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STEREOSPECIFIC SYNTHESIS OF *d,l*-CYCLOSATIVENE. ALKYNE CAPTURE OF AN HOMOALLYLIC CARBONIUM ION

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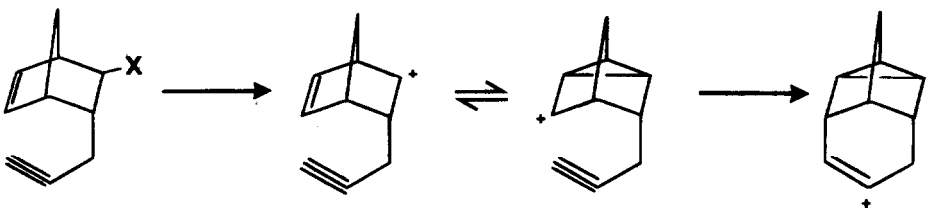
The sesquiterpene cyclosativene[1] 1 possesses unique molecular architecture that has attracted the attention of several groups of synthetic chemists. Two syntheses of cyclosativene have appeared.[2] We now wish to report a stereospecific synthesis of cyclosativene that incorporates a novel intramolecular capture of an homoallylic carbonium ion by an alkynyl side chain as the key carbon-carbon bond forming step (6 → 7).

Of the several mental dissections of 1 that suggest potential synthetic routes, we were attracted by the possibility that the basic ring system might be prepared by solvolysis of a suitably substituted norbornenyl compound as shown below. Model studies verified this prediction and demonstrated the superiority of the alkynyl substituent (versus alkenyl) in achieving the desired nucleophilic capture.[3] An application of these studies to the synthesis of cyclosativene is presented here.



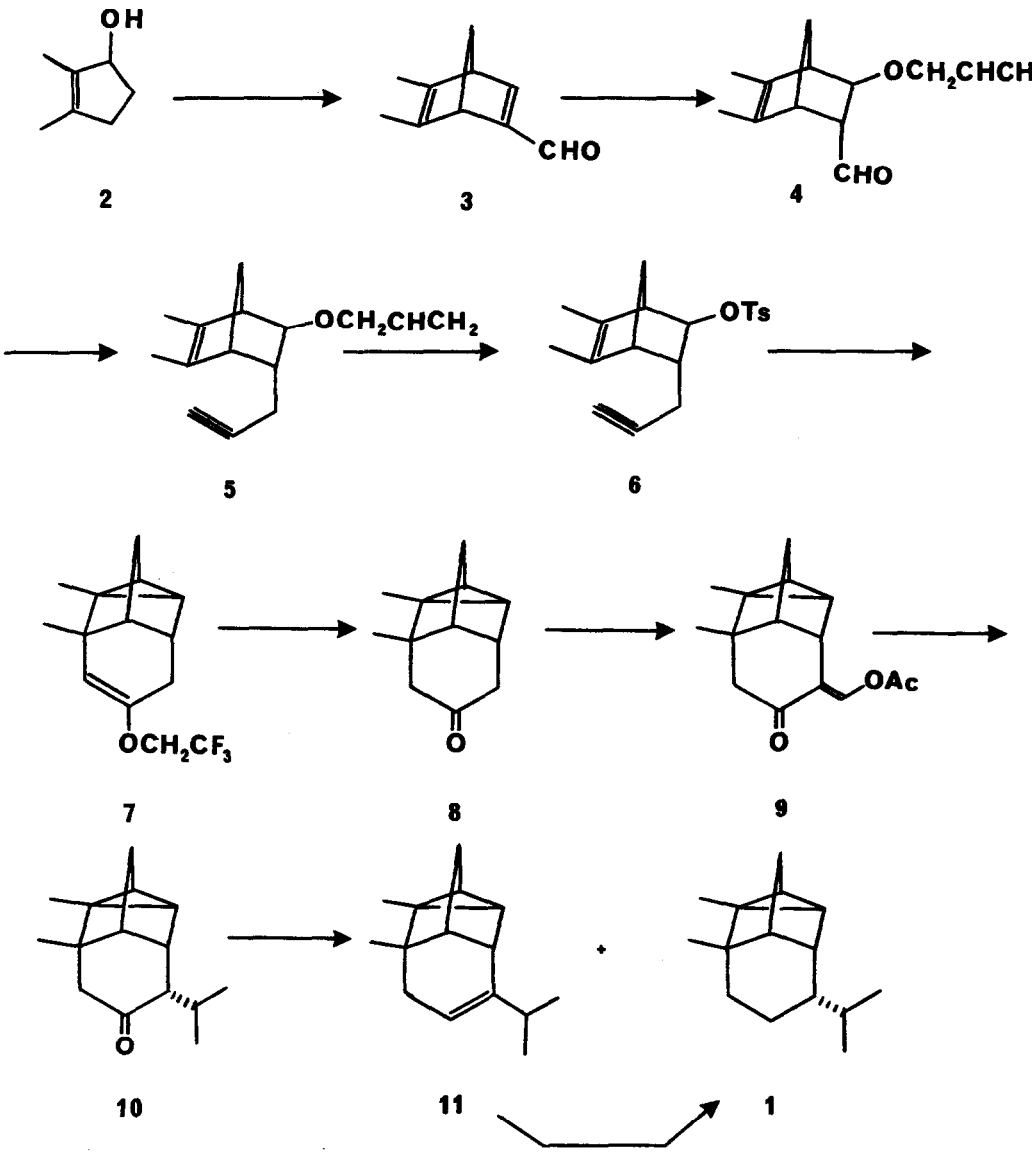
The preparation of the substituted norbornene 6 necessary for the solvolysis was efficiently carried out in eight steps. Reaction of 2,3-dimethylcyclopentadiene[4] (generated in situ

