above acetylene (21.8 g, 0.156 mol), palladium chloride (200 mg, 1.30 mmol), copper(II) chloride (42.1 g, 0.312 mol), and sodium acetate (25.8 g, 0.311 mol) in 650 mL of absolute methanol was stirred under an atmosphere of carbon monoxide for 3 h, whereupon the mixture became homogeneous. The methanol was removed in vacuo, and the residue was taken up in ether. The ether solution was washed with water, 50% aqueous ammonium hydroxide, and brine, dried, and concentrated. Distillation at reduced pressure gave 22.3 g (72%) of diester **14** as a clear liquid: bp 84–86 °C (1.0 mm); 100-MHz ^1H NMR ($CDCl_3$, δ) 1.31 (s, 6 H), 2.52 (s, 2 H), 3.62 (s, 3 H), 3.65 (s, 3 H).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.44; H, 7.06.

2-Carbomethoxy-5,5-dimethyl-3-(2-methyl-2-hepten-6-yl)cyclopent-2-en-1-one (15). A solution of Grignard reagent [prepared from 2-chloro-6-methyl-5-heptene (4.98 g, 34.0 mmol) and magnesium (1.12 g, 46 mmol)] in 50 mL of dry tetrahydrofuran was added dropwise to a

(28) Steglich, W.; Hofle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.
(29) We thank Prof. David E. Cane, Brown University, for providing authentic comparison spectra.
(30) Gerlach, H.; Huong, T. T.; Müller, W. *J. Chem. Soc., Chem. Commun.* **1972**, 1215.
(31) Agosta, W. C.; Wolff, S. *J. Org. Chem.* **1975**, *40*, 1699.

stirred mixture of dry copper (I) iodide (4.38 g, 23.0 mmol) and dry tetramethylethylenediamine (5.13 mL, 34.0 mmol) in 150 mL of dry THF at −78 °C. This mixture was stirred for 1 h at −78 °C, and a solution of diester **14** (4.5 g, 23.0 mmol) in 10 mL of dry THF was added dropwise. The mixture was stirred at −78 °C for 1 h, warmed to room temperature over 2 h. The reaction was quenched by slowly pouring the mixture into 10% HCl. The mixture was extracted with ether, and the ether layer was washed with saturated sodium bicarbonate, dried, and concentrated. The residue was flash chromatographed on 200 g of silica gel with 5% ethyl acetate/hexane to give 3.08 g (48%) of **15** as a pale yellow oil: 250-MHz ^{1}H NMR ($CDCl_3$, δ) 1.14 (s, 6 H), 1.17 (d, J = 6.5 Hz, 3 H), 1.53 (m, 2 H), 1.57 (br s, 3 H), 1.68 (br s, 3 H), 1.95 (m, 1 H), 2.51 (AB q, 2 H), 3.50 (tq, J = 6.5 and 6.5 Hz, 1 H), 3.84 (s, 3 H), 5.08 (br t, J = 7 Hz, 1 H).

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.38; H, 9.32.

Conversion of 15 to 13. A solution of **15** (17.4 g, 62.6 mmol) in 400 mL of dichloromethane was treated with excess ozone (until the solution turned blue), and then 10 mL of dimethyl sulfide was added. The solution was stirred for 15 min at −78 °C and then warmed to room temperature. The solution was washed with water (2×), dried, and concentrated to provide the crude aldehyde **16** as a clear oil: 100-MHz ^{1}H NMR (CCl_4, δ) 1.08 (s, 6 H), 1.15 (d, J = 6.5 Hz, 3 H), 1.5–2.1 (m, 2 H), 2.44 (m, 4 H), 3.31 (m, 1 H), 3.71 (s, 3 H), 9.55 (t, J = 1.5 Hz, 1 H). Without purification this material was dissolved in 250 mL of dichloromethane, and (carbethoxymethylene)triphenylphosphorane (29 g, 83.3 mmol) was added. The mixture was heated at reflux for 3 h, cooled, and concentrated. The residue was diluted with hexane and filtered. The hexanes were concentrated, and the residual material was flash chromatographed on 300 g of silica gel with 10% ethyl acetate/hexane to yield 18.40 g (91%) of ester **13** as a colorless oil: 250-MHz ^{1}H NMR ($CDCl_3$, δ) 1.15 (s, 6 H) 1.20 (d, J = 6.5 Hz, 3 H), 1.30 (t, J = 6.5 Hz, 3 H), 1.68 (br q, J = 7.5 Hz, 2 H), 2.20 (m, 2 H), 2.52 (AB q, 2 H), 3.52 (tq, J = 6.5 m and 6.5 Hz, 1 H), 3.85 (s, 3 H), 4.19 (q, J = 6.5 Hz, 2 H), 5.83 (d, J = 15 Hz, 1 H), 6.92 (dt, J = 15 and 6.8 Hz, 1 H).

Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.71; H, 8.35.

Irradiation of 13. To a photochemical immersion well (250 mL) equipped with a reflux condenser and a water-cooled Pyrex immersion well was added a solution of 8.00 g (24.8 mmol) of diene **13** in 250 mL of hexane. A uranium glass filter sleeve was placed in the immersion well, and a 450-W Hanovia medium pressure mercury vapor lamp was lowered inside the filter sleeve. The lamp was started, and the solution was irradiated for 36 h. Concentration of the solution provided a clear, viscous oil which was flash chromatographed on 250 g of silica gel with 10% ethyl acetate/hexane to provide 5.80 g (73%) of photoadducts **12** as a 10:3:1 mixture by integration of the secondary methyl resonances in the 250-MHz ^{1}H NMR: 250-MHz ^{1}H NMR (major isomer) ($CDCl_3$, δ) 0.88 (d, J = 7.5 Hz, 3 H) 1.20 (s, 3 H), 1.25 (t, J = 7 Hz, 3 H), 1.31 (s, 3 H), 1.55 (m, 2 H), 1.92 (m, 3 H), 2.02 (AB q, J = 14 Hz, 2 H), 2.98 (brt, J = 6.5 Hz, 1 H), 3.36 (d, J = 6.5 Hz, 1 H), 3.73 (s, 3 H), 4.11 (dq J = 7 and 3.5 Hz, 2 H).

Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.32; H, 8.01.

Reductive Cleavage of 12. Liquid ammonia which had been dried for 30 min over lithium wire was condensed in a flask containing 190 mg (27.3 mmol) of lithium wire until 100 mL of ammonia had collected. This dark blue solution was stirred for 15 min at −78 °C, whereupon a solution of **12** (2.950 g, 9.61 mmol) in 10 mL of dry ether was added rapidly. After 8 min the reaction was rapidly quenched by the addition of saturated ammonium chloride. The ammonia was evaporated, and the residue was acidified with 10% HCl and extracted with ether. The ether layers were washed with saturated sodium bicarbonate, dried, and concentrated to provide 2.665 g (90%) of a clear, viscous oil identified as **11** (13:1 mixture of **11a**:**11b**): 250-MHz ^{1}H NMR ($CDCl_3$, δ) 0.79 (d, J = 7.5 Hz, 3 H), 1.15 (s, 3 H), 1.24 (t, J = 7.5 Hz, 3 H), 1.29 (s, 3 H), 1.68–2.62 (m, 10 H), 3.77 (s, 3 H), 4.07 (q, J = 7.5 Hz, 2 H) 11.55 (s, 1 H).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.60, H, 8.72.

Hydrolysis of 11 to 18. A mixture of 2.200 g (6.79 mmol) of diester **11**, 45 mL of acetic acid, 30 mL of concentrated HCl, and 15 mL of water was heated at reflux for 5.5 h and cooled to room temperature. The acetic acid was removed at reduced pressure, and the residue was extracted with ether. The combined ether extracts were washed with brine, dried (Na_2SO_4), and concentrated to give 1.620 g (100%) of acid **18** as a thick oil which crystallized on standing. A single recrystallization from hexane provided analytically pure colorless needles: mp 85.5–87 °C; 250-MHz ^{1}H NMR ($CDCl_3$, δ) 0.93 (d, J = 7.5 Hz, 3 H), 1.14 (s, 6 H), 1.2–2.54 (m, 12 H), 10.56 (br s, 1 H); IR ($CDCl_3$) 1740, 1716 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}O_3$:C, 70.56; H, 9.30. Found: C, 70.69; H, 9.14.

Esterification of 18. A solution of 0.8 mL (0.739 g, 7.32 mmol) of trimethyl orthoformate, five drops of concentrated H_2SO_4, and 1.620 g (6.81 mmol) of acid **18** in 100 mL of absolute methanol was heated at reflux for 6 h and cooled to room temperature. The methanol was removed in vacuo and the residue was taken up in ether, washed with saturated $NaHCO_3$, dried, and concentrated to give 1.712 g (100%) of **19** as a pale yellow oil. Flash chromatography (10% ethyl acetate in hexane) provided an analytical sample: 250-MHz ^{1}H NMR ($CDCl_3$, δ) 0.92 (d, 7 Hz, 3 H), 1.11 (s, 6 H), 1.15–2.28 (m, 12 H), 3.69 (s, 3 H); IR (film) 1747 cm^{-1}.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.43; H, 9.42.

