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GENERAL APPROACH FOR THE SYNTHESIS OF POLYQUINANES

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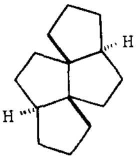
Summary: The diborane-mediated reduction of labile β-diketones 4, 5 and 6 has been employed as the key step in the synthesis of the three polyquinanes, all-*cis*-tetracyclo-[6.6.0.0^{1,5}.0^{8,12}]tetradecane 1, all-*cis*-tricyclo[6.3.0.0^{1,5}]undecane 2 and all-*cis*-tetracyclo-[5.5.1.0^{4,13}.0^{10,13}]tridecane, staurane 3, respectively.

During the last several years we have been involved in the development of a general synthetic route to polyquinanes[1] which has recently been expanded to polyquinenes.[2] In previous work, the three β-dicarbonyl compounds 4,[1] 5[1] and 6[3] were prepared in anticipation of their conversion into the parent hydrocarbons. It was subsequently found, however, that the β-dicarbonyl groups present in 4, 5 and 6, respectively, underwent retro-Claisen reactions on treatment with alkoxide[4] and ring-cleavage reactions in the presence of other nucleophiles. This behavior has been observed by Eaton *et al.*[5] in similar *cis*-bicyclo[3.3.0]octane-2,8-dione systems. To circumvent this problem an aldol approach was developed which resulted in the preparation of the 3,6,10,13-tetraene derivative of 1,[6] but this method failed when applied to the synthesis of the 2,5,8,11-tetraene derivative of 3.[7] However, during these studies it was found that the tetraone 4 could be reduced with borane-tetrahydrofuran to provide the corresponding tetrol 7 in 80% yield (Scheme I) with no apparent cleavage of the β-dicarbonyl carbon-carbon bonds. The reasons for the absence of ring-fragmentation reactions have been communicated.[7] The following paper describes the results of the diborane approach which culminated in a short synthesis of polyquinanes 1, 2 and 3.



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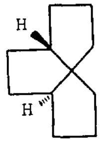

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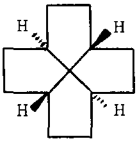

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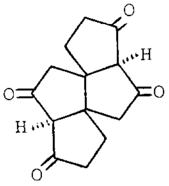

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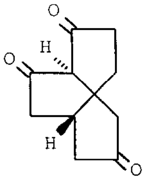

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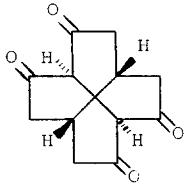
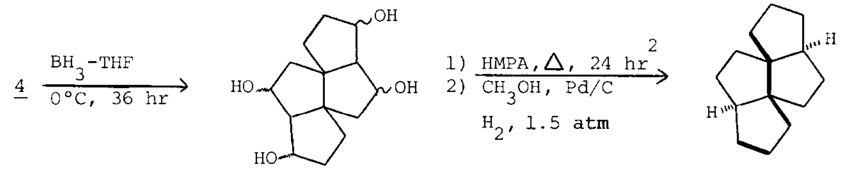


6

The tetraketone 4, available in gram quantities from earlier work,[1] was stirred with borane-tetrahydrofuran complex at 0°C for 36 hours. This procedure gave an 80% yield of the corresponding tetrol 7, as mentioned, and this material was subsequently heated in HMPA at reflux for 2 days. This furnished the 3,6,10,13-tetraene (80%) accompanied by a small amount of the bridgehead alkene (20%) in 65% overall yield (Scheme I).[6] Treatment of the mixture of alkenes with hydrogen in the presence of Pd/C cleanly gave the parent hydrocarbon 1[8] in 92% yield. The structure of 1 was proven by spectroscopy. The carbon spectrum was particularly informative for a seven line spectrum was observed in agreement with the C_2 axis of symmetry present in 1.

Scheme I

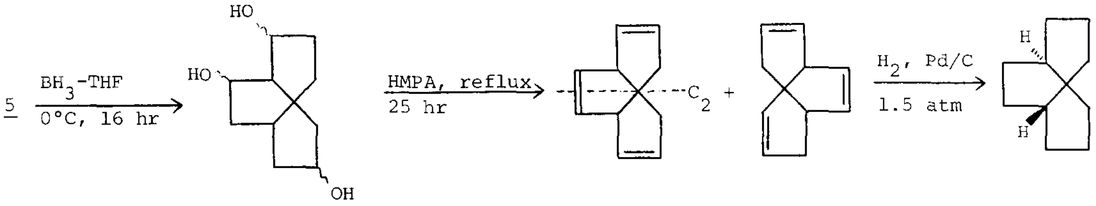


7, 80%

1, 92%

With this result in hand, attention now turned to the preparation of the triquinane 2. This molecule is interesting for it comprises the parent ring system of a number of polyquinane natural products,[9] moreover, the pentaene (i),[10] potentially derivable from 2, has been proposed by Wynberg[10] as a molecule of particular interest in regard to the planarization of tetracoordinate carbon. The triketone 5, available from levulinic acid via the method of Oehldrich et al.,[1,11] was stirred in borane-THF at 0°C for 16 hours. The reaction was quenched with methanol and the methanol removed with heat under reduced pressure to convert the boronic esters into trimethoxyboron, which can be easily removed. This procedure gave the triol 8[12] present as a mixture of stereoisomers in excellent yield. This material was then heated in refluxing HMPA[2,13] for 25 hours to provide two trienes, 9[14] and 10,[15] in a ratio of 43 to 57. The overall yield of this process varied from 65 to 70%. The structure of 9[14] was readily assigned from the carbon spectrum for this triene 9 clearly had a C_2 axis of symmetry which resulted in a six-line CMR spectrum.[14] The structure of the less symmetrical isomer 10 was deduced from the eleven-line CMR spectrum, as well as coupled and decoupled spectra (see reference 15 for details). Although these two trienes are potential intermediates on the route to the highly strained triquinane pentaene (i)[10] discussed by Wynberg,[10] in the present case the mixture of alkenes was simply reduced (Pd/C, H_2) to the parent hydrocarbon 2.[16] This provides, for the first time, a short, simple synthesis of 2.

