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Intramolecular Photocycloaddition–Cyclobutane Fragmentation: A Highly Stereoselective Total Synthesis of (±)-Pentalenic Acid

Summary: An efficient total synthesis of pentalenic acid has been accomplished by utilizing an intramolecular photocycloaddition–cyclobutane fragmentation as the key reaction sequence.

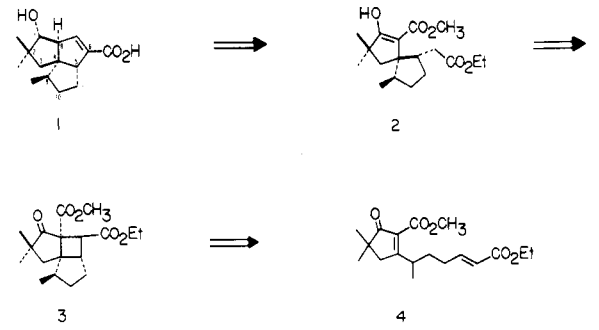
Sir: Several variously substituted triquinane natural products have recently been isolated and characterized.[1-5] One of the more important and more highly functionalized members of this growing class of compounds has been identified as a key intermediate in the biosynthesis of the biologically important pentalenolactones and has been designated pentalenic acid (1).[5,6] Pentalenic acid has previously been prepared through a biogenetic-like synthesis from humulene.[5b]

This report describes an efficient, highly stereoselective total synthesis of pentalenic acid by utilizing an intramolecular photocycloaddition–cyclobutane fragmentation[7] to introduce three of the necessary stereocenters. The effectiveness of intramolecular photocycloadditions in synthesis has previously been demonstrated by Pirrung's[1b] synthesis of isocomene and Oppolzer's synthesis of α-acoradiene[8] and longifolene.[9]

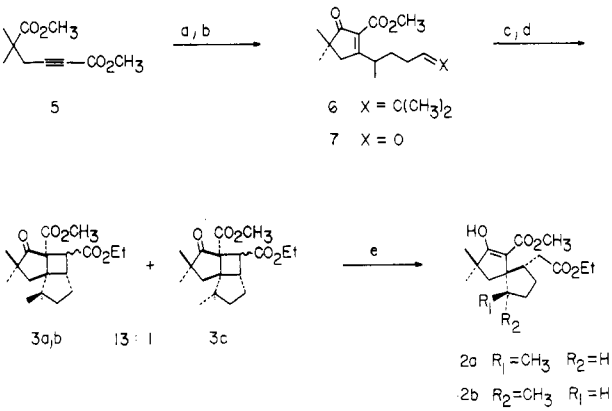
Retrosynthetically, **1** was seen as being accessible from β-keto ester **2** (Scheme I). In turn, **2** could be produced through a reductive cleavage of the tricyclic cyclobutane diester **3**, the product of an intramolecular [2 + 2] photocycloaddition of diene **4**.

Our plan for the construction of **4** centered around a new conjugate addition–cycloacylation[10] sequence on acetylenic diester **5** which was prepared from methyl isobutyrate in

Scheme I

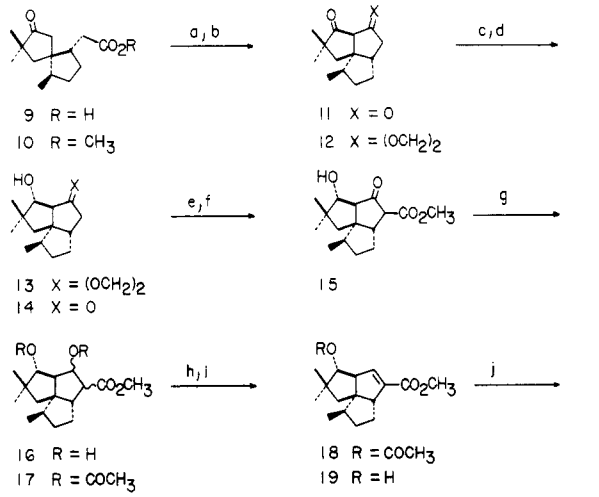


Scheme II[a]



[a] (a) $CH_3CHMgClCH_2CH_2CH{=}C(CH_3)_2$, CuI, THF, TMEDA, −78 °C, 2 h to 25 °C, 2 h. (b) O_3, CH_2Cl_2, −78 °C, then $(CH_3)_2S$, 25 °C; (c) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 40 °C, 6 h; (d) 1 h, hexane, 366 nm; (e) Li, NH_3, Et_2O, −78 °C.

