

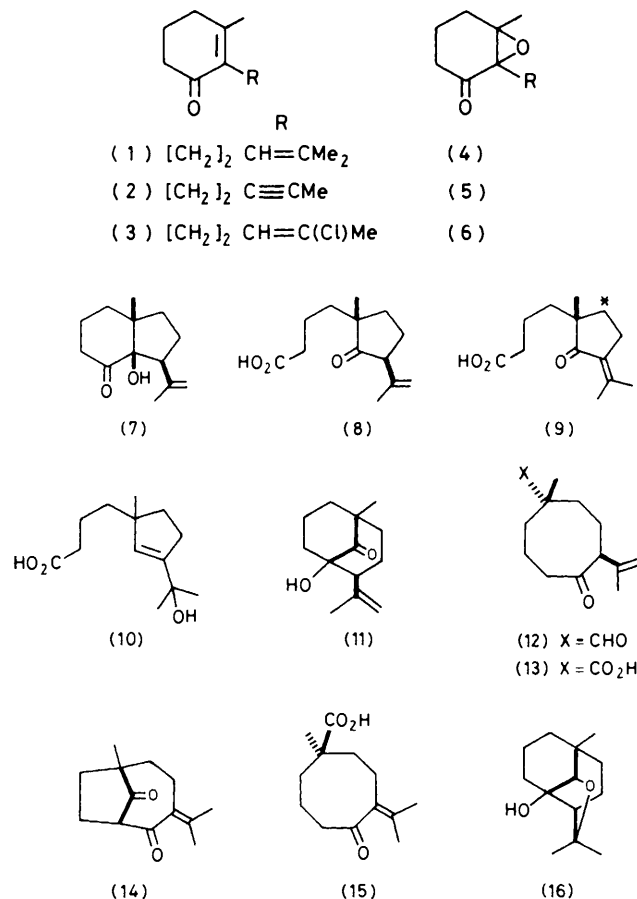
3-Methylcyclohex-2-enone Derivatives as Initiators of Cyclisation. Part 3.† Cyclisation to form Five-membered Rings

Joseph A. Amupitan, Edward G. Scovell, and James K. Sutherland *

Chemistry Department, The Victoria University of Manchester, Manchester M13 9PL

2-Substituted 3-methylcyclohex-2-enones and the derived epoxides have been cyclised to a variety of hydrindanone derivatives. When the 2-substituents are pent-3-ynyl or 4-chloropent-3-enyl the cyclisations take a predictable course; however, with 4-methylpent-3-enyl in the enone, the initial cyclisation product undergoes hydride and methyl migration. In the related epoxide an unexpected 'ene' reaction occurs.

