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A NEW APPROACH TO THE BICYCLO[3.2.1]OCTANE RING SYSTEM: INTRAMOLECULAR MICHAEL AND ALDOL REACTIONS OF 3-(5-OXOHEXYL)-2-CYCLOPENTENONES.

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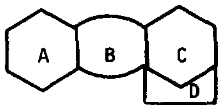
Bicyclo[3.2.1]octanes fused to other rings (general structure 1) are a basic structural unit found in various important natural products. Examples include the plant-growth stimulator gibberelic acid (2),[1] the antibiotic phlebiakauranol (3),[2] and the fragrant norsesquiterpene khusimone (4).[3] Synthetic strategies for construction of bicyclo[3.2.1]octanes fused to one other ring (*i.e.*, rings BCD of structure 1) have usually involved *sequential* construction of the three rings, with the most common approach being attachment of ring D onto a preformed BC system.[4] Coates' protocol involved attachment of ring B onto a preformed CD system,[5] and Trost's recent approach utilized bicycloannulation of ring C onto a spiro BD ring system.[4b] In each of these approaches a third ring is added to two existing carbocycles. A more convergent and biogenetically patterned strategy would involve elaboration of the BCD tricyclic array *directly* from a monocyclic precursor. Pattenden has suggested a photochemical variation of this convergent approach,[6] and Buchi has successfully used a monocyclic 5-(4-hexenyl)-1,3-cyclohexadiene in an intramolecular Diels-Alder cyclization followed by an acid-catalyzed skeletal rearrangement to form bicyclooctane khusimone (4).[3] Because of our interest in cyclopentanoid natural products,[7] we had occasion to prepare 3-(5-oxohexyl)-2-cyclopentenone 5 via a simple and efficient route as described in the accompanying communication.[8] We report here that monocyclic cyclopentenone 5 undergoes a mild, efficient, base-promoted, double cyclization to form a *tricycle* containing the bicyclo[3.2.1]octane ring system (eq. 1).



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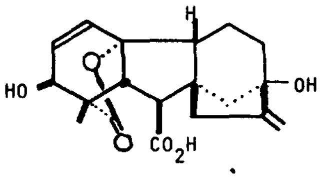

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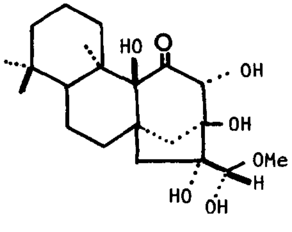

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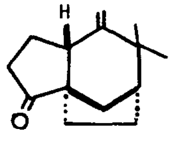

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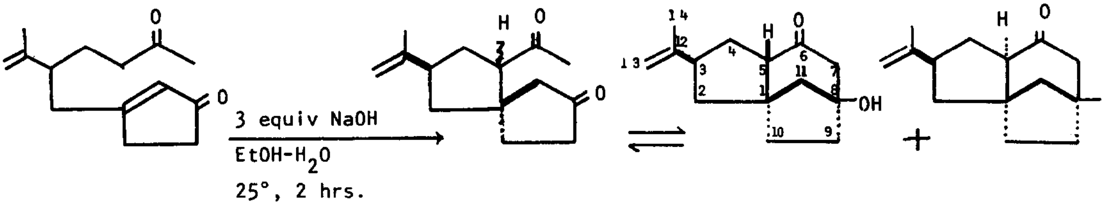


5 **6** **7a** **7b** (1)

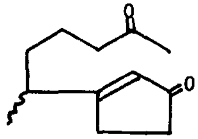
Exposing cyclopentenone **5** to sodium hydroxide in aqueous ethanol for 2 hours at 25° led to complete disappearance of the ir and nmr signals characteristic of cyclopentenone **5**. Repeated fractional crystallization of the crude product from chloroform and petroleum ether gave crystalline bicyclo[3.2.1]octanone **7a** and crystalline **7b** in 38% and 11% yields, respectively. The mother liquor had spectral properties consistent with spiro-cyclopentanone **6** (*e.g.*, a ^{13}C nmr signal at 213.23 ppm). Treating the mother liquor with sodium hydroxide in aqueous ethanol produced the same mixture of **6**, **7a** and **7b** as was formed from monocyclic cyclopentenone **5**. Likewise, ketols **7a** and **7b** when submitted to these conditions produced the same product distribution of **6**, **7a** and **7b**. Thus the initial Michael addition appears to be irreversible for this system under these conditions, whereas the subsequent aldol condensation seems to be reversible.

