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1,4-Dioxene in Organic Synthesis: Generation and Reactivity of Epoxydioxenes

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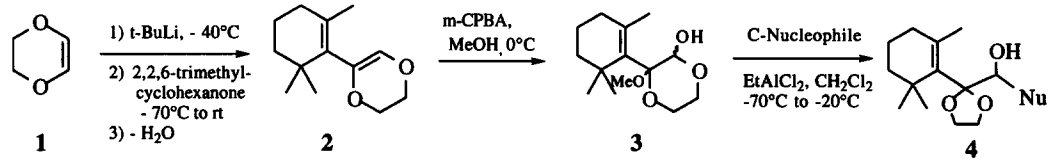
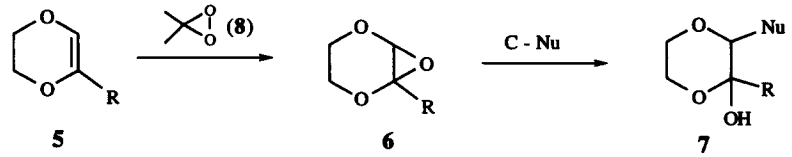
Abstract: *Oxidation of various alkyldioxens with dimethyldioxirane is described. While pure epoxides were isolated from 4-dioxenylcyclohexanone **10** and diether **9**, vinyldioxenes **11-14** gave the corresponding epoxide rearrangement products, α-ketal aldehydes **20-24**, in excellent yields.*

1,4-Dioxene **1** was found to be a valuable synthon for carbon-carbon bond formation with simultanenous introduction of functional groups.[1-3] As part of synthetic studies towards polyoxygenated natural products, we recently described a method for the introduction of a second C-C bond with opening of the dioxene ring and release of oxygenated functionalities. Thus, treatment of acetal **3**, readily prepared by regioselective oxidation of diene **2** with m-chloroperbenzoic acid in methanol at 0°C, with carbon nucleophiles in the presence of a Lewis acid leads to the formation of α-hydroxyketals **4** in good yields. [2a]



1 **2** **3** **4**

As an alternative approach, however, we wished to explore the possibility of introducing of a second C-C bond from epoxides **6**, which could be prepared from **5**. Such an epoxide would be expected to be highly labile by virtue of the fact that it is fused to the dioxane ring, and could thus react with carbon nucleophiles to afford **7** (eq. 1).



5 **6** **7** (eq 1)

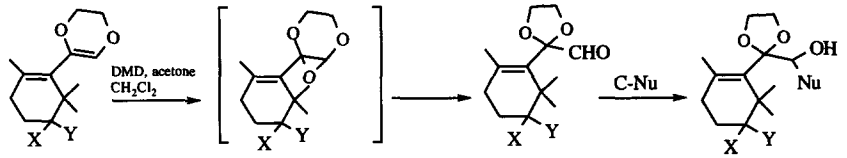
It is well known that epoxidation of enol derivatives using peracids does not lead to isolable epoxides. Instead, the initially formed product reacts either with the solvent or with the carboxylic acids derived from reduction of peracids.[4] In contrast, 3,3-dimethyldioxirane (DMD) **8** [5] was found to be an efficient epoxidant under mild neutral conditions and was used in particular for the preparation of labile epoxides from various enol-type alkenes.[6] Accordingly, we have examined the behavior of this reagent towards dioxene derivatives **5**. This communication discloses our preliminary results.

Dimethyldioxirane, prepared according to the procedure of Adam and co-workers, was used as a solution in acetone.[7] As shown in the Table, only epoxides **18** and **19** were isolated in pure form. Homoallylic alcohol **8** afforded tetrahydrofuran derivative **17** as a mixture of diastereomers by intramolecular nucleophilic attack on the initially formed epoxides by the hydroxyl group.

More interestingly, compound **11**, containing the trimethylcyclohexenyl substructure, underwent a regioselective oxidation of the dioxene ring to give only the rearrangement product **20** in quantitative yield. The presence of additional functionality such as a ketal (**12**), a ketone (**13**), a triple bond (**14**) or an electron-poor olefin such in **15**[8], did not affect the reaction, and the corresponding α-ketal adehydes **21**, **22**, **23** and **24**[12] were obtained in excellent yields[12] (Table).