Scheme III[a]



[a] (a) CH_3OH, H_2SO_4, $(CH_3O)_3CH$, reflux, 4 h; (b) t-BuO^-K^+, C_6H_6, reflux; (c) p-TSA, C_6H_6, $(CH_2OH)_2$, reflux, 4 h; (d) Li, NH_3OH, −33 °C; (e) 10% HCl, acetone, 5 h; (f) LDA, THF, −78 °C; CO_2; 10% HCl, −20 °C; CH_2N_2, CH_2Cl_2, 40 °C; (g) $NaBH_4$, CH_3OH, 2 h; (h) Ac_2O, DMAP, Et_3N; (i) DBU, C_6H_6; (j) KOH, CH_3OH, 25 °C, 3 h.

(1) Isocomene. (a) Isolation: Zalkow, L. H.; Harris, R. N., III; Van Derveer, D.; Bertand, J. A. *J. Chem. Soc., Chem. Commun.* **1977**, 456. Zalkow, L. H.; Harris, R. N., III; Burke, N. I. *J. Natl. Prod.* **1979**, *42*, 96. Bohlmann, F.; LeVan, N.; Pickhardt, J. *Chem. Ber.* **1977**, *110*, 3777. (b) Synthesis: Paquette, L. A.; Han, Y. K. *J. Org. Chem.* **1979**, *44*, 4014; *J. Am. Chem. Soc.* **1981**, *103*, 1835. Oppolzer, W.; Battig, K.; Hudlicky, T. *Helv. Chim. Acta* **1979**, *62*, 1493; *Tetrahedron* **1981**, *37*, 4359. Pirrung, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 7130; **1981**, *103*, 82. Dauben, W. G.; Walker, D. M. *J. Org. Chem.* **1981**, *46*, 1103. Wender, P. A.; Dreyer, G. B. *Tetrahedron* **1981**, *37*, 4445.

(2) Silphenene. (a) Isolation: Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259. (b) Synthesis: Paquette, L. A.; Leone-Bey, A. *J. Org. Chem.* **1982**, *47*, 4173. Tsunoda, T.; Kodama, M.; Ito, S. *Tetrahedron Lett.* **1983**, *24*, 83.

(3) Senoxydene. (a) Isolation: Bohlmann, F.; Zdero, C. *Phytochemistry* **1979**, *18*, 1747. (b) Attempted Synthesis: Paquette, L. A.; Galemmo, R. A., Jr.; Springer, J. P. *J. Am. Chem. Soc.* **1983**, *105*, 6975.

(4) Pentalenene. (a) Isolation: Seto, H.; Yonehara, H. *J. Antibiot.* **1980**, *33*, 92. (b) Synthesis: Paquette, L. A.; Annis, G. D. *J. Am. Chem. Soc.* **1982**, *104*, 4504. Misumi, S.; Ohtsuka, T.; Ohfune, Y.; Sugita, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1979**, 31. Crimmins, M. T., manuscript in preparation.

(5) Pentalenic Acid. (a) Isolation: Seto, H.; Sasaki, T.; Uzawa, J.; Takeuchi, S.; Yonehara, H. *Tetrahedron Lett.* **1978**, 4411. (b) Synthesis: Sakai, K.; Ohtsuka, T.; Misumi, S.; Shirahama, H.; Matsumoto, T. *Chem. Lett.* **1981**, 355.