(3aα,5aβ,8β,8aβ)-1,2,3a,5,5a,6,7,8-Octahydro-2,2,8-trimethylcyclopenta[*c*]pentalene-3,4-dione (10). A solution of 8.2 mL (8.2 mmol) of 1.0 M potassium *tert*-butoxide in THF and 50 mL of dry benzene were heated to reflux, whereupon a solution of 1.712 g (6.79 mmol) of keto ester **19** in 5 mL of dry benzene was added slowly to the refluxing solution. Then 30 mL of the benzene was distilled off over 30 min. The resulting red solution was cooled, acidified with 10% HCl, washed with saturated $NaHCO_3$, dried, and concentrated to give a yellow solid. Flash chromatography (15% ethyl acetate in hexane) followed by recrystallization from hexane yielded 1.126 g (75%) of **10** as colorless prisms: mp 71–72 °C; 250-MHz ^{1}H NMR ($CDCl_3$, δ), 1.05 (d, J = 7 Hz, 3 H), 1.09 (s, 3 H), 1.13 (s, 3 H), 1.3–2.34 (m, 8 H), 2.44 (m, 2 H), 3.98 (s, 1 H); IR ($CDCl_3$) 1765 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.49; H, 9.07.

Conversion of 10 to 21. To a 100-mL round bottom flask equipped with a Dean-Stark trap, magnetic stirrer, and a reflux condenser was added 993 mg (4.52 mmol) dione **10**, a few crystals of *p*-toluenesulfonic acid, 352 mg (5.68 mmol) of ethylene glycol, and 50 mL of dry benzene; this mixture was heated at reflux with the continuous removal of water for 4 h. After cooling, the mixture was washed with half-saturated $NaHCO_3$, dried, and concentrated to afford **20** as a clear oil which was generally used without further purification.

The above crude ketal was taken up in 5 mL of THF and added to 50 mL of liquid ammonia and 5 mL of methanol. To this solution at −33 °C was added 200 mg (33.33 mmol) of lithium wire in small portions, and the mixture was stirred for 15 min after all the lithium had been added. Solid NH_4Cl was added to quench the reaction, and the ammonia was allowed to evaporate. The residue was extracted with ether, dried, concentrated, and flash chromatographed (15% ethyl acetate/hexane) to give 972 mg (81%) of **21** as a colorless oil: 250-MHz ^{1}H NMR ($CDCl_3$, δ) 0.93 (s, 3 H), 0.95 (d, J = 7 Hz, 3 H), 1.06 (s, 3 H), 1.10–2.32 (m, 12 H), 3.63 (dd, J = 9 and 2 Hz; d, J = 9 Hz when D_2O added, 1 H) 3.91 (m, 4 H); IR (film) 3495 cm^{-1}.

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.10; H, 9.70.

(3aα,3aα,5aβ,8β,8aβ)-Octahydro-3-hydroxy-2,2,8-trimethylcyclopenta[*c*]pentalen-4(5*H*)-one (22). A solution of 972 mg (3.65 mmol) of ketal 21 in 100 mL of acetone and 10 mL of 10% HCl was stirred 10 h at room temperature. The acetone was removed at reduced pressure, and the residue was dissolved in ether. The ether layer was washed with saturated $NaHCO_3$, dried, and concentrated to produce 811 mg (100%) of **22** as a thick oil which crystallized on standing. A single recrystallization from hexane provided analytically pure material: mp 61.5–63 °C; 250-MHz ^{1}H NMR ($CDCl_3$, δ) 0.97 (s, 3 H), 0.98 (d, J = 7 Hz, 3 H), 1.33 (m, 2 H), 1.70–2.35 (m, 10 H), 2.38 (br d, J = 7 Hz, 1 H), 2.81 (dd, 1 H), 3.69 (d, J = 7 Hz, 1 H); IR ($CDCl_3$) 3620, 1735 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.78; H, 9.80.

(5aβ,8β,8aβ)-1,2,5a,6,7,8-Hexahydro-2,2,8-trimethylcyclopenta[*c*]-pentalen-4(5*H*)-one (27). A solution of 0.421 mL (4.28 mmol) of methanesulfonyl chloride in 5 mL of dry dichloromethane was added dropwise to 811 mg (3.65 mmol) of alcohol **22** and 0.765 mL (4.28 mmol) of triethylamine in 15 mL of dry dichloromethane. After the mixture was stirred for 3 h the dichloromethane was evaporated and the residue dissolved in ether. The ether was washed with water, dried, and concentrated. The residue was dissolved in 20 mL of dichloromethane, and DBU (7.1 mmol) was added. The mixture was stirred for 10 h, washed with 10% HCl and saturated $NaHCO_3$, dried, and concentrated at reduced pressure. Chromatography of the residue (25% ethyl acetate in hexane) afforded 602 mg (81%, 65% from **10**) of enone **27** as white prisms: mp 51.5–53 °C; 250-MHz ^{1}H NMR ($CDCl_3$, δ) 1.02 (d, J = 7 Hz, 3 H) 1.18 (s, 3 H), 1.20 (s, 3 H), 1.25–2.40 (m, 9 H), 2.80 (m, 1 H), 6.14 (s, 1 H); IR ($CDCl_3$) 1716, 1638 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.43; H, 9.73.