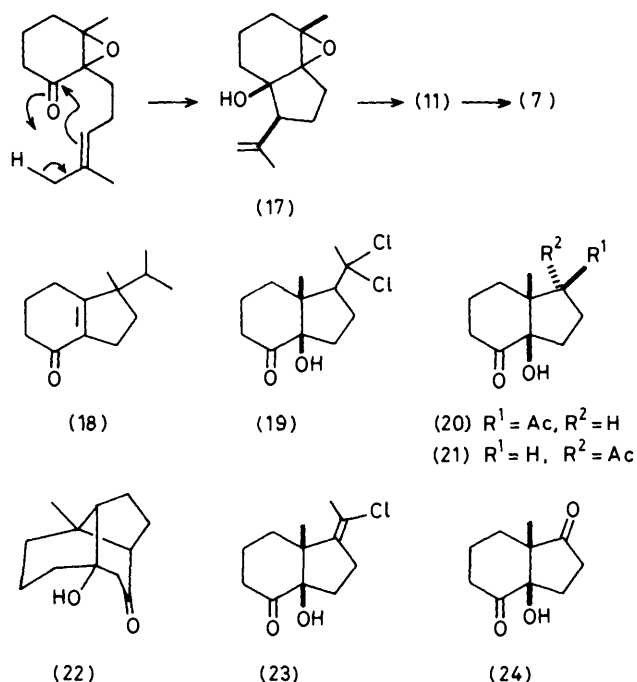
Cation-induced cyclisation of appropriate electronically unbiased alkenes predominantly favours six-membered ring formation¹ (6-*endo*-Trig) rather than five-membered ring formation (5-*exo*-Trig). When substitution on the alkene is electronically biased in favour of the latter such cyclisation does occur but is frequently followed by secondary processes such as hydride or alkyl migrations.² In order to test the feasibility of 5-membered ring formation using cyclohexenone derivatives as initiators, we examined the cyclisation of compounds (1)–(6). Reaction of (4) with SnCl₄–CH₂Cl₂ at –20 °C gave a product (94%), the analytical and spectroscopic properties of which [ν_{\max} . CHCl₃ 3 490 and 1 715 cm⁻¹; τ 9.0 (3 H, s), 8.3 (3 H, s), 6.15 (1 H, t, *J* 8 Hz), 5.26 (1 H, s), and 5.13 (1 H, s)] were in accord with those expected for the direct cyclisation product. However, degradation established the unexpected structure (7). NaBH₄ reduction of (7) gave a diol which was oxidized first with HIO₄ to a ketoaldehyde [τ 0.2 (1 H, t), 5.0br (1 H, s), 5.1br (1 H, s), 7.12 (1 H, dd), 8.2br (3 H, s), and 8.96 (3 H, s); ν_{\max} . CHCl₃ 1 735 cm⁻¹] and then with Jones' reagent to the acid (8) [ν_{\max} . 1 740 and 1 715 cm⁻¹; τ 5.1br (1 H, s), 5.2br (1 H, s), 7.16 (1 H, dd), 8.27br (3 H, s), and 9.0 (3 H, s)]. Treatment of (8) with acid or base converted it into (9) [ν_{\max} . 1 720 and 1 670 cm⁻¹; τ 7.78 (3 H, s), 8.17 (3 H, s), and 9.0 (3 H, s); λ_{\max} . (EtOH) 253 nm (ϵ 9 900)]. These spectroscopic data establish the structure of the latter compound as (9) or the isomer in which Me, (CH₂)₃CO₂H are bonded to C*; that the former is correct follows from reduction of (9) with NaBH₄ and acidic work-up to give (10) [τ 8.67 (6 H, s), 4.7 (1 H, t, *J* 1.2 Hz)]. These experiments allow the unambiguous assignment of constitution to (7). The relative stereochemistry of (7) was deduced from the constitution and stereochemistry of its precursor. If the cyclisation of (4) was carried out at –78 °C then ketol (11) (96%) was formed; reaction of (11) with SnCl₄ at –20 °C or with aqueous NaOH quantitatively converted it into (7). The structure of (11) was secured by the following degradation. NaBH₄ reduction of (11) gave a mixture of diols which were oxidized with HIO₄ to the aldehyde (12) [ν_{\max} . 1 740 and 1 705 cm⁻¹; τ 8.93 (3 H, s), 8.25 (3 H, s), 5.14br (1 H, s), 5.06br (1 H, s), and 0.6 (1 H, s)]. Jones' oxidation of (12) gave the acid (13) [τ 8.78 (3 H, s), 8.25 (3 H, s), 5.11br (1 H, s), and 5.04br (1 H, s)] which on treatment with toluene-*p*-sulphonic acid-benzene gave the dione (14) [λ_{\max} . (EtOH) 253 nm (ϵ 5 500); ν_{\max} . 1 740 and 1 685 cm⁻¹; τ 8.85 (3 H, s), 8.32 (3 H, s), and 8.15 (3 H, s)]. Basic hydrolysis of (14) yielded the acid (15) [λ_{\max} . 252 nm (ϵ 1 750); τ 8.80 (3 H, s), and 8.3 (6 H, s)]. These data unambiguously establish the constitution of (11). The relative stereochemistry of (11) was made apparent by conversion of one component of the mixture of derived diols from (11) [Hg(OAc)₂–water then NaBH₄] into the ether (16)



