Enzymatic Resolution of Bicyclo[4.2.0]oct-2-en-7-ol and the Preparation of some Polysubstituted Bicyclo[3.3.0]octan-2-ones *via* Highly Strained Tricyclo[4.2.0.0^{1,5}]octan-8-ones

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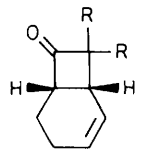
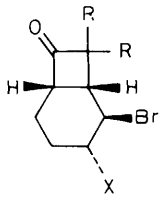
Several tricyclo[4.2.0.0^{1,5}]octan-8-ones (**13**)—(**19**) have been prepared and the crystal structure of one member of the series [compound (**14**)] has been determined; the strained tricyclic ketones react with a range of nucleophiles to give polysubstituted bicyclo[3.3.0]octan-2-ones.

Bicyclo[4.2.0]oct-2-en-7-ones (**1**)—(**3**) are readily prepared by cycloaddition of the appropriate ketene and cyclohexadiene.[1] Hydrodechlorination of ketone (**1**) gave the 8-unsubstituted compound (**4**). Derivatization of the alkene unit in compounds (**2**)—(**4**) occurred with high selectivity to give the bromo ketones (**5**)—(**10**).[2] The alcohols (**5**) and (**9**) were converted into the t-butyldimethylsilyl derivatives (**11**) and (**12**), respectively.

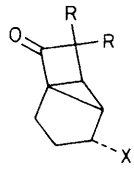
Treatment of the compounds (**6**)—(**8**) and (**10**)—(**12**) with potassium t-butoxide in ether gave the corresponding strained tricyclic compounds (**13**)—(**18**) in practically quantitative yield.[3] The formation of the tricyclo[4.2.0.0^{1,5}] ring system from compounds (**6**) and (**11**) was unexpected in the light of



(**1**) R = Cl
(**2**) R = Me
(**3**) R = Ph
(**4**) R = H



(**5**) R = H, X = OH
(**6**) R = H, X = OAc
(**7**) R = Me, X = Br
(**8**) R = Me, X = OAc
(**9**) R = Ph, X = OH
(**10**) R = Ph, X = OAc
(**11**) R = H, X = OSiMe$_2$Bu^t
(**12**) R = Ph, X = OSiMe$_2$Bu^t



(**13**) R = H, X = OAc
(**14**) R = Me, X = Br
(**15**) R = Me, X = OAc
(**16**) R = Ph, X = OAc
(**17**) R = H, X = OSiMe$_2$Bu^t
(**18**) R = Ph, X = OSiMe$_2$Bu^t
(**19**) R = Me, X = Cl

Figure 1

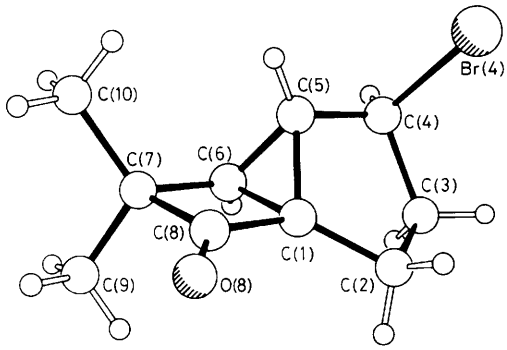
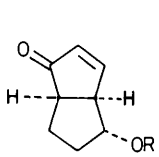


Figure 2. The molecular structure of (**14**). Selected bond lengths (Å) and angles (°): C(1)–C(2) 1.561(11), C(1)–C(5) 1.568(7), C(1)–C(6) 1.579(8), C(1)–C(8) 1.502(10), C(2)–C(3) 1.509(11), C(3)–C(4) 1.601(9), C(4)–C(5) 1.516(10), C(5)–C(6) 1.479(8), C(6)–C(7) 1.570(10), C(7)–C(8) 1.564(8) C(2)–C(1)–C(5) 112.0(6), C(2)–C(1)–C(6) 126.0(6), C(5)–C(1)–C(6) 56.1(3), C(2)–C(1)–C(8) 138.5(5), C(5)–C(1)–C(8) 107.5(5), C(6)–C(1)–C(8) 86.6(5), C(1)–C(5)–C(6) 62.3(4), C(1)–C(6)–C(5) 61.6(4), C(1)–C(6)–C(7) 92.6(5), C(6)–C(7)–C(8) 84.8(5), C(1)–C(8)–C(7) 95.9(4). Dihedral angles between rings: 5-ring/3-ring 73, 3-ring/4-ring 67, 4-ring/5-ring 49°. C(1) lies 0.12 A below the plane of its substituents [C(2), C(5), and C(8)], towards C(6).

