The Reaction of the Epoxy Acetal 4,4-Dimethyl-3,5,7-trioxabicyclo-[5.1.0]octane with Aryllithiums

T. A. HASE, L. LAHTINEN and E. R. MAMIA

Department of Chemistry, Helsinki University of Technology, SF-02150 Espoo 15, Finland

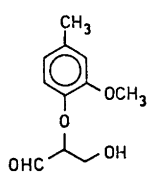
We have recently reported[1] a convenient synthesis of the lignin model compound *1*, the key step being the addition of the anion *2* to the epoxide *3*, followed by acetonide cleavage and *vic*-glycol oxidation. We were thus prompted to attempt the synthesis of the isomer *4* using the same approach, *i.e.*, addition of the anion 5 * to the same epoxide *3* to give *6*. Although no direct precedent exists for Grignard or organolithium additions to *3*, lithium dimethylcuprate is known[2,3] to react with *3* in the required manner.

Using 1:1 stoichiometry, *5* and *3* reacted to give a 33 % yield of *7*, the structure of which was readily confirmed by the direct reaction of *5* with acetone. Significantly, a fraction of both starting materials was recovered (*8*, 59 % and *3*, 49 %). The above ratio of *7*, *8* and *3* was established after a 30 min reaction time, and did not change thereafter. Furthermore, the absence of the anion *5* after a 30 min reaction time was shown by the non-formation of appropriate products upon the addition of another electrophile (D_2O or acetone) to the reaction mixture. Finally, *o*-lithiomethoxymethoxybenzene gave an analogous product mixture with *3*, whereas phenyllithium gave a very complex mixture of products which was not examined further.

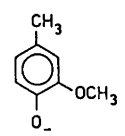
Examples are known of acetal cleavage resulting from the attack of carbanionic species (alkyl Grignards,[5,6] allyl Grignards,[7,8] alkyllithiums[9] and 2-lithio-1,3-dithiane derivatives[10]). In the present case no trace was found of the remaining C_4 portion of the epoxide *3*. The large quantity of *8* recovered indicates that at some stage, proton abstraction from *3* must have occurred. Anomalous reactions of epoxides with organolithiums are indeed known, involving either the direct metallation of an epoxide carbon atom (to give carbene intermediates)[11] or of the α-carbon.[12] For *3*, several such mechanisms can be suggested where acetone is produced. A rearrangement of the epoxide, caused by the Lewis acidity of organolithiums,[13,14] may also intervene. In such cases the carbonyl compounds generated should react further with the carbanion giving readily isolable characteristic products, revealing their own origin.

To clarify the reaction path taken, the epoxide *3* and the anion *5* were reacted using 1:3 stoichiometry. In addition to *7* (59 % based on *3*) and recovered *8* (29 %), two other compounds were isolated and identified as *9* and 10 (45 and 18 %, respectively, based on *3*). Clearly, these products will arise, presumably roughly in the ratio indicated, if the intermediate *11* is present. Thus, a unifying mechanism leading to *11* and acetone may be depicted as follows. Although this means that two negative species (*5* and *11*) are postulated to react with each other, it is rather obvious that a free acetyl group could not have survived and would therefore have to have been present as the enolate anion as shown. The protonated form of *11* (*i.e.*, methyl vinyl ketone epoxide)

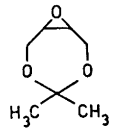
* Lithiation of *O*-methoxymethyl protected phenols by butyllithium occurs selectively at the position *ortho* to the methoxymethoxy function.[4]



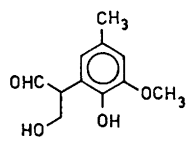
1



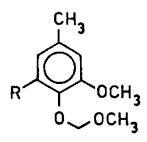
2



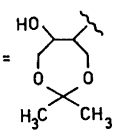
3



4



5 R = Li

6 R = 

7 R = $C(CH_3)_2OH$

8 R = H

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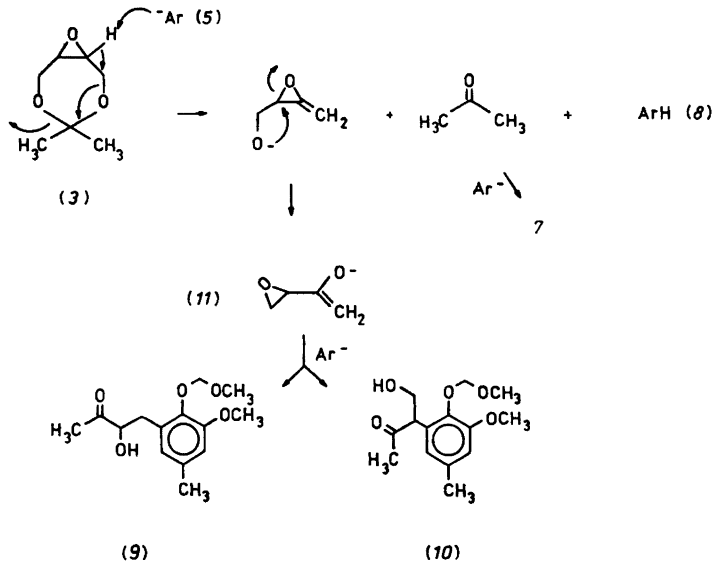

