Reductive and Regioselective Cleavage of Oxetanes Assisted by the Neighboring Hydroxyl

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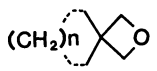
(Received December 11, 1985)

Synopsis. On exposure to lithium aluminium hydride, 1,6-dioxadispiro[2.0.3.4]undecane and 5-methl-2-oxaspiro-[3.5]nonan-5-ol gave 1,2-dimethyl-*c*-2-(hydroxymethyl)-*r*-1-cyclohexanol (**5**) which was produced from regioselective C–O bond cleavage of oxetane rings by an intramolecular attack of hydride. The stereochemistry of **5** was confirmed by an unambiguous synthesis based on the Sharpless oxidation of 1-methyl-2-methylenecyclohexanemethanol.

On treatment with lithium aluminium hydride, oxetanes generally undergo reductive fission of their C–O bonds to produce alcohols.[1] On this reduction, it is known that boiling in tetrahydrofuran for several hours is an indispensable conditions for obtaining a reasonable reaction rate and yield.[2] While reduction of 2-oxaspiranes **1**(n=0—2) with this reductant led to the expected 1-methylcycloalkanemethanol **2**(n=0—2), 2-oxaspiro[3.5]nonane **1**(n=3) was reported to be exceptionally sluggish on the reduction.[3]



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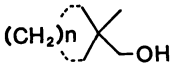

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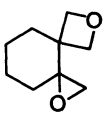
We wish to report here that treatment of 1,6-dioxadispiro[2.0.3.4]undecane (**3**) and 5-methyl-2-oxaspiro[3.5]nonan-5-ol (**4**),[4] derivatives of **1**(n=3) possessing additional oxygen functions, with lithium aluminium hydride resulted in unexpectedly facile and regioselective cleavage of their oxetane rings.



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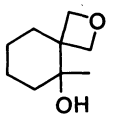

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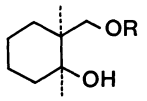
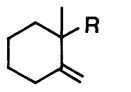
In the course of our synthetic study of a natural product, we have prepared hydroxy oxetane **4** in high yield by reduction of epoxy oxetane **3** with super hydride ($LiBHEt_3$).[4] When **3** was, on the other hand, treated with lithium aluminium hydride in place of the above reductant, the reduction proceeded smoothly even at room temperature, and the sole product obtained in 97% yield was not the hydroxy oxetane **4** but an unexpected diol, 1,2-dimethyl-*c*-2-(hydroxymethyl)-*r*-1-cyclohexanol (**5**). The diol **5** was also produced by treatment of **4** obtained above with lithium aluminium hydride under the same reaction conditions. Acetylation of the diol **5** with acetic anhydride in pyridine gave a crystalline acetoxy alcohol **6**, in which no evidence could be found for formation of its diastereomer.

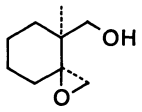


5 R=H
6 R=Ac

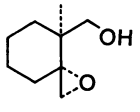
The stereochemistry of **5** was confirmed by an unambiguous synthesis starting with ethyl 1-methyl-2-oxo-cyclohexanecarboxylate.[5] Methylenation of the ester by the Wittig reaction with methylenetriphenylphosphorane provided unsaturated ester **7** in 60% yield, and the product was reduced with lithium aluminium hydride to the corresponding unsaturated alcohol **8** quantitatively. The alcohol **8** was then submitted to the Sharpless oxidation.[6] The reaction proceeded stereoselectively to provide hydroxy epoxide **9** in 73% isolated yield together with a small amount of its stereoisomer **10** (~1%).



7 R=CO_2Et
8 R=CH_2OH



9

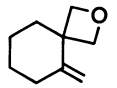


10

It is reasonable to surmise that the stereoselectivity of the above reaction would be controlled by the syn-directive effect of the homoallylic hydroxyl group in **8**. In other words, the epoxide oxygen of the major product **9** can be expected to have a syn configuration with respect to the hydroxymethyl group on the basis of the well-documented stereoselectivity.[6] Finally, reduction of **9** with lithium aluminium hydride afforded a single diol, whose physical properties (IR and ^1H NMR) were identical with those of the diol **5** prepared from **3** or **4**.

Mechanistic rationalization for the facile and regioselective cleavage of the oxetane ring would be given as follows. Since treatment of 5-methylene-2-oxaspiro[3.5]nonane (**11**)[4] with lithium aluminium hydride also resulted in recovery of **11** in the same way as the reduction of **1**(n=3), it is demonstrated that the presence of a hydroxyl group α to the oxetane ring plays an important role for the reductive cleavage with great facility. Apparently, the hydride reacts initially with the hydroxyl group in **4** to afford an alkoxy hydride **12**, which is also derived from preferential reduction of the epoxide ring in the

course of reduction of **3**. Thus the facile reductive cleavage of the oxetane ring would occur by internal hydride attack based on neighboring assistance. In the intermediate **12**, energetically favorable chelation between the aluminium and oxetane oxygen atoms would be attained with the equatorially oriented alkoxide group, and this conformational fixation would also be convenient for the intramolecular attack of hydride at the oxetane methylene carbon in the anti position regarding to the alkoxide group.



