# A New Intramolecular Aldol based Route to Benzannelated Bicyclo[3.3.1]nonane Derivatives

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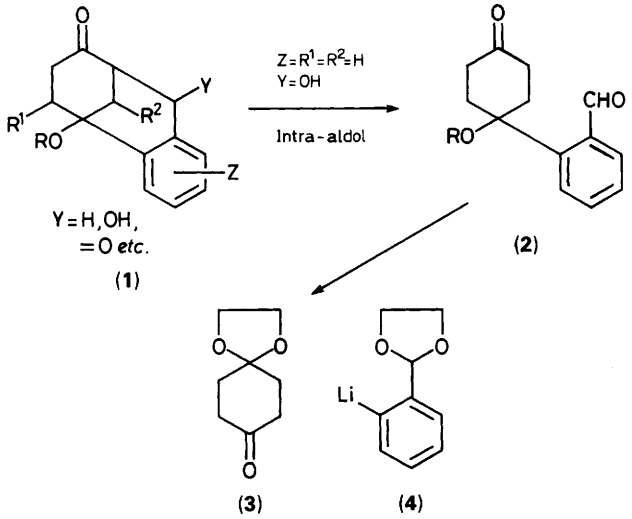
A synthetic route to the title compounds is described based on the addition of 2-lithiobenzaldehyde ethylene ketal to cyclohexane-1,4-dione ethylene ketal followed by acid-catalysed deprotection and *in situ* intramolecular stereospecific aldol cyclisation, which gives 8-hydroxy-1-methoxytricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-trien-10-one (**1a**); the synthetic potential of the methodology for preparation of various derivatives is described.

As part of a programme to design and synthesise novel analgesics, we required an efficient route to benzannelated bicyclo[3.3.1]nonanones (**1**) that would be of utility for the preparation of a range of derivatives as shown in Scheme 1. The parent hydrocarbon, tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene, is known but the synthetic route is not adaptable to the preparation of functionalised derivatives such as (**1**).[1] A review of published synthetic approaches to bicyclo[3.3.1]-nonanones reveals that most utilise annelation between C-2 and C-6 of cyclohexanones and therefore result in the

formation of 9-keto-derivatives, *i.e.*, the carbonyl group is on the one carbon bridge.[2] In addition, the published approaches to bicyclo[3.3.1]nonanes have been described as involving 'monumental labor'[3] and so provide little inspiration for the task in hand. A novel approach to compounds of type (**1**) was therefore required.

Retrosynthetic analysis indicated that one of the shortest routes to compounds (**1**) (Y = OH) was based on the intramolecular aldol approach as shown in Scheme 1. Given that the key cyclisation precursor (**2**) appeared to be readily accessible from commercially available cyclohexane-1,4-dione ethylene ketal (**3**) and a 2-metallated benzaldehyde derivative (**4**), this approach was explored (Scheme 2).

Treatment of cyclohexane-1,4-dione ethylene ketal (**3**) with




Scheme 1

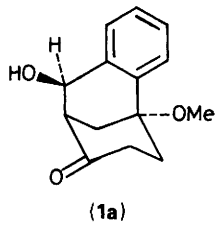
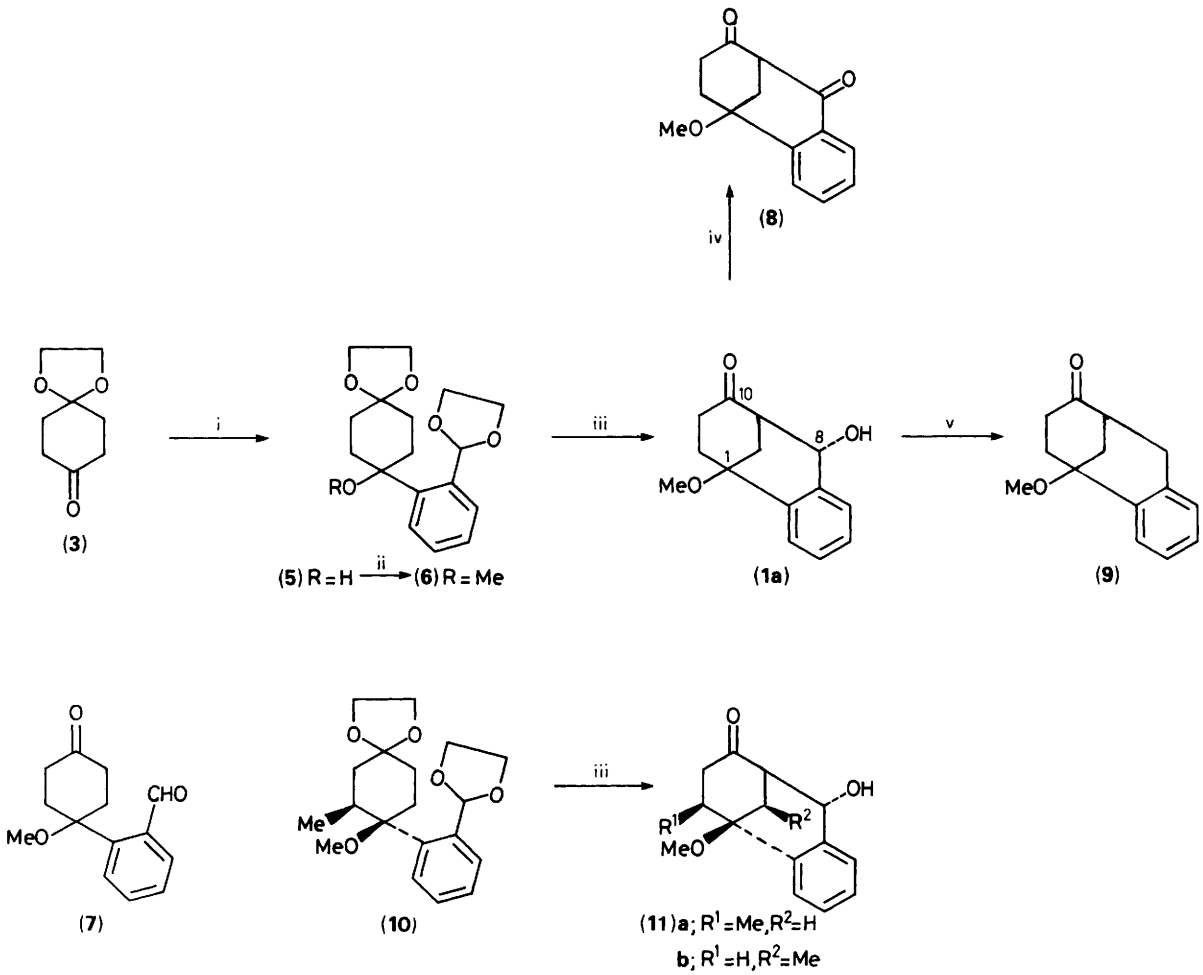