from allylic alcohol 2) with propynal afforded the difficultly purified Diels-Alder adduct 3. Exposure of crude 3 to excess allyl alcohol containing suspended potassium carbonate at 0° then yielded ether 4 as a single isomer (28% yield from 2). We have recently shown this process to be a convenient preparation of protected 3-exo-hydroxy 2-endo-acyl-5-norbornene derivatives.[5] Sequential treatment of 4 with $LiAlH_4$ and $(C_6H_5)_3P{\cdot}Br_2$[6] followed by displacement of the resultant bromide by the lithium acetylide•ethylenediamine complex in DMSO[7] produced alkyne 5 (36% yield). The allyl ether protecting group of 5 was cleaved (90%) by successive treatment with methyl lithium (to preform the acetylide anion) followed by reduction with sodium in liquid ammonia.[8] Acylation of the derived alcohol (TsCl, 92%) then afforded norbornene 6 suitable for subsequent solvolysis.

Dissolution of 6 in trifluoroethanol[9] containing two equivalents of pyridine led to the rapid formation of one major product (> 90% of all volatile products by gas chromatography).[10] Isolation and spectral analysis of this material revealed it to be enol ether 7 by virtue of its empirical formula ($C_{14}H_{17}F_3O$) and the presence of a single vinyl resonance (δ 4.35) and a methylene quartet for the $-OCH_2CF_3$ group (δ 3.98; J = 8 Hz) in the pmr spectrum. In addition sharp methyl resonances at δ 0.91 and δ 1.05 are consistent with the presence of the quarternary methyl groups on the nortricyclyl ring.[11] Further confirmation of the structure of 7 was obtained by the formation of ketone 8 (1722 cm^{-1}) on acidic hydrolysis (57% from 6).

Regiospecific introduction of the isopropyl group of cyclosativene was accomplished by the addition-elimination-addition reaction of $LiCu(CH_3)_2$ with enol acetate 9 as developed independently by Coates and Casey.[12] Treatment of 8 with sodium methoxide and ethyl formate in benzene produced a crystalline formyl compound (66% yield). Although the regiochemistry of the formylation was difficult to determine at this stage, the derived acetate 9 (90%) showed the product to be isomerically pure and with the anticipated regiochemistry. Particularly diagnostic were absorptions at δ 2.92 (allylic methine proton) and an AB quartet centered at δ 2.32 (isolated methylene adjacent to ketone). The reaction of 9 with $LiCu(CH_3)_2$ gave isopropyl ketone 10 as a single semi-crystalline product (90%), assumed to have the isopropyl group in the more stable equatorial configuration.