11

12

Experimental

Melting points are uncorrected. IR spectra were obtained with a JASCO A-3 infrared spectrometer. ^{1}H NMR spectra were recorded on a JEOL FX90Q spectrometer. Gas chromatography was carried out on a JEOL JGL-20K gas chromatograph. Dry tetrahydrofuran (THF) was obtained by distillation over sodium benzophenone ketyl. Column chromatography was performed by using silica gel (Merck, kieselgel 60, 70—230 mesh), and kieselgel GF_{254} was employed for preparative thin-layer chromatography as an absorbent.

Lithium Aluminium Hydride Reduction of Oxetane 3. A mixture of **3**[4] (80 mg, 0.52 mmol), lithium aluminium hydride (30 mg, 0.78 mmol), and THF (5 ml) was stirred at room temperature for 5 h under nitrogen and quenched with wet ether. A solid was filtered and washed with ether, and the combined ethereal solutions were dried ($MgSO_4$). Removal of the solvent left an oil, which was purified by preparative thin-layer chromatography (50% ether in hexane as an eluent) and subsequent solvent removal gave 79 mg (96%) of **5** as a viscous oil: IR (neat) 3300 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.82 (3H, s, C-CH_3), 1.21 (3H, s, O-C-CH_3), 1.0—2.2 (8H, m), 3.0—3.9 (3H, m, CH_2-OH). The oil was used in the next reaction.

Acetylation of Diol 5. A mixture of **5** (45 mg), acetic anhydride (0.8 ml), and pyridine (0.4 ml) was stirred at room temperature for 20 h under nitrogen, and poured into ice-water. The solution was extracted with ether and the combined extracts were washed successively with water and brine, and dried ($MgSO_4$). Evaporation of the solvent left 54 mg (95%) of **6** as crystals. Analysis by gas chromatography (10%-SE-30, 2 m×1 mm; vaporizer, 250 °C; column temperature, 170 °C; helium flow, 1 kg cm^{-2}) indicated a single peak with retention time 2.8 min. An analytically pure sample was obtained by recrystallization from ether–hexane (1:1): mp 88—89 °C; IR (KBr) 3480, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.99 (3H, s, C-CH_3), 1.21 (3H, s, O-C-CH_3), 1.2—1.8 (9H, m), 2.10 (3H, s, $COCH_3$), 4.13 and 4.23 (1H, d, J=11.1 Hz each, CH_2-O).

Found: C, 65.64; H, 10.02%. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07%.

Reduction of Hydroxy Oxetane 4 with Lithium Aluminium Hydride. A suspension of **4** (20 mg. 0.13 mmol) and lithium aluminium hydride (6 mg, 0.15 mmol) in THF (1 ml) was stirred at room temperature for 7 h under nitrogen and quenched with wet ether. A solid was filtered and washed with ether, and the combined extracts were dried ($MgSO_4$). Removal of the solvent left an oil, which was purified by filtration through a short silica gel column with 30% ether in hexane to give 18 mg (90%) of a viscous oil whose IR and ^{1}H NMR spectra were identical with those of diol **5** prepared above.

Ethyl 1-Methyl-2-methylenecyclohexanecarboxylate (7). To a stirred suspension of methyltriphenylphosphonium bromide (7.23 g, 20.2 mmol) in THF (40 ml) was added dropwise a solution of 1.5 M butyllithium in hexane (13.5 ml, 20.2 mmol) at 0 °C under nitrogen. The cooling bath was removed and the mixture was stirred at room temperature for 2 h. A solution of ethyl 2-methyl-2-oxo-1-cyclohexanecarboxylate (3.68 g, 20.2 mmol) in THF (5 ml) was added dropwise and stirring was continued for an additional hour at room temperature, and then at 60 °C for 10 h. After cooling to room temperature, water was added and the aqueous solution was extracted with ether. The combined extracts were washed successively with water and brine, and dried ($MgSO_4$). A residue obtained by concentration was chromatographed by eluting with 20% ether in hexane to give 2.04 g (60%) of **7** as a colorless oil: IR (neat) 3060, 1725, 1640, 890 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.23 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$), 1.30 (3H, s, C-CH_3), 1.1—1.8 (6H, m), 2.2 (2H, m, CH_2-C=), 4.18 (2H, q, J=7.2 Hz, $CO_2CH_2CH_3$), 4.78 and 4.87 (1H, br s each, C=CH_2).