A typical procedure is as follows : to a stirred solution of **11** (104 mg, 0.5 mmol) in dry CH_2Cl_2 (3 mL) at - 40°C under a nitrogen atmosphere, was added a solution of DMD in acetone (ca. 0.1 M). The reaction was monitored by TLC until complete consumption of the starting material. The solvent and excess reagent were removed under reduced pressure to afford quantitatively the rearrangement product **21**, as confirmed by IR, ^1H and ^{13}C NMR spectral data.[12]

As expected, ketal aldehydes **26** prepared in this way, underwent addition with various carbon nucleophiles affording α-hydroxyketals **27** (eq 2). It is worthy of note that this reaction may be accomplished in the same flask just after evaporation of the solvents. The overall result of this *one pot* sequence is the introduction of the a new C-C bond with concomitant release of the oxygenated functionalities latent in dioxene.

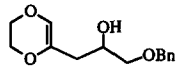
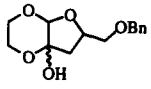
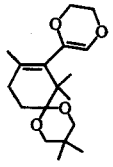
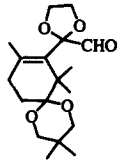
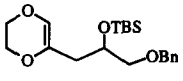
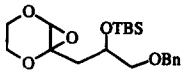
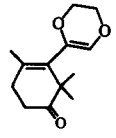
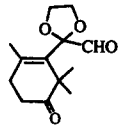
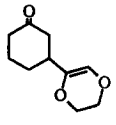
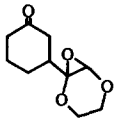
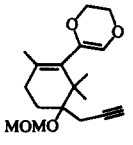
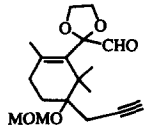
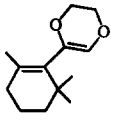
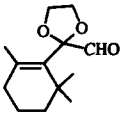
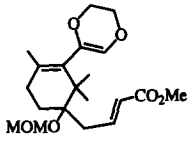
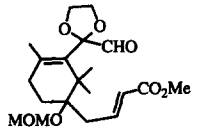


25 **26** **27** (eq. 2)

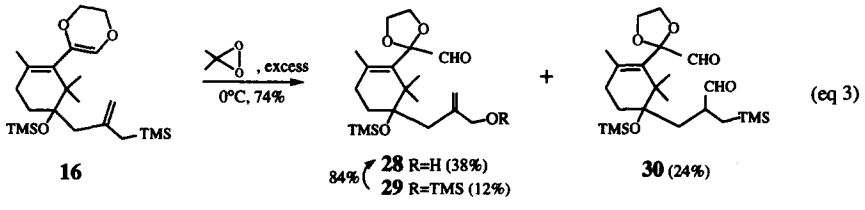
Attempts to achieve the same regioselectivity by treatment of **16** with one equivalent of DMD failed even at low temperature. Instead, a synthetically useless mixture was obtained. However, in the presence of an excess of the epoxidant, **16**[8] led to a mixture of **28** (38 %) , **29** (12 %) and **30** (24 %) which were separated by flash chromatography (eq 3). These structures were assigned on the basis of analytical and spectroscopic data, and confirmed by the mild hydrolysis (Na_2CO_3, MeOH, rt)[13] of the primary trimethylsilyl ether in **29** to give allylic alcohol **28**. Formation of these compounds could be reasonably explained in terms of rearrangement of initially formed epoxide from the allylsilane moiety.

Although the reaction of these vinyldioxenes with DMD did not permit the isolation of the corresponding epoxydioxenes, the present procedure constitutes a convenient method for the preparation of mono protected α-ketoaldehydes. The use of these products to the synthesis of polyoxygenated natural products is under study in our laboratory.

Table : Oxidation[a] of Alkyldioxenes by Dimethyldioxirane (as Acetone Solution)

Substrate[b]	Product[c]	Isolated[d] yield %	Substrate[b]	Product[c]	Isolated[d] yield %
 **8**	 **17**	ca. 100	 **12**	 **21**	ca. 100
 **9**	 **18**	94	 **13**	 **22**	90
 **10**	 **19**	ca. 100	 **14**	 **23**	ca. 100
 **11**	 **20**	ca.100	 **15**	 **24**	84

[a] In CH_2Cl_2 - CH_3COCH_3 under N_2 atmosphere. [b] compouds **8** and **10** are prepared as in Ref. 2c; Preparation of **12** - **15** is given in Ref. 8. [c] Selected spectral data of products **20**, **21**, **23**, **24** are given in Ref. 12. [d] Yield of isolated pure product after evaporation of the solvents under reduced pressure.