Removal of the ketone carbonyl was accomplished by reduction of 10 to the α-alcohol ($LiAlH_4$, 90%) and treatment of the subsequently derived mesylate (100%) with the mixed copper hydride reagent developed by Masamune[13] to give a 3/2 mixture of alkene 11 and cyclosativene 1.



Catalytic hydrogenation (5% Pd/C) of this mixture then afforded pure 1. Alternatively reaction of the mesylate with KOtBu/DMSO gave a mixture of alkenes which could also be smoothly reduced to cyclosativene. Spectra derived from synthetic *d,l*-cyclosativene produced by this route were identical in all respects with published data for the natural material.[11a]

Footnotes

1. L. Smedman and E. Zavarin, Tetrahedron Lett., 3833 (1968).

2. (a) J. E. McMurry, ibid., 55 (1969); (b) E. Piers, M. B. Geraghty, and M. Soucy, Synth. Commun., 3, 401 (1973).

3. S. W. Baldwin and J. C. Tomesch, manuscript in preparation.

4. (a) V. A. Mironov, E. V. Sobolev, and A. N. Elizarova, Tetrahedron, 19, 1939 (1963); (b) S. McLean and P. Haynes, ibid., 21, 2313 (1965).

5. S. W. Baldwin and J. C. Tomesch, J. Org. Chem., 39, 2382 (1974).

6. J. P. Schaefer, J. G. Higgins, and P. K. Shenoy, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N. Y., 1973, p. 249. The reaction was carried out with 1 equivalent of pyridine to remove the HBr byproduct.

7. W. N. Smith and O. F. Beumel, Jr., Synthesis, 441 (1974), and references cited therein.

8. The masking of a terminal alkyne as the sodium salt during the Na/NH_3 reduction of an internal alkyne has been reported. N. A. Dobson and R. A. Raphael, J. Chem. Soc., 3558 (1955).

9. We wish to thank Professor Kenneth Wiberg for initially pointing out the merits of this unique solvent. For leading references concerning trifluoroethanol as a solvolysis medium, see D. J. Raber, M. D. Dukes, and J. Gregory, Tetrahedron Lett., 667 (1974).

10. The remarkable nucleophilitity of sp carbon in cationic cyclizations has been observed by several workers; eg. (a) P. E. Peterson and R. J. Kamat, J. Amer. Chem. Soc., 91, 4521 (1969); (b) W. S. Johnson, M. B. Gravestock, R. J. Parry, R. F. Myers, T. A. Bryson, and D. H. Miles, ibid., 93, 4330 (1971) and accompanying communication; (c) R. L. Markezich, W. E. Willy, B. E. McCarry, and W. S. Johnson, ibid., 95, 4414 (1973), and accompanying communications; (d) W. D. Closson and S. A. Roman, Tetrahedron Lett., 6015 (1966); (e) H. Stutz and M. Hanack, ibid., 2457 (1974); M. H. Sekera, B. Weissman, and R. G. Bergman, J. Chem. Soc., Chem. Commun., 679 (1973).

11. (a) L. A. Smedman, E. Zavarin, and R. Teranishi, Phytochemistry, 8, 1457 (1969), (b) E. Piers, R. W. Britton, R. J. Keziere, and R. D. Smillie, Can. J. Chem., 49, 2623 (1971); (c) U. R. Nayak and S. Dev., Tetrahedron Lett., 243 (1963).

12. (a) R. M. Coates and R. L. Sowerby, J. Amer. Chem. Soc., 93, 1027 (1971); (b) C. P. Casey, D. F. Marten, and R. A. Boggs, Tetrahedron Lett., 2071 (1973); (c) C. P. Casey and D. F. Marten, Synth. Commun., 4, 321 (1973).

13. S. Masamune, P. A. Rossy, and G. S. Bates, J. Amer. Chem. Soc., 95, 6452 (1973). The ratio of the two products, 1 and 11, from this reaction was seemingly very sensitive to the concentration of the reducing agent. We can not be sure at this time whether the elimination product was derived from the copper hydride reagent or from some other basic contaminant.

14. Financial support from the Merck Foundation For Faculty Development and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. We are also indebted to Dr. David Rosenthal and Mr. Fred Williams of the Research Triangle Institute for Mass Spectrometry (supported by NIH grant RR 00330) for mass spectral determinations.