Found: C, 72.15; H, 9.75%. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96%.

1-Methyl-2-methylenecyclohexanemethanol (8). To a stirred suspension of lithium aluminium hydride (237 mg, 6.25 mmol) in THF (10 ml) at 0 °C under nitrogen was added dropwise a solution of **7** (1.14 g, 6.25 mmol) in THF (2 ml). After removal of the cooling bath, stirring was continued for an additional 15 h at room temperature. The reaction was quenched by the addition of wet ether followed by a small amount of water. A solid was filtered and washed with ether, and the combined ethereal solutions were dried ($MgSO_4$). An oily residue obtained by evaporation was chromatographed by eluting with 50% ether in hexane to give 787 mg (90%) of **8** as a colorless oil: IR (neat) 3350, 3070, 1640, 900 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.08 (3H, s, CH_3), 1.1—1.8 (7H, m), 2.2 (2H, m, CH_2-C=), 3.38 (1H, d, d, J=10.4 and 7.2 Hz, CH_aH_b-O), 3.70 (1H, d, d, J=10.4 and 5.4 Hz, CH_aH_b-O), 4.75 and 4.87 (1H, s, with fine splittings each, =CH_2); ^{1}H NMR ($CDCl_3$-D_2O) δ=3.38 and 3.70 (1H, d, J=10.4 Hz each).

Found: C, 77.04; H, 11.80%. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50%.

Sharpless Oxidation of Homoallylic Alcohol 8. A solution of **6** (437 mg, 3.12 mmol) and vanadyl acetylacetonate (17 mg, 0.06 mmol) in dry benzene (8 ml) was warmed at 80 °C under nitrogen. A solution of 3M *t*-butyl hydroperoxide in toluene (1.2 ml, 3.43 mmol) was added dropwise to the above solution with stirring. Stirring was continued for an additional 2 h and, after cooling, the reaction was quenched by the addition of aqueous sodium hydrogensulfite solution followed by water. The benzene layer was separated and aqueous layer was extracted with benzene. The combined extracts were washed successively with water and brine, and dried ($MgSO_4$). An oily residue obtained by evaporation was chromatographed by eluting with 50% ether in hexane to give two products, **9** (355 mg, 73%) and **10** (4 mg, ~1%). **9**: IR (neat) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.98 (3H, s, CH_3), 1.1—2.2 (9H, m), 2.48 (1H, d, J=3.6 Hz, epoxide CH_aH_b), 2.9—3.58 (3H, m); ^{1}H NMR ($CDCl_3$-D_2O) δ=3.10 (1H, d, J=3.6 Hz, epoxide CH_aH_b), 3.15 and 3.44 (1H, d, J=11.2 Hz each, CH_2-O). Found: C, 69.20; H, 10.79%. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32%. **10**: IR (neat) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.13 (3H, s,

CH_3), 1.0—2.1 (9H, m), 2.55 (1H, d, J=3.6 Hz, epoxide CH_aH_b), 3.12 (1H, d, J=3.6 Hz with fine splittings, epoxide CH_aCH_b), 3.3—3.7 (2H, m); ^{1}H NMR ($CDCl_3$–D_2O) δ=3.25 and 3.55 (1H, d, J=11.2 Hz each, CH_2–O). Found: C, 68.90; H, 10.17%. Calcd for $C_9H_{16}O_2$: C, 69.12; H, 10.32%.

Reduction of Epoxy Alcohol 9 with Lithium Aluminium Hydride. A suspension of **9** (355 mg, 2.28 mmol) and lithium aluminium hydride (258 mg, 6.83 mmol) in THF (10 ml) was warmed with stirring at 50 °C for 15 h under nitrogen. After cooling to room temperature, the mixture was quenched with wet ether. A solid was filtered and the filtrate was dried ($MgSO_4$). Removal of the solvent left an oily residue which was purified by preparative thin-layer chromatography (70% ether in hexane as an eluent) to give 244 mg (93%) of a viscous oil, whose IR and ^{1}H NMR were identical with those of **5** prepared by reduction of **3**.

Treatment of Oxetane 11 with Lithium Aluminium Hydride. A suspension of **11** (25 mg, 0.18 mmol) and lithium aluminium hydride (14 mg, 0.36 mmol) in THF (2 ml) was stirred at room temperature for 20 h, and then at 60 °C for 5 h under nitrogen. After cooling to room temperature, the reaction was quenched with wet ether and a solid was filtered. The filtrate was dried ($MgSO_4$). An oily residue obtained by concentration was purified by passing through a short silica-gel column with 10% ether in hexane to give 21 mg of an oil whose ^{1}H NMR spectrum was identical with that of starting **11**.

References

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