[τ 9.05 (3 H, s), 8.61 (3 H, s), 8.39 (3 H, s), and 6.61 (1 H, s)]; reaction of the diol mixture with aqueous HCl–EtOH converted both epimers into the ether (16). The increasing reduction in u.v. extinction coefficient and chemical-shift differences between the vinylic methyls in the series (9) to (14) to (15) presumably reflects the increasing departure from planarity of the cisoid enone systems.

The conversion of the epoxide (4) into the ketols (7) and (11) (which are simply related by a ketol shift) can be formulated in a number of ways. An itinerary which accounts for (11) as the kinetic product and (7) as the thermodynamic is Lewis acid catalysed 'ene' reaction (or Prins reaction) to the epoxyalcohol (17) which undergoes epoxide to ketone rearrangement (Lewis acid catalysis) to give the ketol (11). Thus the cyclisation of (4) is not an epoxy-olefin cyclisation whereas the corresponding reactions to form six-membered rings do involve direct substitution of the epoxide. Two possibilities

† Part 2, preceding paper.



to account for these differences are, first, that the formation of the decalin derivatives requires initial attack at the α -position followed by C and O migrations; similar reaction of (4) would lead to four-membered ring formation which is disfavoured compared to the 'ene' reaction. Two arguments against this route for the decalins are the di-equatorial ring opening and the 5-*endo*-Trig transition state required. We regard the second possibility as more likely, *viz.* that the activated complex leading to the 'ene' process is less strained than that leading to cyclisation. The greater thermodynamic stability of (7) compared with (11) would appear to contradict this but (7) exists in the 'non-steroid' conformation whereas the conformation of the activated complex leading to cyclisation would be 'steroid' if the rule of diaxial attack obtains.

Cyclisation of the enone (1) *via* enol trifluoroacetate gave the enone (18) (51%) [ν_{max} . CHCl_3 1 660 cm^{-1} ; λ_{max} . EtOH 249 nm (ϵ 12 000); τ 8.92 (3 H, s), 9.10 (3 H, d, J 7 Hz), and 9.24 (3 H, d, J 7 Hz)] in which hydride and methyl migrations followed the initial cyclisation. These processes have ample precedent.³ Reaction of the epoxide (6) with $\text{BCl}_3\text{-CH}_2\text{Cl}_2$ at -78°C gave the ketol (19) (54%) [ν_{max} . 3 480 and 1 710 cm^{-1} ; τ 7.80 (3 H, s) and 8.85 (3 H, s)]. Degradation in the standard way gave a cyclopentanone (ν_{max} . 1 740 cm^{-1}) which did not eliminate HCl under conditions where β -chloro-ketones might be expected to dehydrochlorinate. The enone (3) cyclised with $(\text{CF}_3\text{CO})_2\text{O-CF}_3\text{CO}_2\text{H}$ to give, after hydrolysis, a mixture (34%) of hydrindanones (20) [ν_{max} . 1 710 cm^{-1} ; τ 7.89 (3 H, s) and 8.95 (3 H, s)] and (21) [ν_{max} . 1 710 cm^{-1} ; τ 7.81 (3 H, s) and 8.72 (3 H, s)]. The same products (49%) were obtained by cyclisation of the alkyne (2) when the presumed intermediate bis-trifluoroacetate was hydrolysed with $\text{NaHCO}_3\text{-MeOH}$. When the cyclisation product was treated with KOH-MeOH the ketol (22) (54%) [ν_{max} . 3 580 and 1 705 cm^{-1} , τ 7.43 (1 H, d, J 17.5 Hz), 7.81 (1 H, d, J 17.5 Hz), and 9.03 (3 H, s)] was isolated. Similar treatment of a mixture of (20) and (21) gave aldol condensation product (22).

