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THE CONSTRUCTION OF THE C/D RING SYSTEM PRESENT IN THE DITERPENOID ALKALOIDS ATISINE AND GARRYFOLINE

Russell A. Bell and Robert E. Ireland
Department of Chemistry, The University of Michigan
Ann Arbor, Michigan

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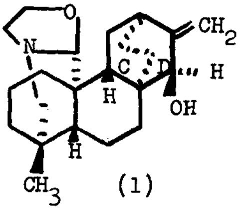
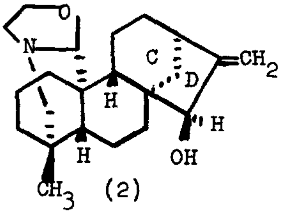
One phase of any successful totally synthetic approach to the construction of the diterpenoid alkaloids atisine (1)[1] and garryfoline (2)[1,2] must be the elaboration of the C/D bicyclic ring system. While a method for the construction of such ring systems would be premature without the availability of the necessary tetra- or pentacyclic substrates on which it could be applied, the recent successes of Edwards[3] and Shimizu[4] in this latter endeavor suggests the value of reporting a C/D ring system synthesis at this time.



(1)



(2)

We recently reported[5] the conversion of the unsaturated

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[1] For a recent review of the chemistry of these substances, see S. W. Pelletier, Tetrahedron 14, 76 (1961).

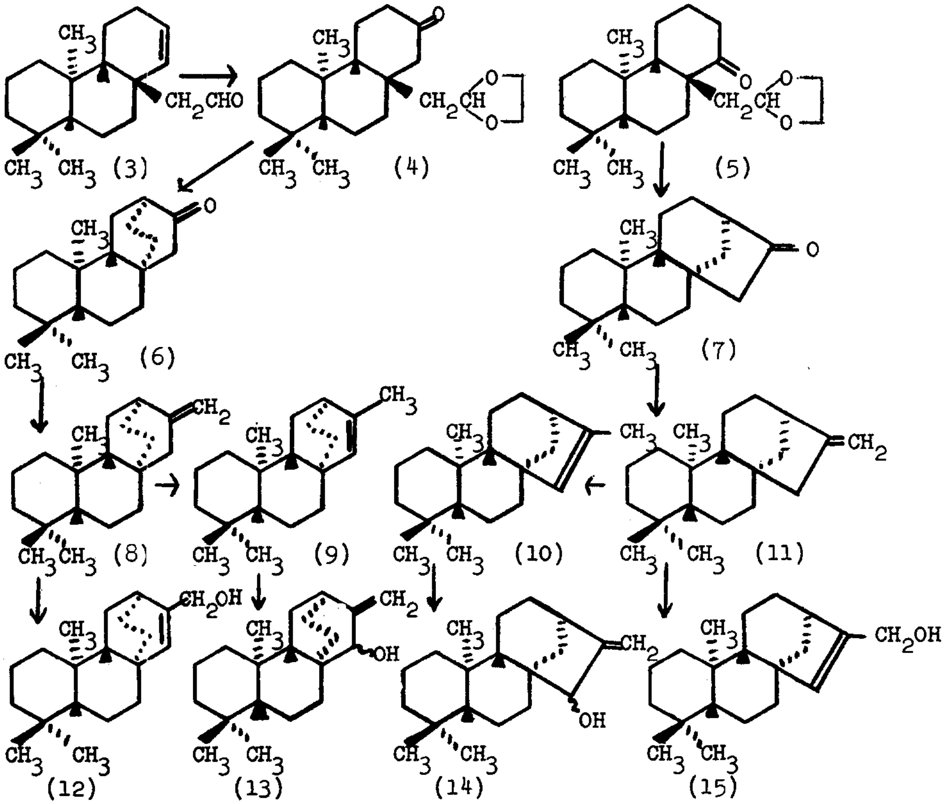
[2] C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Fegdor and J. Herran, J. Am. Chem. Soc. 77, 4801, 6633 (1955).

[3] J. W. ApSimon and O. E. Edwards, Can. J. Chem. 40, 896 (1962).

[4] I. Iwai, A. Ogiso and B. Shimizu, Chem. and Ind. 1288 (1962).

[5] R. A. Bell, R. E. Ireland and R. A. Partyka, J. Org. Chem. 27, 3741 (1962).

aldehyde (3)[*] to the 13-ketoacetal (4) and 14-ketoacetal (5), and the transformation of the latter to dl-kaurene (11). In this work it was observed that the desired bicyclic system was readily established by mild treatment of the ketoacetal (5)



with dilute aqueous mineral acid. We now find that the resulting hydroxy ketone may be converted to the ketone (7) (m.p. 122-

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[*] Although the formulae depicted represent only one enantiomer, they are taken to mean a racemate in every case unless otherwise specified.