(3aα,4α,5β,5aβ,8β,8aβ)-Decahydro-4-hydroxy-2,2,5,8-tetramethylcyclopenta[*c*]pentalene (29). A solution of lithium diisopropylamide was prepared by addition of 0.471 mL (1.18 mmol) of 2.5 M *n*-butyllithium in hexane to 0.173 mL (1.23 mmol) of diisopropylamine in 8 mL of dry THF at 0 °C. After stirring for 10 min at 0 °C the solution was cooled to −78 °C, and a solution of 200 mg (0.980 mmol) of ketone **27** in 2 mL of dry THF was added dropwise. The solution was warmed to 0 °C over 40 min, whereupon 0.610 mL (9.80 mmol) of freshly distilled methyl iodide was added. The mixture was stirred at 0 °C for 50 min and quenched by the addition of saturated NH_4Cl. After diluting with ether the organic layer was washed with H_2O, dried, and concentrated at reduced pressure. The residual oil was flash chromatographed (2% ethyl acetate in hexane) to provide 181 mg (85%) of the monomethyl ketone **28**: 250-MHz ^1H NMR ($CDCl_3$, δ) 1.03 (d, J = 7.5 Hz, 3 H), 1.10 (d, J = 7.5 Hz, 3 H), 1.20 (s, 3 H), 1.22 (s, 3 H), 1.38–2.22 (m, 7 H), 2.24 (dq, J = 7.5 and 10 Hz, 1 H), 5.18 (s, 1 H); IR (film) 1730, 1639 cm^{-1}. Enone **28** (213 mg, 0.977 mmol) in 2 mL of THF was added to a mixture of 2 cm of lithium wire in 25 mL of dry ammonia at −33 °C. This mixture was stirred for 15 min at −33 °C, whereupon 2 mL of methanol and an additional 2 cm of lithium wire were added. After stirring for an additional 20 min, the reaction was quenched by the cautious addition of solid NH_4Cl, and the ammonia was allowed to evaporate. The residue was extracted with ether, and the ether solution was dried and concentrated at reduced pressure. Flash chromatography (5% ethyl acetate in hexane) produced 178 mg (82%) of alcohol **29** as a colorless oil: 250-MHz ^1H NMR ($CDCl_3$, δ) 0.87 (d, J = 7.5 Hz, 3 H), 1.00 (s, 3 H), 1.01 (d, J = 7 Hz, 3 H), 1.09 (s, 3 H), 1.10–2.06 (m, 12 H), 3.52 (dd, J = 7 and 9 Hz, 1 H); IR (film) 3305 cm^{-1}.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.33; H, 11.82.

Pentalenene (1). A mixture of alcohol **29** (92 mg, 0.41 mmol), 4-*N*,*N*-dimethylaminopyridine (60 mg, 0.49 mmol), and *O*-4-methylphenyl chlorothioformate (110 mg, 0.59 mmol) in 10 mL of dichloromethane was stirred for 48 h, whereupon the mixture was washed with 10% HCl and saturated $NaHCO_3$, dried, and concentrated. The residue was flash chromatographed (2% ethyl acetate in hexanes) to give 138 mg (90%) of the thiocarbonate. This material was placed in a kugelrohr oven under vacuum (20 mm) and slowly warmed to 200 °C. The distillate was flash chromatographed in hexane to produce 51 mg (60%) of pentalenene (**1**) as a colorless oil: 250-MHz ^1H NMR ($CDCl_3$, δ) 0.92 (d, J = 7 Hz, 3 H), 0.98 (s, 3 H), 0.99 (S, 3 H), 1.1–1.91 (m, 9 H), 2.57 (m, 1 H), 2.66 (m, 1 H), 5.16 (brS, 1 H).

