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A NEW METHOD OF INTRODUCING THE ANGULAR METHYL GROUP INTO FUSED RING SYSTEMS

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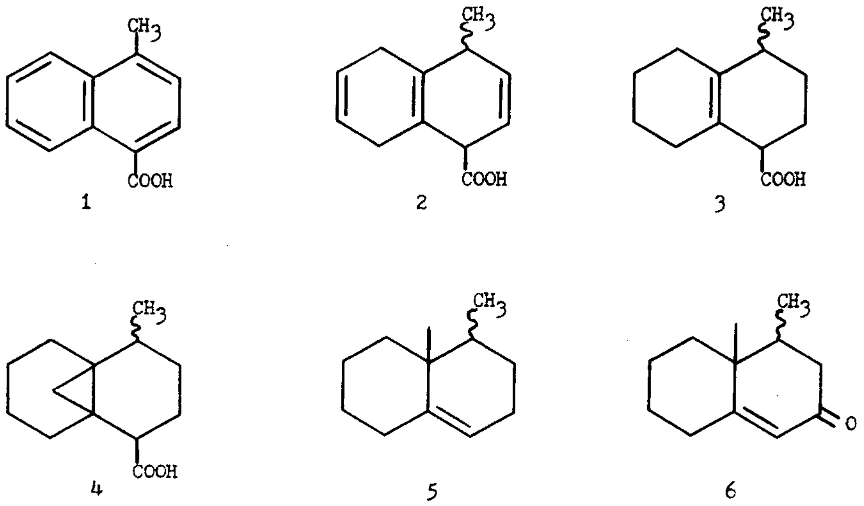
One of the pivotal operations in the total synthesis of polycyclic terpenoids is the stereospecific introduction of the angular methyl group (1). There is a limited number of methods for accomplishing the task; an entire synthesis may be based upon the intermediates necessary for generating this synthon (2). Most successful synthetic schemes are based on the Robinson annelation (3) or various modifications (1b,c,4,5) of this basic transformation.

Two large classes of intermediates excluded by use of the Robinson annelation are fused aromatic compounds and fused alicyclic ring systems. We should like to report here an alternative synthetic scheme, which makes use of these neglected intermediates. It should be of significant value in providing potential new routes to polycyclic terpenoids.

SCHEME I



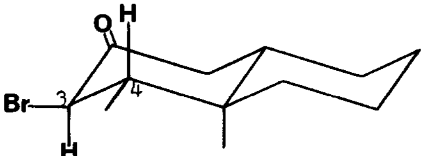
Scheme I outlines the synthesis of the *cis* and *trans* isomers of the dimethyloctalone 6. The *cis* isomer has the natural relationship of the methyl groups like the group of rearranged sesquiterpenes related to eremophilone (6).

The sequence started with 4-methyl-1-napthoic acid (7) which was smoothly reduced with $Li/NH_3/(CH_3)_2CHOH$ to a mixture of tetrahydro acids, *cis* (8) and *trans* (8) 2 (96%, *cis*/*trans*, 2/1, (9) *vide infra*). The *trans* isomer (mp. 180-182°) crystallized from the crude reaction product leaving the oily *cis* isomer almost pure. Each acid was carried through the remaining steps. Ethereal diazomethane formed the esters *cis* (8) and *trans* (8) 2 $COOCH_3$. Hydrogenation of the outside double bonds was carried out smoothly with PtO_2/ether. The *trans* ester gave a mixture of the desired *trans* 3 (8) $COOCH_3$ (79%) and 4-methyl-1,2,3,4-tetrahydro-1-napthoic acid (8) (21%); *cis* 2 $COOCH_3$ gave less disproportionation yielding *cis* 3 (8) (90%) plus the aromatic compound. Simmons-Smith (10) reaction of the esters 3 gave in each case a single compound assigned (11) the structures *cis* (8) (82%) and *trans* (8) (99%) 4 $COOCH_3$. Saponification gave crystalline acids *cis* (8) (mp 89-91°) and *trans* (8) (mp 62-63) 4.

Decarboxylation of the acids at reflux (200-220°, N_2) yielded in each case a single olefin; *cis* 4 giving *cis* 5 (8) (87%) and *trans* 4 giving *trans* 5 (8) (76%). The nmr spectra of the olefins were very similar showing one broad vinyl hydrogen; *cis* (τ4.83) *trans* (4.81), a singlet methyl; *cis* (9.07), *trans* (8.92), and a doublet methyl; *cis* (9.01, J = 5.0 Hz.), *trans* (9.13, J = 6.0 Hz). The overall yield from 2 to 5 was 38% in the *trans* series and 19% in the *cis* series.

The proof of structure of the olefins 5 and to which series it belonged *cis* or *trans* was accomplished by allylic oxidation with *tert*-butyl chromate (13). Each olefin gave a single, different α,β-unsaturated ketone as evidenced by ir and uv spectra. The ketone, *cis* 6 (8) (mp 63-4), derived from the oily acid, *cis* 2, gave nmr signals at τ9.09 (3H, d, J = 6.0 Hz), 8.95 (3H,S) and 4.42 (1H,s). The *cis* relationship of the methyl groups in this ketone was shown by the reduction, bromination sequence of Mac Leod (14) which led to the equatorial bromoketone 7 (8) (mp 131.5-132.5). The nmr spectrum of 7 showed a doublet (τ5.42, J = 12 Hz) for $C\underline{H}Br$. The high coupling constant requires an axial-axial, *trans*, relationship of this proton and the C-4 proton to which it is coupled. Thus the methyl groups are *cis*. The second ketone, *trans* 6 (8) was identical to a compound prepared by Coates and Shaw (15). The mass spectra of the two ketones revealed no major fragmentation differences and only small differences in the intensity of lines of a given m/e.

The same sequence has been carried out with two other systems, 8 giving 9 (8) and 10 giving 11 (8).



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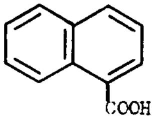

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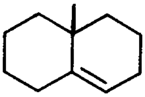

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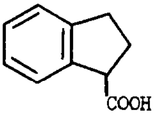

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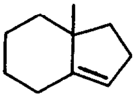

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5. A synthesis of tetrahydroeromophilone, which is not based on the Robinson annelation, has been reported by S. Murayama, D. Chan, and M. Brown, *Tetrahedron Lett.*, 3715 (1968).
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8. The indicated new compounds were fully characterized spectrally and gave acceptable microanalyses.

9. To our knowledge this is the first time that the sterochemical result of a Birch reduction of a 1,4-substituted aromatic system has been reported. cf. F. Camps, J. Coll and J. Pascual, *J. Org. Chem.*, **32**, 2563 (1967); G. W. Brown and F. Sondheimer, *J. Am. Chem. Soc.*, **89**, 7116 (1967).

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11. We have previously (12) shown that the carbomethoxy group directs formation of the cyclopropane *cis* to itself. Thus *cis* 4 has the carboxyl, the methyl and the cyclopropane ring all on one side of the plane defined by the decalin skeleton; *trans* 4 has the carboxyl and the cyclopropane ring on one side of the plane and the methyl on the opposite side.

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