is known [15] to polymerize very readily under basic conditions. Presumably, this polymerization proceeds *via 11* itself. Thus it is not surprising that we were unable to isolate methyl vinyl ketone epoxide from the 1:1 stoichiometric reactions, or to trap *11* with acetyl chloride, methyl iodide or trimethylsilyl chloride.

Lithium diorganocuprates have been shown [13,14] to suppress the above-mentioned side reactions, giving improved yields of epoxide addition products, *i.e.*, alcohols. However, the *5*-derived lithium diarylcuprate did not react with *3*.

Finally, an attempted reaction of *5* with *3* in the presence of excess 12-crown-4, a lithium cation complexing agent,[16] again gave *7* and *8*. This experiment was carried out because molecular models indicate that *3* may itself act as a crown ether by reverting to a conformation where all oxygen atoms occupy the same face of the molecule. In this conformation, the environment of the oxirane carbon atoms will be hindered by the axial (methylene) hydrogen atoms, preventing the approach of a bulky carbanion (*i.e.*, *5*). Thus, the actual conformation of *3* is unlikely to be of importance in our reactions, and our failure to obtain the required product *6* under any conditions may be simply due to the excessive steric requirements of the carbanion.

Experimental. NMR values (60 MHz for ^{1}H, 15 MHz for ^{13}C) are from $CDCl_3$ solutions with internal TMS.

1-Methoxymethoxy-2-methoxy-4-methylbenzene (8) 2-Methoxy-4-methylphenol (19.0 g, 0.138 mol) was added with stirring to sodium hydride (55 % in paraffin oil, 6.9 g, 0.159 mol) in dry DMF (100 ml). After 3 h, 11.7 ml (0.146 mol) of chloromethyl methyl ether was added and stirring was continued for 16 h at ambient temperature. The mixture was then poured into aqueous KOH (5 %, 250 ml), extracted twice with ether and the combined extracts washed twice with water. After drying, ether was removed and the residue distilled (b.p. 92–96 °C/0.6 Torr) to give 19.9 g (79 %) of *8*, ^{1}H NMR δ 2.23, 3.42 and 3.73 (each 3 H, s), 5.00 (2 H, s), 6.56 (3 H, m).

Reaction of 3 and 5 with isolation of 7, 8, 9 and 10. The above ether *8* (1.82 g, 10 mmol) in dry THF (50 ml) under Ar was treated with 4.65 ml (10.23 mmol) of 2.2 M BuLi/hexane at 0 °C. After 10 min, 4,4-dimethyl-3,5,7-trioxabicyclo[5.1.0]-octane [2] (0.48 g, 3.33 mmol) in dry THF (10 ml) was added, and stirring was continued for 6 h. The mixture was then poured into water and treated as above. After removal of the solvent, the residue was chromatographed on preparative TLC plates (Merck PF_{254}) eluting with 4:1 chloroform–hexane to give oily *8*, *7*, *9* and *10* (R_F 0.82, 0.55, 0.39 and 0.29, respectively).

2-(3-Methoxy-2-methoxymethoxy-5-methylphenyl)-2-propanol (7). (0.47 g, 59 %); $\bar{\nu}_{max}$ 3415 cm^{-1} (film); ^{1}H NMR δ 1.63 (6 H, s), 2.30, 3.60 and 3.82 (each 3 H, s), 4.5 (1 H, br s, exch. D_2O), 5.20 (2 H, s), 6.67 and 6.75 (each 1 H, br s). The same product was also obtained in 71 % yield from the reaction of acetone and *5*.

3-Hydroxy-4-(3-methoxy-2-methoxymethoxy-5-methylphenyl)-2-butanone (9). (0.40 g, 45 %); $\bar{\nu}_{max}$ 3450, 1705 cm^{-1} (film); ^{1}H NMR δ 2.20, 2.30, 3.58 and 3.83 (each 3 H, s), 2.96, 3.03 and 4.41 (each 1 H, ABX, J_{AB} = 15 Hz, J_{AX} = 10 Hz, J_{BX} = 5 Hz), 5.08 (2 H, s), 6.67 (2 H, s).