(3α,3aα,5α,5aβ,8β,8aβ)-Octahydro-5-carbomethoxy-3-hydroxy-2,2,8-trimethylcyclopenta[*c*]pentalen-4(5*H*)-one (23). To a solution of diisopropylamine (0.56 mL, 4.0 mmol) in 5 mL of tetrahydrofuran at 0 °C was added 1.6 mL (4.0 mmol) of a 2.5 M solution of *n*-butyllithium in hexane. After stirring for 30 min the solution was cooled to −78 °C, whereupon 222 mg (1.0 mmol) of keto alcohol **22** in 2 mL of THF was added dropwise, and the reaction was stirred for 2 h at −78 °C. Excess carbon dioxide was then bubbled into the solution while warming to room temperature. After recooling to −23 °C, the reaction was quenched with 5% HCl and extracted into dichloromethane. The organic extract was dried over magnesium sulfate, filtered, cooled to −78 °C, and treated with excess diazomethane in ether. After the mixture was stirred for 30 min at −78 °C, excess diazomethane was destroyed by the addition of acetic acid. The solution was washed with saturated $NaHCO_3$, dried, and concentrated. Purification by flash chromatography (25% ethyl acetate in hexanes) yielded 80 mg of ketone **22** and 129 mg of keto ester **23** (91% based on recovered starting material): 250-MHz ^1H NMR ($CDCl_3$, δ) 0.93 (d, J = 6.5 Hz, 3 H), 0.98 (s, 3 H) 1.01 (s, 3 H), 1.25–2.41 (band, 7 H), 2.68 (dd, J = 5 and 1 Hz, 1 H), 2.82 (m, 1 H), 3.68 (d, J = 5 Hz), 3.76 (s, 3 H), 10.35 (s, 1 H); IR (film) 3490, 1755, 1736, 1669, 1628, 1451 cm^{-1}.

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.27; H, 8.67.

(3α,3aα,5aβ,8β,8aβ)-1,2,3,3a,5a,6,7,8-Hexahydro-3-acetoxy-2,2,8-trimethylcyclopenta[*c*]pentalene (26). Reduction of 23. To a solution of 34.5 mg (0.123 mmol) of keto ester **23** in 5 mL of methanol was added an excess of sodium borohydride. After 2 h the reaction was quenched by the addition of 10% HCl. The methanol was removed in vacuo, the aqueous layer was extracted several times with ether, and the combined ether layers were washed with sodium bicarbonate and dried over sodium sulfate. Filtration, solvent evaporation, and flash chromatography (50% ethyl acetate in hexanes) provided 35 mg (100%) of diol **24** as a mixture of diastereomers: 250-MHz ^1H NMR (major isomer) ($CDCl_3$, δ) 0.93 (d, J = 6.5 Hz, 3 H), 0.95 (s, 6 H), 1.1–2.3 (band, 7 H), 2.38 (m, 1 H), 2.86 (dd, J = 6 and 7 Hz, 1 H), 3.75 (s, 3 H), 4.01 (d, J = 7.5 Hz, 1 H), 4.72 (t, J = 7.5 Hz, 1 H); IR (film) 3425, 1740, 1440 cm^{-1}.

Acetylation of 24. To a solution of 35 mg (0.12 mmol) of diol **24** in 3 mL of acetic anhydride was added 0.5 mL of triethylamine and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine. The resulting yellow solution was stirred overnight at room temperature, whereupon solid sodium bicarbonate and ether were added. The reaction mixture was poured into saturated sodium bicarbonate and extracted with ether, and the combined ether extracts were washed again with saturated $NaHCO_3$, dried, concentrated, and flash chromatographed (25% ethyl acetate in hexanes) to provide diacetate **25** as a mixture of diastereomers (32 mg, 70%): 250-MHz ^1H NMR (major isomer) ($CDCl_3$, δ) 0.96 (d, J = 6.5 Hz, 3 H), 0.97 (s, 3 H), 0.98 (s, 3 H), 1.2–2.1 (band, 8 H), 2.23 (s, 6 H), 2.57 (m, 1 H), 3.70 (s, 3 H), 5.18 (d, J = 9 Hz, 1 H), 5.52 (m, 1 H); IR (film) 1740–1750 broad cm^{-1}.

Elimination of 25. A solution of 32 mg (0.87 mmol) of diacetate **25**, 1 mL of diazabicycloundecene, and 20 mL of benzene was heated at reflux for 48 h. The mixture was cooled, washed with 10% HCl, and dried over magnesium sulfate. Filtration and removal of solvents yielded 26 mg (96%) of essentially pure ester **26**. Flash chromatography (25% ethyl acetate in hexanes) provided an analytically pure sample: 250-MHz ^1H NMR ($CDCl_3$, δ) 0.96 (d, J = 6.5 Hz, 3 H), 0.98 (s, 3 H), 1.01 (s, 3 H), 1.1–2.2 (band, 7 H), 2.08 (s, 3 H), 2.77 (m, 1 H), 3.06 (m, 1 H), 3.73 (s, 3 H), 4.55 (d, J = 4.2 Hz, 1 H), 6.80 (m, 1 H); IR ($CDCl_3$) 1750, 1729, 1645 cm^{-1}.

