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A New Strategy for the Synthesis of Spiro[4,5]decanes: A Formal Total Synthesis of Acorone

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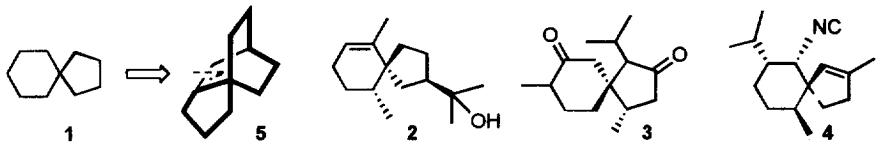
Abstract: A new strategy for the construction of spiro[4,5]decanes is described and involves a bridgehead substitution of a methoxyl group in **6** by a methyl group, followed by an oxidative cleavage resulting in a stereogenic spirocentre which culminated in the formal synthesis of acorone.

The spiro[4,5]decane **1** ring system, present in many natural sesquiterpenes, is represented by three groups, (i) spirovetivanes, e.g. hinesol **2**, (ii) acoranes, e.g. acorone **3**, and (iii) axoisonitrile **4**, which differ in the substitution of their functional groups. Although several syntheses[1] of natural spiro[4.5]decanes have been accomplished, they continue to interest the synthetic chemist because of (a) the difficulty in the construction of the stereogenic spirocentre and (b) delineating the relative stereochemistry of the functional groups. Earlier we reported[2] a synthesis of hinesol **2** by a new method which involved the construction of the spiro[4.5]decane framework by an oxidative cleavage of a tricyclo [7.2.1.$0^{1,6}$]dodecane derivative. Recently we have developed[3] a method for the bridgehead substitution of a methoxyl group by a methyl group in the bicyclic and tricyclic systems which culminated in the total synthesis of pupukean-2-one[3a] and *allo* cedrol.[3b] We now report a new strategy for constructing the spiro[4,5]decane framework through the bridgehead substitution method and the oxidative cleavage of the tricyclo [5.2.2.$0^{1,5}$]undecane framework (**5**→**1**) is exemplified by a formal total synthesis of acorone **3**, a sesquiterpene, isolated[4] from the sweet flag, *Acorus calamus* L.



Reaction of the ketone[5] **6** with BF_3\MeOH in dry CH_2Cl_2 afforded[3b,9] a (1:9) mixture of enones **7** and **8** readily separated by column chromatography. Addition of MeLi to **8** in ether gave the allylic alcohol[9] **9**, which smoothly rearranged in presence of catalytic aqueous perchloric acid to the tricyclic ketone **10** (2,4-DNP.,m.p 145°C). Reduction of **10** with DIBAL gave a separable mixture of *endo*- and *exo*-alcohols (**11** & **12**) in the ratio of 8:1. This mixture (**11** & **12**) was ozonized and subjected to oxidative work-up to afford the hydroxy-acid **13**, characterized as its methyl ester[9] **14**. Several methods[6] are known for the decarboxylative elimination of β-hydroxy-carboxylic acids to olefins. Attempted conversion of the hydroxy-acid **13** into the spiroketone **15** through the β-lactone formation by heating with N,N-dimethyl formamide dimethyl acetal failed. However, the decarboxylative elimination was finally accomplished by treating the acid **13** with Ph_3P\DEAD[7] in anhydrous THF, resulting in a (1:1) mixture of isomeric spiroketones[9] **15** & **16** in 60% yield, identical with the authentic[8] spectra of the mixture. Since the spiroketones **15** & **16** have earlier been converted into acorone, acoradiene and alaskene and related compounds, this constituted a formal total synthesis of acorone **3**.

In conclusion, we describe a facile approach for the stereospecific construction of a spiro[4,5]decane by the oxidative cleavage of a tricyclo[5.2.2.$0^{1,5}$]undecane, derived through the bridge-head substitution method, which is

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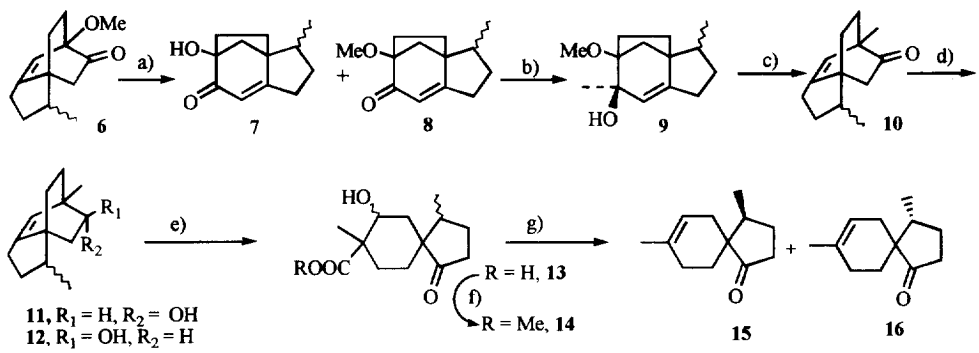
an intermediate in the synthesis of acorone. Application of this methodology to the synthesis of other natural sesquiterpenes possessing the spiro[4,5]decane framework is in progress.



a) BF_3/MeOH, CH_2Cl_2, 12h, 80% b) MeLi, Et_2O, 0°C, 90% c) cat H^+, CH_2Cl_2, 85%, d) DIBAL-H, THF, -78°C, 95% e) i) O_3, CH_2Cl_2, 40 min ii) H_2O_2, AcOH, H_2O, 12h, rt. f) CH_2N_2, ether, 0°C g) Ph_3P, DEAD, THF, 30 min, rt, 55% .

