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. 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. Pentalenic acid has previously been prepared through a biogenetic-like synthesis from humulene.

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

Retrosynthetically, I 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.


two steps. Alkylation\(^{11}\) of the lithium enolate of methyl isobutyrinate with propargyl bromide (THF, -78 °C, 80% yield) followed by carbomethoxylation of the resultant terminal acetylene by the method of Tsujii\(^2\) (CO, PdC\(_2\), CuCl, NaOAc; 72% yield) provided diester 5.\(^3\) Exposure of 5 (Scheme II) to the Grignard reagent prepared from 2-chloro-6-methyl-5-heptene\(^4\) in the presence of added TMEDA and copper(I) iodide (THF, -78 to 25 °C) resulted in 1,4 addition\(^4,5\) and subsequent cyclization of the intermediate vinylcopper species to yield 48% of cyclopentene 6.\(^6\) Selective ozonolysis of the trisubstituted olefin (O, CH\(_2\)Cl, -78 °C; then Me& -78 to 25 °C) generated aldehyde 7. Treatment of 7 with carboxethoxy-methylenetriphenylphosphorane (CH\(_2\)Cl\(_2\), 40 °C, 6 h) provided the desired diester 4 in 81% yield from 6.

With ready access to the highly functionalized cyclopentene 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 mixture of diastereomers. Cleavage of the cyclobutane of 3 with lithium-ammonia\(^18\) at -78 °C led to a 13:1 mixture of spinpofused esters 2a:2b in 90% yield. Thus, the two major isomers obtained from the photocycladdition must contain the same relative stereochemistry at C-9 but are epimeric at the cyclobutyl carbon bearing the carboxethoxy group.

The excellent stereoselectivity\(^19\) in the photoannellation might be explained on thermodynamic grounds analogously to the system studied by Oppolzer.\(^9\) 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–carboxylation of the β-keto ester 2a (HCl, H\(_2\)O, HOAc, 6 h, reflux; 90% yield)\(^21\) provided acid 9 (mp 85.5–87 °C). Fischer esterification \([\text{CH}_2\text{OH}, (\text{CH}_2\text{O})_2\text{CH}]\) of the important triquinane pentalenic acid \([\text{C}_9\text{H}_8\text{O}]\) was hydrolyzed \((\text{KOH}, \text{H}_2\text{O}, \text{MeOH})\) to penta- lenic acid (1). Spectra of the methyl ester of synthetic 1 were identical with those of authentic samples.\(^24\)

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.

Acknowledgment. We are deeply indebted to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health (AI-20285) for generous financial support. Thanks are due to L. D. Bredon and Dr. D. H. Harris for help in recording 250-MHz \(^1\)H NMR spectra. We also thank Professor David E. Cane, Brown University, for providing us with authentic spectra of methyl pentalenate.

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

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

Sir: The frontal gland secretion of Cubitermes soldiers (Isoperta Termidae Termitinae) is known to consist of diterpene hydrocarbons.\(^1\) We now report the structure of cubogene (1), an unstable bicyclic diterpene occurring in the secretion gland of Cubitermes ugandensis soldiers, and its oxidation product (2).

The termitc was collected from Eldama Ravine (eleva- tion 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-

---


\(^{13}\) All new compounds gave satisfactory \((\pm 0.4\%)\) combustion analyses and consist of 250-MHz \(^1\)H NMR and infrared spectra.


\(^{25}\) We thank Professor David E. Cane, Brown University, for providing authentic comparison spectra.

Michael T. Crimmins,* Joe A. DeLoach
Venable and Kenan Laboratories
University of North Carolina
Chapel Hill, North Carolina 27514
Received February 9, 1984

---