9-Acetate $\bar{\nu}_{max}$ 1720–1740 cm^{-1} (film), ^{1}H NMR δ 2.08, 2.13, 2.30, 3.57 and 3.83 (each 3 H, s), 3.01, 3.11 and 5.34 (each 1 H, ABX, J_{AB} = 16 Hz, J_{AX} = 9 Hz, J_{BX} = 5 Hz), 5.10 (2 H, s), 6.63 (2 H, br s); ^{13}C NMR δ 20.53 and 21.18 (CH_3COO and CH_3Ar), 26.90 (CH_3CO-C), 31.45 (CH_2Ar), 26.90 and 31.45 (2 × CH_3O), 78.50 ($CHOAc$), 99.15 (OCH_2O), 112.41 (arom. C-4), 123.32 (arom. C-6), 129.69 and 133.85 (arom. C-1 and C-5), 142.55 (arom. C-2), 151.78 (arom. C-3), 170.36 (CH_3COO), 205.44 (CH_3CO-C); *m/e* 310 (16 %, M$^{\cdot+}$).

4-Hydroxy-3-(3-methoxy-2-methoxymethoxy-5-methylphenyl)-2-butanone 10 (0.16 g, 18 %); $\bar{\nu}_{max}$ 3450, 1720 cm^{-1} (film); ^{1}H NMR δ 2.07, 2.27, 3.57 and 3.82 (each 3 H, s), 3.9 (3 H, m), 5.11 (2 H, s), 6.45 and 6.68 (each 1 H, br s).

10-Acetate $\bar{\nu}_{max}$ 1720–1745 cm^{-1} (film); ^{1}H NMR δ 2.00, 2.10, 2.27, 3.60 and 3.86 (each 3 H, s), 4.45 (3 H, m), 5.12 (2 H, s), 6.52 and 6.73 (each 1 H, br s); ^{13}C NMR δ 20.53 and 20.99 (CH_3COO and CH_3Ar), 28.85 (CH_3CO-C), 50.03 ($CHAr$), 55.42 and 57.24 (2 × CH_3O), 63.80 (CH_2OAc), 99.15 (OCH_2O), 112.66 (arom. C-4), 119.81 (arom. C-6), 128.65 and 134.43 (arom. C-1 and C-5), 142.09 (arom. C-2), 151.84 (arom. C-3), 183.41 (CH_3COO), 205.84 (CH_3CO-C); *m/e* 310 (13 %, M$^{\cdot+}$).

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C=C Ozonolysis with Concomitant Introduction of Ester α,β-Unsaturation. A Short Synthesis of (*E*)-10-Hydroxy-2-decenoic Acid (Royal Jelly Acid) and of (*E*)-2-Decenedioic Acid

T. A. HASE and R. KIVIKARI

Department of Chemistry, Helsinki University of Technology, SF-02150 Espoo, Finland

The selenoxide *syn* elimination is a highly efficient method for the stereoselective introduction of carbonyl α,β-unsaturation.[1] The oxidation of the intermediate α-phenylselenide may be carried out with ozone, among other reagents. It appeared probable that this reaction could be combined in a one-pot operation with the ozonolysis of another double bond present in the same molecule. At low temperatures, the selenoxide formed would probably be stable while the double bond is being attacked, and should eliminate only at or near room temperature, thus yielding the α,β-enoic system, which in turn should be stable towards the usual ozonide reduction or oxidation reagents.

We now report that the above speculations can indeed be realised to provide the generalized transformation *1*→*2*, involving overall a dehomologation with oxidative transposition of the double bond.

By way of illustration, the above sequence provides a very short synthesis of esters of (*E*)-10-hydroxy-2-decenoic acid (*3*) and (*E*)-2-decenedioic acid (*4*), compounds involved in honeybee biochemistry.[2] The former is the well-known royal jelly acid, a substance possessing antibiotic [3] and antitumour [4] properties and the object of numerous syntheses in the past.*

Thus, ethyl 10-undecenoate (*5*) was converted to the α-phenylselenide (*6*) which was directly treated, after change of solvent, with ozone at −78 °C followed by sodium borohydride at room temperature, giving ethyl (*E*)-10-hydroxy-2-decenoate (*3*) in 46 % yield. Replacing sodium borohydride in the last step by peracetic acid gave the ethyl hydrogen (*E*)-2-decenedioate (*4*) in 26 % yield. An improved yield (58 % overall) of *4* is obtained by first treating the ozonide with triethyl phosphite followed by isolation of the aldehyde (*7*) (68 %) which is then oxidised to *4* (pyridinium dichromate in DMF [8]).

*Experimental. Ethyl (*E*)-10-hydroxy-2-decenoate* 3. Ethyl 10-undecenoate (K & K Chemicals) (1.5 g, 7 mmol) in dry tetrahydrofuran (THF) (35 ml) was added dropwise with stirring into 8 mmol of lithium diisopropylamide (from 1.13 ml of diisopropylamine and 3.4 ml of 2.14 M

* For recent syntheses of *3* and *4*, and references to earlier work, see Refs. 5–7.