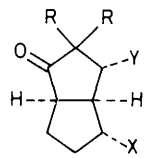
our earlier work on the corresponding bicyclo[3.2.0]heptan-6-ones.[4] For the smaller molecule, intramolecular attack is preferred through displacement of the bromide ion by C(7), while in the larger ring system, the carbanion at C(6) is the favoured participant in the reaction (Figure 1). This switch obviously results from a difference in the ability of the carbanion derived from the active methylene group to participate in the intramolecular S_N2 reaction at C(2) and almost certainly mirrors the change in the preferred conformation of the starting materials (Figure 1). We have argued that the bromine atom in the bicyclo[3.2.0] system is pseudoaxial (J_{12} ~0, J_{23} ~2 Hz);[5] in (**6**) and (**11**) the bromine atom is in an equatorial situation ($J_{12} \simeq J_{23}$ ~9 Hz) and must be less prone to attack by the C(8)-carbanion.

The tricycloalkanones (**13**) and (**17**) are relatively unstable and rearrange under acidic or basic conditions to give the enones (**20**) and (**21**), respectively, in 80—85% yield. On the other hand, the tricyclic compounds (**14**)—(**16**) and (**18**) are relatively stable and could be purified by column chromatography; the bromo ketone (**14**) was obtained in crystalline form (Figure 2).† The highly strained nature of the compound

† *Crystal data* for (**14**): $C_{10}H_{13}OBr$, M = 229.1, monoclinic, a = 8.821(3), b = 11.977(5), c = 10.923(4) Å, β = 111.86(3)°, U = 1071 Å^3, space group $P2_1/n$, Z = 4, D_c = 1.42 g cm^{-3}, μ(Cu-K_α) = 49 cm^{-1}. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. The structure was solved by the heavy atom method and refined anisotropically using absorption corrected data to give R = 0.062, R_w = 0.080 for 1270 independent observed reflections [$|F_o| \geq 3\sigma(|F_o|)$, $\theta \leq 58°$]. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.



(**20**) R = Ac
(**21**) R = $SiMe_2Bu^t$



(**22**) R = Me, X = Br, Y = SCH_2Ph
(**23**) R = Me, X = OAc, Y = I
(**24**) R = Me, X = OH, Y = N_3
(**25**) R = Ph, X = OH, Y = N_3
(**26**) R = H, X = $OSiMe_2Bu^t$, Y = SCH_2Ph
(**27**) R = Ph, X = $OSiMe_2Bu^t$, Y = CN

Table 1. Nucleophilic attack on tricycloalkanones (**14**)—(**18**).

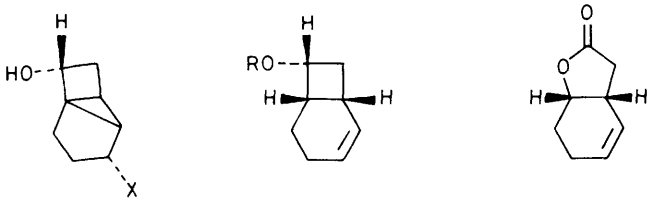
Substrate	Nucleophile (catalyst)	Product	Yield
(**14**)	$PhCH_2SH$ (piperidine)	(**22**)	87
(**15**)	NaI	(**23**)	50
(**15**)	NaN_3	(**24**)	63
(**16**)	NaN_3	(**25**)	50
(**17**)	$PhCH_2SH$ (piperidine)	(**26**)	61
(**18**)	Et_2AlCN	(**27**)	67

(**14**) obviously gives rise to the unusual steric arrangement of substituents around C(**1**) and some unexpected carbon–carbon bond lengths. For example, the angle C(2)–C(1)–C(8) is relatively large at 138.5°. Furthermore, the angle C(5)–C(1)–C(6) is pinched to 56.1° and the C(5)–C(6) bond is short (1.479 Å). The latter effects result in C(1) moving closer to the plane of the substituents C(2), C(5), and C(8). We believe that this is the first time that a detailed structural analysis has been achieved on a highly strained compound of the type represented by the ketone (**14**).