References & Notes:

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8. Marx, J.N.; Norman, L.R.; *J. Org. Chem.*, **1975**, *11*, 1602; We thank Prof. Marx for sending us the authentic spectra of **15** & **16**.
9. All the new compounds exhibited satisfactory spectral and analytical data. Spectral data for some selected compounds:

7: IR (Neat): γ_{max} 3440, 1660 and 1620 cm^{-1}. ^1H NMR (90MHz, $CDCl_3$): 0.93 and 1.06 (3H, d, J 7Hz, Me), 1.1-2.3(9H, m), 2.44-2.76(2H, m, allylic CH_2) and 5.9 (1H, m, =< H). **8:** IR (Neat): γ_{max} 1665, 1625 and 1320 cm^{-1}. ^1H NMR (90MHz, $CDCl_3$): 0.96 and 1.06 (3 H, d, J 7Hz, Me), 1.16-2.3 (9 H, m), 2.42-2.72 (2 H, m, allylic CH_2), 3.4 (3H, s, OMe), and 5.81 (1H, m, =< H). ^{13}C NMR (22.5MHz, $CDCl_3$): 12.6, 16.0, 24.6, 29.1, 29.6, 30.3, 30.7, 31.6,34.1, 38.7, 39.8, 42.6, 44.5, 53.2, 56.3, 56.8, 87.6, 88.7, 119.2, 179.3 and 199.6. m /z 206 (M^+); (Found : M^+, 206.1309. $C_{13}H_{18}O_2$ requires M, 206.1307). **9:** IR (Neat): γ_{max} 3420 and 1445 cm^{-1}. ^1H NMR (90MHz, $CDCl_3$): 0.95 (3H, d, J7Hz, Me) 1.2-2.4 (11H, m), 1.37 (3H, s, Me), 3.36 (3H, s, OMe) and 5.06 (1H, m, =< H). m/z 222 (M^+); (Found : M^+, 222.1605. $C_{14}H_{22}O_2$ requires M, 222.1620). **10:** IR (Neat): γ_{max} 1710 and 1440 cm^{-1}. ^1H NMR (90MHz, $CDCl_3$): 0.98 and 1.04 (3H, d, J7.2Hz. Me), 1.2 and 1.23 (3H, s, Me), 1.24-2.48 (11H, m), 5.47 (1H, m, =< H). ^{13}C NMR (22.5MHz, $CDCl_3$): 13.7, 14.2, 17.6, 25.4, 28.7, 29.0, 30.1, 31.9, 32.2, 34.0, 34.4, 40.0, 40.8, 41.6, 45.6, 48.3, 49.1, 120.8, 121.3, 156.0, 156.7, 213.6, and 214.0. m/z 190(M^+); (Found, M^+, 190.1337, $C_{13}H_{18}O$ requires,190.1339). **11:** IR (Neat): γ_{max} 3430 and 1640 cm^{-1}. ^1H NMR (90MHz, $CDCl_3$): 0.96 and 1.0 (3H, d, J 6.4Hz, Me), 1.1 & 1.16 (3H, two s, Me), 1.2 –2.48 (11H, m), 3.4 (1H, broad d, J 11.5Hz, HC-OH), 5.44 (1H, broad s, =< H): m/z 192 (M^+);(Found : M^+,192.1464; $C_{13}H_{20}O$ requires 192.1489). **14:** IR (Neat): γ_{max} 3430 and 1735 cm^{-1}. ^1H NMR (270MHz, $CDCl_3$): 1.04 and 1.08 (3H, two d, J 6Hz & 6.3Hz, Me), 1.16 and 1.19 (3H, two s, Me), 1.2-2.5(11H, complex), 3.32(1H, m, -CH-OH) and 3.77 and 3.8 (3H, two s, -COOMe). (Found C, 67.58, H, 8.23, $C_{15}H_{22}O_4$ requires C, 67.65, H, 8.33%). **15:** IR (Neat) γ_{max} 2950 and1735 cm^{-1}. ^1H NMR (90MHz, $CDCl_3$): 0.9 & 0.95 (3H, two d, J 6.4Hz, Me), 1.6 (3H, s, allylic Me), 1.6-2.4 (11H, complex), and 5.21 (1H, bs, =< H). m /z 178(M^+);[Found C, 80.50, H, 10.01; $C_{12}H_{18}O$ requires C, 80.85 and H, 10.18%].