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 70.57; H, 8.74. Found: C, 70.56; H, 8.55.

Pentalenic Acid (2). A solution of 17 mg (0.056 mmol) of unsaturated acetate **26**, 3 mL of methanol, and 5 mL of 10% aqueous potassium hydroxide was heated at reflux for 3 h and cooled to room temperature. The methanol was removed in vacuo, and the reaction mixture was acidified to pH 2 with 10% HCl. The mixture was extracted with ether, and the ether layer was dried over magnesium sulfate, filtered, and concentrated to yield 10 mg (87%) of pentalenic acid (**2**), which displayed spectral properties identical with literature values. The methyl ester gave 250-MHz ^1H NMR and I values identical with spectra of natural pentalenic acid provided by Professor David Cane:[29] 250-MHz ^1H NMR ($CDCl_3$, δ) 0.95 (d, J = 6.5 Hz, 3 H), 0.98 (s, 3 H), 1.00 (s, 3 H), 1.2–2.05 (band, 5 H), 2.01 (ABq, 2 H), 2.75 (m, 1 H), 3.01 (m, 1 H), 3.45 (d, J = 5.5 Hz, 1 H), 6.94 (m, 1 H).

Methyl ester: ($CDCl_3$, δ) 0.93 (d, J = 6.5 Hz, 3 H), 0.95 (s, 3 H), 0.98 (s, 3 H), 1.40 (d, J = 12 Hz, 1 H), 1.4–2.1 (band, 5 H), 1.98 (d, J = 12 Hz, 1 H), 2.73 (m, 1 H), 3.00 (m, 1 H), 3.42 (d, J = 5.5 Hz, 1 H), 3.72 (s, 3 H), 6.83 (m, 1 H).

(5aα,8β,8aβ)-1,2,5a,6,7,8-Hexahydro-8-methylcyclopenta[*c*]pentalen-4(5*H*)-one (34). A solution of 2.7 M *n*-butyllithium in hexane (0.26 mL, 0.70 mmol) was added to a cooled (0 °C) solution of diisopropylamine (0.10 mL, 0.70 mmol) in 5 mL of tetrahydrofuran. The solution was stirred for 30 min and cooled to −78 °C, whereupon enone **27** (61 mg, 0.30 mmol) in 5 mL of THF was added dropwise. The mixture was stirred for 2 h, and excess CO_2 was bubbled through the mixture as it warmed to room temperature. After recooling to −78 °C the mixture was acidified with 5% HCl and extracted with dichloromethane. The organic layer was dried, cooled to −78 °C, and treated with excess diazomethane in ether. After 30 min at −78 °C acetic acid was added to destroy excess diazomethane, and the mixture was warmed to room temperature, washed with saturated $NaHCO_3$, dried, and concentrated to produce 78 mg (100%) of essentially pure keto ester **34**: 250-MHz ^1H NMR ($CDCl_3$, δ) 1.04 (d, J = 6.5 Hz, 3 H), 1.22 (s, 6 H), 1.3–2.1 (band, 7 H), 2.70 (dd, J = 9 and 9.5 Hz, 1 H), 3.28 (d, J = 9 Hz, 1 H), 3.77 (s, 3 H), 6.30 (s, 1 H); IR (film) 1758, 1728, 1645, 1582 cm^{-1}. Note: Attempted purification of this unstable oil resulted in loss of material; the highest yield obtained after chromatography was 60% based on recovered enone **27**. M^+ calcd. for $C_{16}H_{22}O_3$, 262.1569; found, 262.1573.

(3aα,5aβ,8β,8aβ)-1,2,3,3a,5a,6,7,8-Hexahydro-2,2,8-trimethylcyclopenta[*c*]pentalene (38). Reduction of Keto Ester 34. Sodium borohydride (56 mg, 1.46 mmol) was added in portions to a solution of 181 mg (0.69 mmol) of keto ester **34** in 20 mL of methanol. After 1 h the reaction was quenched by the addition of 10% HCl, and the methanol was removed in vacuo. The residue was extracted with ether, and the combined ether extracts were washed with saturated $NaHCO_3$, dried, and concentrated to yield 179 mg (99%) of allylic alcohol **36** as a clear oil which was used without further purification: 250-MHz ^1H NMR ($CDCl_3$, δ) 0.99 (d, J = 6.5 Hz, 3 H), 1.15 (s, 3 H), 1.16 (s, 3 H), 1.2–2.05 (band, 7 H), 2.36 (m, 1 H), 2.96 (dd, J = 5.5 and 10 Hz, 1 H), 3.70 (s, 3 H), 4.85 (dd, J = 10 and 2 Hz), 5.37 (d, J = 2 Hz); IR ($CDCl_3$) 3470, 1741, 1518, 1479 cm^{-1}.