Cyclisation of the epoxide (5) with $\text{SnCl}_4\text{-CH}_2\text{Cl}_2$ gave the hydrindanone (23) (94%) [ν_{max} . 3 490 and 1 715 cm^{-1} ; τ 7.85 (3 H, t, J 1.5 Hz), and 8.96 (3 H, s)]. These data do not allow ready distinction between five- or six-membered ring cyclis-

ation products but on ozonolysis (23) was converted into the dione (24) [ν_{max} . 3 490, 1 750, and 1 710 cm^{-1} ; τ 8.96 (3 H, s)]. This preference for 5-*exo*-Dig cyclisation with electronically unbiased alkynes is in accord with previous work.

Experimental

For general comments see Part 2.

Cyclisation of Epoxide (4).—(a) SnCl_4 (0.5 ml) was added dropwise during 10 min to a stirred solution of the epoxide (4) (533 mg) in anhydrous CH_2Cl_2 (20 ml) at -78°C under dry N_2 . After 1 h further SnCl_4 (0.1 ml) was added and after 45 min the reaction mixture quenched with aqueous NaHCO_3 . Work-up in the usual way gave the oily ketol (11) (528 mg) (Found: C, 75.0; H, 9.6. $\text{C}_{13}\text{H}_{20}\text{O}_2$ requires C, 75.0; H, 9.7%).

(b) SnCl_4 (0.5 ml) was added dropwise to a stirred solution of the epoxide (325 mg) in anhydrous CH_2Cl_2 (15 ml) at -78°C under dry N_2 . After 2 h t.l.c. indicated that conversion into (11) was complete and the reaction mixture was allowed to warm to -20°C . More SnCl_4 (0.4 ml) was added and after 2 h the reaction mixture was quenched with aqueous NaHCO_3 . Work-up in the usual way gave the oily ketol (7) (Found: C, 75.1; H, 9.6%).

The ketol (7) could also be prepared from the ketol (11) by treatment with 3M-NaOH (1) and EtOH (2).

Degradation of the Ketol (7).—The ketol (253 mg) in 95% EtOH was reduced with NaBH_4 (215 mg) over 12 h at 25°C . Work-up in the usual way gave a mixture of diols (232 mg) as an oil [τ 6.14–6.44 (1 H) (Found: M^+ 210.1615. Calc. for $\text{C}_{13}\text{H}_{22}\text{O}_2$: 210.1620)]. The diols (37 mg) in THF (3 ml) and H_2O (1 ml) were treated with NaIO_4 (95 mg). After 4 h, work-up in the usual way gave an unstable ketoaldehyde (M^+ 208.1463. $\text{C}_{13}\text{H}_{20}\text{O}_2$ requires M 208.1463).

The ketoaldehyde (200 mg) in Me_2CO (10 ml) was oxidised by dropwise addition of Jones' reagent until the supernatant solution showed a permanent red colour. Work-up in the usual way yielded the ketoacid (8) (117 mg), m.p. 56–58 $^\circ\text{C}$ (EtOAc–pentane) (Found: C, 69.3; H, 9.2. $\text{C}_{13}\text{H}_{20}\text{O}_3$ requires C, 69.6; H, 9.0%).

1M-NaOH (8 drops) was added to a solution of the ketoacid (8) (37 mg) in 95% EtOH (2 ml) and the mixture stirred for 1 h. Acidification and work-up in the usual way gave the oily enone (9) (18 mg) (M^+ 224.1418. $\text{C}_{13}\text{H}_{18}\text{O}_2$ requires 224.1412). Reaction of (8) with toluene-*p*-sulphonic acid–benzene at reflux gave the same product.

NaBH_4 (40 mg) was added to a solution of the enone (9) (18 mg) in 95% EtOH (2 ml). After 12 h the solution was acidified with 2M-HCl and worked up in the usual way to give the rearranged alcohol (10) (11 mg) as a viscous oil which showed a single spot on t.l.c. (Me_2CO) (M^+ 226.1565. $\text{C}_{13}\text{H}_{22}\text{O}_3$ requires M 226.1569).