16 — 84% (**28** R=H (38%), **29** R=TMS (12%)) — **30** (24%) (eq 3)

References and Notes

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8. **12** was prepared from the known 3.3-(2,2-dimethylpropyl)-2,2,6-trimethylcyclohexanone[9] by triflation (LDA, HMPA, $PhNTf_2$ THF, -70°C to r.t.) followed by palladium-catalyzed coupling of the resulting enol triflate with 5-tributylstannyl-2,3-dihydro-1,4-dioxin[10]. Acid-catalyzed hydrolysis of **12** (TsOH - aq. acetone, r.t.) afforded **13**. Treatment of **13** with propargyl bromide, methyl-4-bromocrotonate, or 3-iodo-3-[(trimethylsilyl)methyl]propene[11] in the presence of commercial zinc dust in THF under sonication gave, after protection, **14**, **15** or **16** respectively in good yields.
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12. All new compounds are fully characterized by their spectroscopic and analytical data. **20** : IR (CCl_4) : ν_{max} 1737 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) : δ 1.15 (s, 2 Me), 1.30-1.58 (m, 4H), 1.62 (s, Me), 1.95 (t, J = 8 Hz, 2H), 3.85-4.15 (m, 4H), 9.13 (s, 1H) ; ^{13}C NMR (200 MHz, $CDCl_3$) : δ 18.9 (CH_2), 21.9 (Me), 28.5 (2 Me), 34.5 (CH_2), 42.4 (C), 64.6 (2 CH_2), 109.1 (C), 132.5 (C), 137.7 (C), 192.8 (CHO). **21** : IR (CCl_4) : ν_{max} 1737 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) : δ 0.70 (s, Me), 1.17 (s, Me), 1.29 (s, 2 Me), 1.67 (s, Me), 2.00 (br s, 4H), 3.34 (d, J = 11.4 Hz, 2H), 3.63 (d, J = 11.4 Hz, 2H), 3.85-4.25 (m, 4H), 9.18 (s, 1H) ; ^{13}C NMR (200 MHz, $CDCl_3$) : δ 18.0 (CH_2), 21.6 (Me), 22.1 (Me), 22.4 (Me), 23.4 (Me), 29.8 (C), 31.6 (CH_2), 44.0 (C), 64.7 (2 CH_2), 70.2 (2 CH_2), 100.5 (C), 109.0 (C), 131.3 (C), 135.9 (C), 192.8 (CHO). **23** : IR (CCl_4) : ν_{max} 1738, 3311 cm^{-1} ; ^1H NMR (200 Mz, $CDCl_3$) : δ 1.17 (s; Me), 1.26 (s, Me), 1.67 (s, Me), 2.04 (t, J = 2.6 Hz, 1H), 2.53 (d, J = 2.6 Hz, 2H), 3.40 (s, Me), 3.90-4.15 (m, 4H), 4.85 (d, J = 11 Hz, 1H), 4.95 (d, J = 11 Hz, 1H), 9.18 (s, 1H) ; ^{13}C NMR (200 MHz, $CDCl_3$) : δ 19.8 (Me), 21.9 (Me), 24.5 (Me), 24.9 (CH_2), 25.4 (CH_2), 32.0 (CH_2), 43.3 (C), 55.7 (Me), 64.4 (CH_2), 65.3 (CH_2), 70.9 (CH), 79.8 (C), 82.4 (C), 91.5 (CH_2), 100.8 (C), 131.6 (C), 36.7 (C), 192.8 (CHO). **24** : IR (CCl_4) : ν_{max} 1728 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) : δ 1.7 (s, 2 Me), 1.63 (s, Me), 1.7-2.1 (m, 4H), 2.3-2.6 (m, 2H), 3.36 (s, Me), 3.67 (s, Me), 3.80-4.10 (m, 4H), 4.55-4.90 (m, 2H), 5.83 (m, 1H), 7.11 (m, 1H), 9.15 (s, 1H) ; ^{13}C NMR (200 MHz, $CDCl_3$) : δ 20.7 (Me), 21.7 (Me), 24.1 (Me + CH_2), 31.7 (CH_2), 37.7 (CH_2), 43.6 (C), 51.3 (Me), 55.6 (Me), 64.4 (CH_2), 65.2 (CH_2), 81.5 (C), 91.5 (CH_2), 108.9 (C), 122.8 (CH), 132.3 (C), 135.9 (C), 147.2 (CH), 166.7 (C), 192.7 (CHO).
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