(6) Cane, D. E.; Rossi, T.; Pachlatko, J. P. *Tetrahedron Lett.* **1979**, 3639. Cane, D. E.; Rossi, T.; Tillman, A. M.; Pachlatko, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 1838.

(7) For a recent review, see: Oppolzer, W. *Acc. Chem. Res.* **1982**, *15*, 135.

(8) Oppolzer, W.; Zutterman, F.; Battig, K. *Helv. Chim. Acta* **1983**, *66*, 522.

(9) Oppolzer, W.; Godel, T. *J. Am. Chem. Soc.* **1978**, *100*, 2583.

(10) Crimmins, M. T.; Mascarella, S. W.; DeLoach, J. A. *J. Org. Chem.*, in press.

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two steps. Alkylation[11] of the lithium enolate of methyl isobutyrate with propargyl bromide (THF, -78 °C, 80% yield) followed by carbomethoxylation of the resultant terminal acetylene by the method of Tsuji[12] (CO, $PdCl_2$, $CuCl_2$, NaOAc; 72% yield) provided diester **5**.[13] Exposure of **5** (Scheme II) to the Grignard reagent prepared from 2-chloro-6-methyl-5-heptene[14] in the presence of added TMEDA and copper(I) iodide (THF, -78 to 25 °C) resulted in 1,4 addition[15-17] and subsequent cyclization of the intermediate vinylcopper species to yield 48% of cyclopentenone **6**.[10] Selective ozonolysis of the trisubstituted olefin (O_3, CH_2Cl_2, -78 °C; then Me_2S, -78 to 25 °C) generated aldehyde **7**. Treatment of **7** with carbethoxymethylenetriphenylphosphorane (CH_2Cl_2, 40 °C, 6 h) provided the desired diester **4** in 81% yield from **6**.

With ready access to the highly functionalized cyclopentenone **4**, the next stage of the synthesis was to carry out the key photocyclization, and this was accomplished by irradiating a hexane solution of **4** at 366 nm (uranium glass filter). The resulting cyclobutane photoadducts **3** were isolated in 72% yield as a 10:3:1 (**3a:3b:3c**) mixture of diastereomers. Cleavage of the cyclobutane of **3** with lithium-ammonia[18] at -78 °C led to a 13:1 mixture of spirofused esters **2a:2b** in 90% yield. Thus, the two major isomers obtained from the photocycloaddition must contain the same relative stereochemistry at C-9 but are epimeric at the cyclobutyl carbon bearing the carbethoxy group.

The excellent stereoselectivity[19] in the photoannelation might be explained on thermodynamic grounds analogously to the system studied by Oppolzer.[8] However, on the basis of existing data, particularly recent findings by Becker,[20] kinetic control cannot be excluded.

Our next task was to close the remaining five-membered ring to form the basic triquinane skeleton. This was readily accomplished in three high-yield steps (Scheme III). Hydrolysis-decarboxylation of β-keto ester **2a** (HCl, H_2O, HOAc, 6 h, reflux; 90% yield)[21] provided acid **9** (mp 85.5-87 °C). Fischer esterification [CH_3OH, $(CH_3O)_3CH$, p-TSA) gave 97% of ester **10** which was readily cyclized[22] (t-BuO^-K^+, C_6H_6, reflux) to afford a 75% yield of pure dione **11** (mp 71-72 °C) after flash chromatography and recrystallization. The cis stereochemistry of the ring juncture formed in this cyclization is a result of thermodynamic as well as kinetic control.

The remaining portion of the synthesis required differentiation of the two carbonyls of **11**. Selective ketalization was easily achieved to yield ketal **12** due to the vastly different steric environment of the two carbonyls. Thermodynamic reduction (Li, NH_3, CH_3OH) of the ketone gave **13** with the correct stereochemistry of the C-1 hydroxyl. Hydrolysis of the ketal provided keto alcohol **14** in 81% yield from **11**.