Hydrogenation of 36. A mixture of 179 mg (0.68 mmol) of allylic alcohol **36**, 8 mL of absolute ethanol, and catalytic PtO_2 was stirred under an atmosphere of hydrogen for 10 h. The catalyst was removed by filtration and the solvent evaporated to give 180 mg (100%) of alcohol **37** as an oil which was used without purification: 250-MHz ^1H NMR

($CDCl_3$, δ) 0.91 (d, J = 6.5 Hz, 3 H), 1.02 (s, 3 H), 1.10 (s, 3 H), 1.2-2.05 (band, 9 H), 2.32 (m, 1 H), 2.61 (m, 1 H), 3.27 (d, J = 6 Hz, 1 H), 3.74 (s, 3 H), 4.33 (m, 1 H); IR (film) 3460, 1735, 1445 cm^{-1}.

Mesylation and Elimination of 37. A solution of 0.15 mL (2 mmol) of methanesulfonyl chloride in 5 mL of dichloromethane was added dropwise to a stirred solution of triethylamine (6.28 mL, 2.0 mmol) and 180 mg (0.68 mmol) of alcohol **37** in 5 mL of dichloromethane. The mixture was stirred overnight, then washed with 10% HCl and saturated $NaHCO_3$, dried, and concentrated. This crude material was dissolved in 5 mL of dichloromethane to which 1 mL of DBU was added. The mixture was stirred for 12 h, diluted with ether, washed with 10% HCl and saturated $NaHCO_3$, dried, and concentrated. The residue was flash chromatographed (10% ethyl acetate in hexanes) to provide 96 mg (56% from **34**) of ester **38**: 250-MHz ^1H NMR ($CDCl_3$, δ) 0.92 (d, J = 6 Hz, 3 H), 0.99 (s, 3 H), 1.02 (s, 3 H), 1.2-2.1 (band, 9 H), 2.88 (m, 1 H), 3.06 (d, J = 9.5 Hz, 1 H), 3.74 (s, 3 H), 6.64 (m, 1 H); IR ($CDCl_3$) 1730, 1629, 1468, 1432 cm^{-1}.

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.10; H, 9.69.

Deoxypentalenic Acid (3b). A solution of 34 mg (0.14 mmol) of methyl ester **38** and 2 mL of 10% KOH in 4 mL of methanol was heated at reflux for 48 h and cooled to room temperature. The methanol was removed in vacuo, and the residue was partitioned between ether-10% HCl. The aqueous layer was extracted several times with ether, and the combined ether extracts were dried and concentrated to yield 32 mg (100%) of crystalline deoxypentalenic acid (**3b**): mp 107-111 °C; 250-MHz ^1H NMR ($CDCl_3$, δ) 0.96 (d, J = 6 Hz, 3 H), 1.03 (S, 3 H) 1.05 (s, 3 H), 1.2-2.1 (band, 9 H), 2.93 (m, 1 H), 3.09 (d, J = 8.5 Hz, 1 H), 6.82 (brs, 1 H); IR ($CDCl_3$) 1678, 1628, 1282. M^+ calcd for $C_{15}H_{22}O_3$: 234.1620. Found: 234.1598.

Acknowledgment. We are pleased to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health (AI-20283) for their generous financial assistance. Thanks are due to L. D. Bredon and Dr. D. L. Harris for help in recording 250-MHz spectra. We also thank Professor Leo A. Paquette, The Ohio State University, and Professor David E. Cane, Brown University, for providing spectra of pentalenene and methyl pentalenate, respectively, and Lisa C. Battigelli for technical assistance.

Total Synthesis of Mycophenolic Acid

Rick L. Danheiser,*[1] Stephen K. Gee, and Joseph J. Perez

Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. *Received August 14, 1985*

Abstract: A convergent aromatic annulation strategy based on the thermal combination of heterosubstituted acetylenes and cyclobutenones has been applied in an efficient total synthesis of the antitumor antibiotic mycophenolic acid. The key annulation components **3** and **4** are rapidly assembled by straightforward routes and then heated in benzene at 120 °C for 14 h. This annulation reaction generates the pentasubstituted aromatic intermediate **2** in 73% yield. Ortho bromination of this phenol and carboxylation of the aryllithium derivative then furnishes the carboxylic acid **10**, which is converted to mycophenolic acid (**1**) by acid hydrolysis followed by Jones oxidation. This convergent approach delivers mycophenolic acid in nine steps in an overall yield of 17-19%.