Degradation of the Ketol (11).—Compound (11) (257 mg) was reduced with NaBH_4 (300 mg) and worked up as before to yield a mixture of diols (219 mg), m.p. 68–78 $^\circ\text{C}$ [light petroleum (b.p. 40–60 $^\circ\text{C}$)] (Found: M^+ 210.1621. Calc. for $\text{C}_{13}\text{H}_{22}\text{O}_2$: M , 210.1620).

The diols (147 mg) were cleaved with NaIO_4 (391 mg) as described previously. The ketoaldehyde (12) was obtained as a pale yellow oil (138 mg) (single spot on t.l.c.) (M^+ 208.1465. $\text{C}_{13}\text{H}_{20}\text{O}_2$ requires M 208.1463).

Jones' reagent was added dropwise to a stirred solution of the ketoaldehyde (136 mg) in Me_2CO (2 ml) at -20°C until a permanent (>5 min) red colour was observed. MeOH was added and the mixture allowed to warm to ambient temperature. After most of the Me_2CO and MeOH had been re-

moved under reduced pressure work-up in the usual way gave the *ketoacid* (13) (53 mg), m.p. 97–101 °C (aqueous MeOH) (Found: C, 69.6; H, 9.0. $C_{13}H_{20}O_3$ requires C, 69.6; H, 9.0%).

Toluene-*p*-sulphonic acid (10 mg), the *ketoacid* (13) (138 mg), and benzene (15 ml) were refluxed under N_2 for 12 h. Work-up in the usual way gave the *dione* (14) (56 mg), m.p. 80–81 °C (MeOH) (Found: C, 75.3; H, 8.7. $C_{13}H_{18}O_2$ requires C, 75.7; H, 8.8%).

1M-NaOH (0.5 ml) was added to the *dione* (14) (19 mg) in 95% EtOH (2 ml) and the solution refluxed for 1 h. After acidification, work-up in the usual way gave the oily *acid* (15) (18 mg) (single spot on t.l.c.) (Found: M^+ 224.1417. $C_{13}H_{20}O_3$ requires M 224.1412). The same product could be obtained by base catalysed isomerisation of (13).

The diol mixture ex. (11) (81 mg) in THF (1 ml) was mixed with $Hg(OAc)_2$ (356 mg) in water (1 ml). After 3 h $NaBH_4$ (114 mg) in water (1 ml) was added cautiously to the mixture, followed by 3M-NaOH (1 ml). Work-up in the usual way gave a 1 : 1 mixture (as judged by n.m.r. and t.l.c.) of an unchanged diol and an ether. The two components could be separated by chromatography. However, treatment of the mixture in EtOH (4 ml) with 15% aqueous HCl (2 ml) caused complete conversion into the *ether* (16) (Found: M^+ 210.1617. $C_{13}H_{22}O_2$ requires M 210.1620).

Cyclisation of the Enone (1).—The enone (1) (150 mg) was dissolved in CF_3CO_2H (4 ml) and $(CF_3CO)_2O$ (2 ml). After 3.5 h at ambient temperature most of the solvent was evaporated under reduced pressure and the residue solvolysed with $NaHCO_3$ (200 mg) in CH_3OH (10 ml). Work-up in the usual way gave an oil which was purified by preparative t.l.c. with Et_2O -pentane (1 : 1) as eluant to give the *enone* (18) (98 mg) (Found: M^+ 192.1511. $C_{13}H_{20}O$ requires M , 192.1514).