The major product, mp 112-112.5°C, displayed the following spectral data which are consistent with structure **7a**: ir ($CHCl_3$): 3600(m), 3430(b&m), 3080(w), 2995(sh), 2940(s), 2865(m), 1705(vs), 1640(m), 1450(m), 1375(m), 1350(m), 1320(m), 1280(m), 1155(m), 1135(m), 1070(m), 900cm^{-1}(s); ^{13}C nmr ($CDCl_3$): δ207.25(s, C_6), 148.07(q,C_{12}), 108.54(t,C_{13}), 80.02(s,C_8), 60.56(d,C_3), 56.13(t,C_2), 50.89(s,C_1), 49.80(t,C_7), 43.13(d,C_5), 41.86(t,C_{11}), 37.34(t,C_9), 30.09(t,C_4), 25.64(t,C_{10}), 20.70 (q,C_{14}); ^1H nmr ($CDCl_3$): δ4.6(s,2H), 2.85-2.4(m,5H), 2.4-2.0(m,2H), 1.95-1.3(m,11H); Mass spectrum (70eV, rel intensity): 220(M^+,76), 43(100); Anal. Calcd for $C_{14}H_{20}O_2 \cdot \frac{1}{3}H_2O$: C,73.32; H, 9.21. Found: C, 74.36; H, 9.02. This structural assignment was confirmed by x-ray measurements.[9]

The minor product (**7b**), mp 102-102.5°C, had very similar ir and ^1H nmr signals as those of the major product (**7a**). Very small differences in the ^{13}C nmr were evident: ^{13}C nmr ($CDCl_3$): δ207.10(s,C_6), 148.01(q,C_{12}), 108.66(t,C_{13}), 80.08(s,C_8), 60.68(d,C_3), 56.27(t,C_2), 51.02(s,C_1), 49.96(t,C_7), 43.28(d,C_5), 42.04(t,C_{11}), 37.22(t,C_9), 30.22(t,C_4), 25.78(t,C_{10}), 20.70(q,C_{14}).

From the spectroscopic similarity of these two products and the known 2-4:1 equilibrium distribution of closely related hydrindanones,[10] we concluded that bicyclo[3.2.1]octanes 7a and 7b were epimeric at C_5. Further support for the epimeric relationship at C_5 rather than at the isopropenyl-bearing C_3 center came from ^{13}C nmr which showed that the isopropenyl groups in both 7a and 7b had very similar chemical shifts (the largest difference being 0.18 ppm).

Monocyclic 3-(5-oxohexyl)-2-cyclopentenone 8 likewise underwent a base-promoted intramolecular Michael addition followed by an internal aldol cyclization to form a product with spectral data consistent with tricyclic ketol 9. Ketol 9 can be converted[11] into bicyclo[3.2.1]octanone 10 which is the key intermediate in Coates' total synthesis of (±)-zizaene.[5,12,13] The rapid, double cyclization of both methyl-substituted and isopropenyl-substituted 3-(5-oxohexyl)-2-cyclopentenones 8 and 5 suggests that this new approach may also be applicable to direct construction of tetracyclic arrays such as 1 from bicyclic precursors (e.g. 11).



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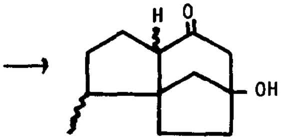

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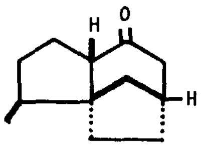

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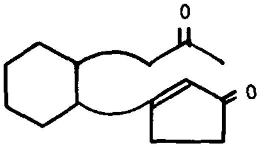

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We anticipate that application of this new, convergent, double cyclization approach will greatly facilitate total synthesis of various important bicyclo[3.2.1]octanes.

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