The *Penicillium* metabolite mycophenolic acid was first isolated in 1896[2] and is one of the oldest known antibiotics.[3] Recently, the compound has been identified as a potent inhibitor of IMP dehydrogenase and GMP synthetase[4] and in addition has been found to possess significant antiviral and antitumor activity.[5] The application of mycophenolic acid in the treatment of psoriasis[6] and leishmaniasis[7] is also currently the subject of active investigation.

The chemical structure of mycophenolic acid incorporates as a key feature a highly functionalized, hexasubstituted aromatic ring. The regiocontrolled synthesis of such highly substituted aromatic systems presents a formidable synthetic challenge, which is often best met by the application of annulation strategies that assemble the requisite aromatic unit in a single step with all (or most) substituents already in place.[8] Recently, we described a regiocontrolled annulation approach to aromatic compounds based on the *one-step* thermal combination of heterosubstituted alkynes with cyclobutenones (Scheme I).[9] In this article, we now report the application of this method in a convergent and highly efficient synthetic route to mycophenolic acid.[10]

Scheme II summarizes our synthetic strategy. The pivotal step in this approach is the construction of the pentasubstituted resorcinol derivative **2** via thermal addition of the alkynyl ether **3** to the cyclobutenone **4**. The indicated regiochemical outcome of this key transformation follows from the results of our earlier investigation,[9] which established that these aromatic annulations proceed via a cascade of four pericyclic reactions to regiospecifically generate products of general structure f as formulated in Scheme I. With the key pentasubstituted aromatic intermediate **2** in hand, completion of the synthesis of mycophenolic acid would simply require the introduction of a carboxyl function at C-6 of the aromatic nucleus and conversion of the resulting acid to the target antibiotic via hydrolysis and oxidation.

The following synthetic routes provided convenient access to the key annulation components **3** and **4**. Reduction of the known

(1) Fellow of the Alfred P. Sloan Foundation, 1981-1985.

(2) *Isolation*: Gosio, B. *Riv. Igiene Sanita publica Ann.* **1896**, *7*, 825. Structure determination: (a) Birkinshaw, J. H.; Raistrick, H.; Ross, D. J. *Biochem. J.* **1952**, *50*, 630. (b) Logan, W. R.; Newbold, G. T. *J. Chem. Soc.* **1957**, 1946.

(3) (a) Abraham, E. P. *Biochem. J.* **1945**, *39*, 398. (b) Florey, H. W.; Gilliver, K.; Jennings, M. A.; Sanders, A. G. *Lancet* **1946**, *250*, 46. (c) Gilliver, K. *Ann. Bot. (London)* **1946**, *10*, 271. (d) Brian, P. W. *Ibid.* **1949**, *13*, 59.

(4) (a) Franklin, T. J.; Cook, J. M. *Biochem. J.* **1969**, *113*, 515. (b) Sweeney, M. J.; Hoffman, D. H.; Esterman, M. A. *Cancer Res.* **1972**, *32*, 1803.

(5) (a) Ando, K.; Suzuki, S.; Tamura, G.; Arima, K. *J. Antibiot.* **1968**, *21*, 649. (b) Carter, S. B.; Franklin, T. J.; Jones, D. F.; Leonard, B. J.; Mills, S. D.; Turner, R. W.; Turner, W. B. *Nature (London)* **1969**, *223*, 848. (c) Sweeney, M. J.; Gerzon, K.; Harris, P. N.; Holmes, R. E.; Poore, G. A.; Williams, R. H. *Cancer Res.* **1972**, *32*, 1795.

(6) (a) Marianarai, R.; Fleischmajer, R.; Schragger, A. H.; Rosenthal, A. L. *Arch. Dermatol.* **1977**, *113*, 930. (b) Lynch, W. S.; Roenigk, H. H. *Ibid.* **1977**, *113*, 1203. (c) Gomez, E. C.; Menendez, L.; Frost, P. *J. Am. Acad. Dermatol.* **1979**, *1*, 531.

(7) Berman, J. D.; Webster, H. K. *Antimicrob. Agents Chemother.* **1982**, *21*, 887.

(8) For a recent review, see: Bamfield, P.; Gordon, P. F. *Chem. Soc. Rev.* **1984**, *13*, 441.

(9) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672.

(10) For earlier syntheses of mycophenolic acid, see: (a) Birch, A. J.; Wright, J. J. *Aust. J. Chem.* **1969**, *22*, 2635. (b) Canonica, L.; Rindone, B.; Santaniello, E.; Scolastico, C. *Tetrahedron* **1972**, *28*, 4395.

0002-7863/86/1508-0806$01.50/0