Cyclisation of Epoxide (5).—Stannic chloride (200 μ l) was added dropwise to a solution of (5) (137 mg) in CH_2Cl_2 (10 ml) at -78 °C under N_2 . After 0.5 h saturated aqueous $NaHCO_3$ was added and then Et_2O . Work-up in the usual way gave the *ketol* (23) (154 mg) as a pale yellow oil. An analytical sample was prepared by chromatography (Found: C, 63.3; H, 7.5; Cl, 15.4. $C_{12}H_{17}ClO_2$ requires C, 63.1; H, 7.5; Cl, 15.5%). Substitution of $TiCl_4$ for $SnCl_4$ gave an identical result.

Ozonolysis of (23).—Ozone was passed through a solution of the *ketol* (23) (154 mg) in CH_2Cl_2 (5 ml) at -78 °C until no starting material remained (t.l.c.; ca. 3 h). Dimethyl sulphide was added and the mixture worked up in the usual way to give an oil (90 mg). Chromatography on silica gel and elution with Et_2O -light petroleum (b.p. 40–60 °C) (10 : 1) gave the *dione* as an oil (36 mg) (Found: M^+ 182.0947. $C_{10}H_{14}O_3$ requires M 182.0943).

Cyclisation of Epoxide (6).—Boron trichloride (ca. 1 g) was added to the epoxide (6) (400 mg) in CH_2Cl_2 (15 ml) at -78 °C

under N_2 . After 1.5 h saturated aqueous $NaHCO_3$ was added and the mixture worked up in the usual way to give an oil (432 mg) which was chromatographed on silica gel. Elution with Et_2O -hexane (1 : 1) gave the *dichloride* (19) (232 mg), m.p. 80–81 °C [light petroleum (b.p. 60–80 °C)] (Found: M^+ 264.0682. $C_{12}H_{18}Cl_2O_2$ requires M 264.0684).

Cyclisation of the Enone (3).—A mixture of CF_3CO_2H (8 ml) and $(CF_3CO)_2O$ (4 ml) cooled to 0 °C was added to the ketone (3) (500 mg). After 6 h, work-up in the usual way gave an oil (572 mg) which was stirred with saturated aqueous $NaHCO_3$ for 2 h and worked up in the usual way to yield an oil (366 mg) which was chromatographed on silica gel. Elution with Et_2O -hexane (1 : 1) gave three fractions. Fraction 1 (128 mg) was a mixture of at least four components (t.l.c.), fraction 2 (114 mg) was a mixture of two components, and fraction 3 (68 mg) a pure compound identical with one of the components of fraction 2. The latter was resolved by preparative t.l.c. [4 elutions with Et_2O -hexane (2 : 1)] to give the less polar β -*acetylketone* (20) (45 mg) and the α -*acetylketone* (21) (127 mg after combination with fraction (3) [Found: M^+ (α) 194.1309; (β) 194.1308. $C_{12}H_{18}O_2$ requires M 194.1307].

Cyclisation of the Enone (2).—The ketone (2) (150 mg) in CF_3CO_2H (3 ml) and $(CF_3CO)_2O$ (1.5 ml) was stirred at ambient temperature for 2.5 h. Evaporation under reduced pressure followed by work-up in the usual way gave an oil which was treated for 1 h at ambient temperature with 20% KOH-MeOH (20 ml). Work-up in the usual way gave a product which was dissolved in $CHCl_3$ (3 ml) and pentane- Et_2O (1 : 1) added to precipitate the *ketol* (22) (97 mg), m.p. 110–112 °C (hexane) (Found: M^+ 194.1309. $C_{12}H_{18}O_2$ requires M 194.1307).

When the cyclisation product was hydrolysed with 10% $NaHCO_3$ - CH_3OH the product could be shown to contain (20) and (21) and separated as above to give the β -isomer (20) (27 mg) and α -isomer (21) (30 mg).

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References

- 1 W. S. Johnson, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 9.
- 2 K. A. Parker and W. S. Johnson, *J. Am. Chem. Soc.*, 1974, **96**, 2556.
- 3 N. L. Wendler in 'Molecular Rearrangements,' ed. P. de Mayo, Interscience Publishers, New York, 1964, Part 2, p. 1099.

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