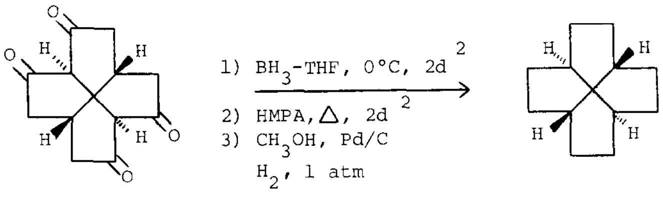
Scheme II



8, 90%   9 (43)   10 (57)   2, 92%

Finally, the synthesis of the [5.5.5.5]fenestrane, staurane 3, was completed via the same technique. As illustrated in Scheme III, the tetraketone 6 was converted in 92% yield into the stereoisomeric mixture of tetrols. The HMPA-mediated dehydration of this mixture gave staurane-tetraene,[2] accompanied by a small amount of the bridgehead isomer.[2] The mixture of alkenes was then reduced (Pd/C, H_2, CH_3OH, 1 atm) to furnish only one product and in 90% yield. The spectroscopic data [(GC-MS), ^1H NMR, and carbon spectrum (three lines)] of this material were identical to those of the all cis[5.5.5.5]fenestrane 3 recently reported by Keese.[17]

Scheme III



6   3

In summary, the B_2H_6-mediated (Lewis acid) reduction of the labile β-dicarbonyl groups of 4, 5 and 6 occurs without fragmentation of the five-membered rings. When this procedure is coupled with the HMPA-mediated dehydration of the corresponding alcohols the result is a simple route to polyunsaturated cyclopentanoid compounds.[2,6,7] These alkenes can then be converted (Pd/C, H_2) into their respective hydrocarbons with ease. The short, simple synthesis of polyquinanes 1, 2 and 3 serves to amply illustrate the generality of the method presented here.

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8. 1: oil (ir, neat) 2950 and 2875 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ1.00-1.70 (m,20H), 1.90 (m,2H); ^{13}C NMR (CDCl$_3$) 27.8 (t), 31.1 (t),35.8 (t), 36.5 (t), 39.3 (t), 50.8 (d), 63.9 (s); mass spectrum (EI), 190 (P, 30), 162 (100), 108 (31), 91 (41).
9. For some representative examples see: F. Bohlmann, N. Van, T. V. Pham, J. Jakupovic, A. Schuster; V. Zabel, W. H. Watson, Phytochemistry, 18, 1831 (1979); L. H. Zalkow, R. N. Harris III, D. Van Derveer and J. A. Bertrand, J. Chem. Soc., Chem. Commun., 456 (1977); F. Bohlmann and C. Zdero, Phytochemistry, 18, 1747 (1979); F. Bohlmann and J. Jakupovic, Phytochemistry, 19, 259 (1980); H. Seto, T. Saski, J. Uzawa, T. Settuo and H. Yonehara, Tetrahedron Lett., 4411 (1978); T. A. Eldrige, D. R. J. Laurs, J. D. McGuiness, A. M. Davis and P. v. R. Shannan, J. Chem. Soc., Perkin Trans. I, 1250 (1979).
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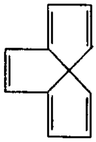

i

11. J. Oehldrich, J. M. Cook and U. Weiss, Tetrahedron Lett., 4549 (1976).
12. 8: oil (ir, neat) 3600-3200 cm^{-1}; mass spectrum (CI,CH$_4$) P+1, 199 (20), 181 (10), 163 (100), 145 (90). Anal. Calcd. for C$_{11}$H$_{13}$O$_3$: C, 66.67, H, 9.09. Found: C, 66.24, H, 9.02.
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14. 9: oil (ir, neat) 3047, 2930 and 802 cm^{-1}; ^{13}C NMR (CDCl$_3$) 48.26 (t), 65.50 (s), 66.92 (d), 128.78 (d), 131.69 (d) and 131.78 (d); mass spectrum (EI, 15 eV) 144 (P, 100), 129 (95), 115 (35), 105 (28), 91 (20).
15. 10: oil (ir, neat) 3047, 2930 and 802 cm^{-1}; ^{13}C NMR (CDCl$_3$) 36.99 (t), 44.17 (t), 56.40 (d), 56.46 (s), 63.15 (d), 127.49 (d), 128.09 (d), 130.64 (d), 132.87 (d), 135.48 (d), 137.22 (d); mass spectrum (CI,CH$_4$) 145 (P+1, 100). This material was contaminated with a small amount of the alkene 9.
16. 2: oil (ir, neat) 2937, 2859 and 501 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ0.90-2.10 (m); ^{13}C NMR (CDCl$_3$) 26.77 (t), 33.44 (t), 33.49 (t), 42.08 (t), 52.32 (d), 61.93 (s); mass spectrum (EI, 15 eV) 150 (7.6), 135 (13.3), 122 (100), 107 (72.7) and 93 (30.1).
17. M. Luyten and R. Keese, Angew. Chem. Int. Ed. Eng., 23, 390 (1984).
18. Unless otherwise stated all new compounds gave satisfactory C,H analysis and high resolution mass spectra.

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