Figure 1




**Scheme 2.** *Reagents*: i, (**4**), tetrahydrofuran (THF) (75%); ii, NaH, MeI, THF (90%); iii, *p*-$MeC_6H_4SO_2OH{\cdot}H_2O$, acetone, heat [(**1a**) 75%; (**11a,b**) 68%, *ca.* 1:1]; iv, $Py_2Cr_2O_7$ (75%); v, $Et_3SiH$, $CF_3CO_2H$, then KOH, MeOH (75%), then $Py_2Cr_2O_7$, $CH_2Cl_2$, 4 A mol. sieves (77%).

2-lithiobenzaldehyde ethylene ketal (**4**)[4]† gave alcohol (**5**) (75%) which was methylated to give ether (**6**) (90%). Attempted deprotection of bis-dioxolane (**6**) using toluene-*p*-sulphonic acid in hot acetone resulted in efficient cyclisation to give the required benzannelated bicyclo[3.3.1]nonanone (**1a**) in 75% recrystallised yield.‡ When the deprotection–cyclisation sequence was effected using pyridinium toluene-*p*-sulphonate (PPTS)[5] in aqueous acetone a small amount of the intermediate dicarbonyl compound (**7**) (15%) was obtained along with the aldol product (**1a**) (60%).

Compound (**1a**) was shown to be a single diastereoisomer (Figure 1) by 400 MHz NMR spectroscopy and NOE difference studies and confirmed by *X*-ray crystallographic analysis.§ The results of these studies will be presented in a full paper.

Preliminary studies were carried out to investigate the synthetic utility of aldol (**1a**) (Scheme 2): thus, oxidation of hydroxyketone (**1a**) gave the expected dione (**8**) and reduction of (**1a**) using triethylsilane[6] followed by reoxidation of the reduced 10-keto-group gave the dehydroxylated analogue (**9**). In addition it was demonstrated that the aldol cyclisation methodology could be used to prepare alkyl substituted benzannelated bicyclo[3.3.1]nonanones (**1**) ($R^1$, $R^2 \neq H$) as shown in Scheme 2. Bis-dioxolane (**10**) was readily prepared from 2-methylcyclohexane-1,4-dione ethylene ketal[7] and 2-lithiobenzaldehyde ethylene ketal (**4**), the stereochemistry being confirmed by high field $^1H$ NMR spectroscopic studies and low temperature NOE difference spectroscopy.§ Acid-catalysed cyclisation as before gave an approximately 1 : 1 mixture of the isomeric tricyclic hydrocarbons (**11a**) and (**11b**) in 68% yield. The structural assignments shown are tentative and made by analogy with structure (**1a**).

We are currently exploring the scope of this methodology and utilising the tricyclic products (**1a**), (**11a**), and (**11b**) in synthetic studies.

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† All new compounds gave consistent spectral and analytical/mass spectrometric data. All synthetic compounds are racemic.

‡ *Selected spectroscopic and physical data* for 1*R*, 8*S*, 9*R*-8-hydroxy-1-methoxytricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-trien-10-one (**1a**); m.p. 148—150 °C; $R_f$ 0.3 (hexane–EtOAc, 3 : 1); IR: $\nu_{max.}$ (solution in $CH_2Cl_2$) 3390br., 1715 $cm^{-1}$; NMR: δ (Bruker WH 400, $CDCl_3$) 7.64—7.58 (1 H, m), 7.50—7.45 (1 H, m), 7.39—7.33 (2 H, m), 5.14 (1 H, d, *J* 6.8 Hz), 3.21 (3 H, s), 3.17—3.13 (2 H, m), 2.52 (1 H, ddd, *J* 12.6, 2.9, 2.3 Hz), 2.39 (1 H, ddd, *J* 14.5, 5.4, 2.3 Hz), 2.21—2.11 (1 H, m), 2.05 (1 H, dd, *J* 12.6, 4.4 Hz), 1.96—1.86 (2 H, m); *m/z* (EI) 232 ($M^+$, 2.3%), 175 (100). Compound (**1a**) gave satisfactory elemental analyses.

§ The *X*-ray study was carried out by Dr. K. C. Molloy, the NMR studies by Dr. O. W. Howarth.

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