Carboxylation of **14** (4 equiv of LDA, CO_2, -78 °C; 10% HCl, -40 °C)[23] followed immediately by diazomethane esterification produced 90% of keto ester **15**. Treatment of **15** with sodium borohydride in methanol generated diol **16** as a mixture of diastereomers in 84% yield. Attempts to selectively mesylate or tosylate **16** to allow introduction of the requisite double bond were unsuccessful. However, bisacetylation (Ac_2O, Et_3N, DMAP)[24] of **16** followed by treatment with DBU gave 90% of the unsaturated ester **18** which was hydrolyzed (KOH, H_2O, MeOH) to pentalenic acid (**1**). Spectra of the methyl ester of synthetic **1** were identical with those of authentic samples.[5a,25]

In summary, an efficient, highly stereoselective synthesis of the important triquinane pentalenic acid (**1**) has been achieved. Similar approaches to other triquinanes utilizing our photocycloaddition-cyclobutane fragmentation sequence are in progress and will be reported in due course.

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(11) Gregge, R. J.; Herrmann, J. L.; Lee, C. S.; Richman, J. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2425.
(12) Tsuji, J.; Takahashi, M.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 849.
(13) All new compounds gave satisfactory (±0.4%) combustion analyses and consistent 250-MHz ^1H NMR and infrared spectra.
(14) Fetizon, M.; Lazare, S.; Pascard, C.; Prange, T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1407.
(15) Siddall, J. B.; Biskup, M.; Fried, J. N. *J. Am. Chem. Soc.* **1969**, *91*, 1853.
(16) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.
(17) Anderson, R. J.; Carbin, V. L.; Cotterrell, G.; Cox, G. R.; Henrick, C. A.; Schaub, F.; Siddall, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 1197.
(18) Coates, R. M.; Senter, P. D.; Baker, W. R. *J. Org. Chem.* **1982**, *47*, 3597. Gassman, P. G.; Crearey, X. *J. Chem. Soc., Chem. Commun.* **1972**, 1214.
(19) For similar photoadditions of cyclohexenones, see ref 7 and Hoye, T. R.; Martin, S. J.; Peck, D. R. *J. Org. Chem.* **1982**, *47*, 331. Fetizon, M.; Khac Manh, D. D.; Ecoto, J.; Colin, H.; Diez-Mala, J. *J. Chem. Soc., Chem. Commun.* **1981**, 953. 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.
(20) Becker, D.; Nagler, M.; Hirsh, S.; Ramun, J. *J. Chem. Soc., Chem. Commun.* **1983**, 371.
(21) Oehldrich, J.; Cook, J. M. *Tetrahedron Lett.* **1976**, 549.
(22) Quesada, M. L.; Schlessinger, R. H.; Parsons, W. H. *J. Org. Chem.* **1978**, *43*, 3968.
(23) Parsons, W. H.; Schelssinger, R. H.; Quesada, M. L. *J. Am. Chem. Soc.* **1980**, 889.
(24) Steglich, W.; Hofle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.
(25) We thank Professor David E. Cane, Brown University, for providing authentic comparison spectra.

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Cubugene, a Diterpenoid with a Novel Carbon Skeleton from a Termite Soldier (Isoptera Termitidae Termitinae)

Summary: Cubugene (**1**), a unique diterpene hydrocarbon, was isolated from the Kenyan termite soldier *Cubitermes ugandensis* (Fuller), and the structure was elucidated together with its oxidation product (**2**).

Sir: The frontal gland secretion of *Cubitermes* soldiers (Isoptera Termidae Termitinae) is known to consist of diterpene hydrocarbons.[1] We now report the structure of cubugene (**1**), an unstable bicyclic diterpene occuring in the secretion gland of *Cubitermes ugandensis* soldiers, and its oxidation product (**2**).

The termite was collected from Eldama Ravine (elevation 2500 m) in Kenya. The soldiers (1200) were chilled and decapitated, and the heads were crushed in hexane to give 197 mg of crude extract. This was first chroma-

(1) Prestwich, G. D. *J. Chem. Ecol.* **1979**, *5*, 459; *Sociobiol.* **1979**, *4*, 127.

0022-3263/84/1949-2077$01.50/0