The unusual structure of the tricyclo[4.2.0.$0^{1,5}$]alkan-8-ones prompted us to examine the associated molecular orbitals. The S.C.F.-M.O. orbitals were calculated using the AM1 S.C.F.-M.O. method[6] for (**19**) [prepared from the alkene (**2**) by reactions complementary to those used to synthesise the ketone (**14**)]. The HOMO (E_1 −10.27 eV) consists of a combination of the in-plane carbonyl oxygen atom lone pair with the σ C–C bonds of the four-membered ring. The next highest occupied orbital (E_1 −10.61 eV) corresponds to the σ C–C bonds of the three-membered ring. These results suggest that the reaction of (**19**) with electrophiles might involve concomitant skeletal rearrangement. The LUMO comprised a normal π* orbital, but the closest equivalent bonding π orbital (E_1 −13.94 eV) involved a hyperconjugative interaction of the two α C–CH_3 σ bonds with the carbonyl oxygen atom lone pair, behaviour typical of cyclobutanone itself.

The tricycloalkanones (**13**)—(**18**) are highly susceptible to nucleophilic attack and a selection of the pertinent results is presented in Table 1. The nucleophilic attack is regiospecific and a highly substituted bicyclo[3.3.0]octan-2-one system is produced as a result. The diphenyltricycloalkanone (**16**) did not react with iodide ion, suggesting that the aromatic substituent(s) restrict(s) the approach of a bulky nucleophile to the adjacent electrophilic carbon atom, C(6). In contrast, reaction of the ketone (**17**) with lithium aluminium hydride in ether at low temperature gave the alcohol (**28**) (60% yield).

The potential usefulness of this route for the preparation substituted bicyclic compounds is considerably enhanced by the ready availability of bicyclo[4.2.0]octenone (**4**) in both enantiomeric forms through an enzyme catalysed enantio-



(28) X = $OSiMe_2Bu^t$ (29) R = H (30) R = COMe (31)

Table 2. Enzyme catalysed enantioelective hydrolysis of (**30**) by lipases.

Enzyme[a]	Amount of enzyme used/g [units]	t/h	Optical purity of alcohol (**29**)/%
Candida cylindracea lipase[b]	0.42 [21 000]	46	85
Mucor Miehei lipase[c]	4.0 [4000]	68	>98
Porcine pancreatic lipase (ppl)[d]	0.8 [8 800; Tai]	48	>98

[a] All reactions were performed in water (buffered with 0.1 M-phosphate) at 25 °C, pH 7.0, using 0.5—2.0 g substrate (**22**), and were stopped after 27 ± 3% conversion. [b] Supplied by Sigma Chemical Company. [c] Supplied by Nova Industri.

specific hydrolysis reaction. The ketone (**4**) was reduced with sodium borohydride to give the *endo*-alcohol (**29**) as the only product[7] and this alcohol was then converted into the acetate (**30**). Stirring this acetate with various lipases gave the optically active alcohol (−)-(**29**) {$[\alpha]_D^{23}$ −113° (*c* 22.2, ether)} and recovered acetate (Table 2).[7] The optical purity of the bicyclo-octenol was assessed by reacetylation, followed by ^1H n.m.r. spectroscopy using a chiral shift reagent. The absolute configuration of the alcohol was determined by Swern oxidation to afford the ketone (+)-(**4**), followed by Baeyer–Villiger oxidation which furnished the known lactone (−)-(**31**).[8] The dextrorotatory alcohol (+)-(**29**) was obtained by stirring the recovered acetate with ppl until no further hydrolysis took place; the acetate (enantiomeric excess >98%) was separated and treated with lithium aluminium hydride to give the optically pure dextrorotatory alcohol. In this way, the ketone (**4**) can be resolved on a multigram scale, providing sufficient material for synthesis. For example (+)-(**4**) {$[\alpha]_D^{23}$ + 94° (*c* 40.8, ether)} was converted into optically pure bicyclo-octanone (**21**) {$[\alpha]_D^{23}$ −130° (*c* 6.9, ether)} *via* the homochiral compounds (**6**) {$[\alpha]_D^{23}$ + 35° (*c* 7.0, ether)} and (**13**) {$[\alpha]_D^{23}$ + 100° (*c* 4.4, ether)}.

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