123°; C, 83.16 ; H, 11.00) in 78% yield by modified Wolff-Kishner reduction[6] of the derived tetrahydropyranyl ether; conversion of the resulting desoxyether to the corresponding alcohol (m.p. 150-151.5°; C, 82.66 ; H, 11.62) with dilute aqueous mineral acid; and finally, oxidation of the alcohol with Jones reagent.[7] Treatment of the ketone (7) with methylenetriphenylphosphorane[8] led to an 86% yield of dl-kaurene (11), a portion of which was treated with iodine to generate a crystalline mixture rich in dl-<u>iso</u>kaurene (10).[9] While this latter transformation is reported[9] to afford pure isokaurene (10), the oxidations reported below indicate that the pure endocyclic olefin is not obtained, but rather an equilibrium mixture of the two olefins.

In a similar fashion we were able to effect the conversion of the 13-ketoacetal (4) to the corresponding exo- and endocyclic olefins (8) and (9) with the bicyclo-[2,2,2]-octane C/D ring system. Thus treatment of the 13-ketoacetal (4) with aqueous mineral acid led to the expected tetracyclic ketoalcohol (m.p. 210-212°; C, 78.4; H,10.49) in 95% yield, and modified Wolff-Kishner reduction[6] of the derived tetrahydropyranyl ether and then acid catalyzed cleavage and oxidation with Jones reagent[7]

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[6] D. H. R. Barton, D. A. J. Ives and B. R. Thomas, J. Chem. Soc. 2056 (1955).

[7] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, J. Chem. Soc. 39 (1946); see also C. Djerassi, R. R. Engle and A. Bowers, J. Org. Chem. **21**, 1547 (1956).

[8] G. Wittig and V. Schöllkopf, Ber. **87**, 1318 (1954).

[9] L. H. Briggs, B. F. Cain, R. C. Cambie, B. R. Davis and P. S. Rutledge, J. Chem. Soc. 1850 (1962).

afforded an 86% yield of the ketone (6) (m.p. 128.5-129.5°; C, 83.00; H,11.13). Treatment of this ketone (6) with methylene phosphorane[8] led smoothly to the exocyclic olefin (8) (m.p. 54-55.5°; C, 88.20; H, 11.90) in 90% yield, and this in turn was converted to the primary allylic bromide (m.p. 119-120°; C, 68.19; H, 9.22; Br, 22.81) in 73% yield with N-bromosuccinimide. Reduction of this bromide with lithium aluminum hydride then afforded a 93% yield of the pure, crystalline olefin (9) (m.p. 51-52.5°; C, 88.00; H, 11.68).

The introduction of the necessary 15-hydroxyl grouping into these two tetracyclic systems, and thus completion of this route to the C/D ring system of atisine (1) and garryfoline (2), was accomplished by photosensitized oxygen oxidation[10] of the isoölefins (9) and (10) to the rearranged allylic hydroperoxides which, without isolation, were reduced with lithium aluminum hydride to the desired allylic alcohols. In the case of the atisine analog two epimeric allylic alcohols were formed, one (m.p. 126-127°; C, 83.37; H, 11.30) in 20% yield and the other (m.p. 153-154°; C, 83.09; H, 11.13) in 29% yield. That these were indeed the desired 15-hydroxyolefins (13) was shown by the presence of bands ($\nu_{max.}^{HCCl_3}$ 1645 and 900 cm^{-1}) attributable to the terminal 16-methylene in their infrared spectra and the fact that a single different primary alcohol was obtained when the olefin (8) was subjected to the same oxidation-reduction sequence. This evidence coupled with the well-documented reports[11] that allylic rearrange-

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[10] A. Nickon and J. F. Bagli, J. Am. Chem. Soc. 83, 1498 (1961).

[11] G. O. Schenck, H. Eggert and W. Denk, Ann. 584, 177 (1953 and G. O. Schenck, Angew. Chem. 69, 579 (1957).

ment always accompanies oxidations under these conditions suffice to establish the structure of the secondary alcohols (13). No effort has been made at this time in this series to determine the stereochemistry of these epimeric alcohols, as the production of the two assures the success of the venture when applied to the necessary atisine precursor.

In the case of the garryfoline analog again two epimeric allylic alcohols (14) were formed; however, their separation in pure conditions proved more difficult. One isomer (m.p. 126-127°; C, 83.46; H, 11.12) was obtained in a pure condition, but the small quantities of dl-isokaurene (10) available for oxidation precluded isolation of the second epimer in a pure state. The mixture of the two epimers was obtained in 46% yield from the equilibrium mixture of dl-kaurene (11) and dl-isokaurene (10) along with a third alcohol. This material was shown to be the dl-primary alcohol (15)[9] (m.p. 121.5-122.5°; C, 83.17 ; H, 11.17) arising from dl-kaurene (11) still present in the dl-isokaurene (10) samples by comparison with a sample prepared by the oxygenation of pure dl-kaurene (11). Again the availability of both secondary alcohol epimers (14) from this process assures eventual success of the method when applied to a garryfoline precursor. Experiments in this direction are underway.

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