Hydroxyl-Directed Reductive Cleavage of 3-Oxetanols as an Entry to Diastereomerically Pure 1,2-Diols

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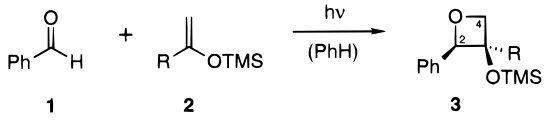
The polarity reversal of a carbonyl compound from an a[1] to a d[1] synthon is a point of continuing interest in organic synthesis.[1] One of the most straightforward solutions to this problem is the photoexcitation of an aldehyde or a ketone. The $^3n\pi^*$ state which is in many cases the lowest lying excited state of these compounds is electronically defined by an electrophilic oxygen and a nucleophilic carbon atom. In particular, aromatic carbonyl compounds which undergo a rapid intersystem crossing from the $^1n\pi^*$ to the $^3n\pi^*$ level behave fairly predictably and may undergo C−C bond formations with suitable carbon nucleophiles. The most common reaction in this context is the Paternò-Büchi reaction in which photoexcited carbonyl compounds are quenched by alkenes to yield oxetanes.[2] We have recently shown that the photocycloaddition of silyl enol ethers **2** to aromatic aldehydes, such as benzaldehyde (**1**), proceeds with excellent diastereo- and regioselectivity (Scheme 1).[3] Many functional groups (ketal, acetal, ester, ether, amide, alkene, silane, chloride) either attached to the aldehyde or to the enol ether are tolerated in this transformation.[4] The decisive C−C bond between the umpoled carbonyl and the (silyloxy)-substituted carbon is formed readily despite the fact that the α-substituents of the silyl enol ether are of considerable bulk.

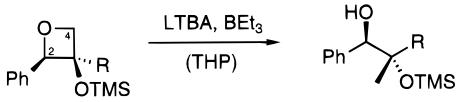
Since the product oxetanes **3** can be envisaged as latent 1,2-diols we looked into the prospect of a selective S_N2-type ring opening at C-4. Our premier choice was a reductive opening which would facilitate the formation of diols in a stereochemically predictable manner. The former methylene group of the enol ether **2** would end up as a methyl substituent on the stereogenic tertiary alcoholic center. However, all attempts to induce a nucleophilic hydride displacement on the C-4 of oxetanes **3** encountered little success. Commonly used aluminum-based hydride reagents[5] failed, whereas catalytic hydrogenolyses resulted in the expected benzylic cleavage between C-2 and O.[6] The best results were obtained with

Scheme 1



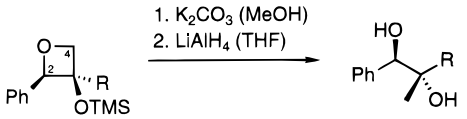
1 **2** **3**

Scheme 2



3a: R = *i*Pr **4a** (30%)
3b: R = Ph **4b** (44%)

Scheme 3



3 **5**

the combination of lithium tris(*tert*-butoxy)aluminum hydride (LTBA) and triethylborane (BEt_3) in tetrahydropyran (THP)[7] the application of which gave access to the monoprotected trimethylsilyl (TMS) diols **4a** and **4b**[3b] in moderate yields (Scheme 2).

Obviously the bulky substituents at the C-3 carbon of the oxetane nucleus prevent the approach of the incoming nucleophile. Unfortunately, all attempts to increase the electrophilicity of the four-membered heterocycle are limited by a facile S_N1-type ring opening at C-2 which leads to rearranged material.[8] An intramolecular delivery of the hydride occurred to us as a possible way to overcome the described obstacles. Since the TMS group of **3** can be readily cleaved in essentially quantitative yield to furnish the corresponding 3-oxetanol[9] we intended to utilize the 3-hydroxyl substituent as a possible control element. In a representative study we employed the oxetanes depicted in Scheme 3 as starting materials. After deprotection of the oxetanes **3** with K_2CO_3 in methanol we were pleased to observe that treatment of the crude oxetanol with $LiAlH_4$ in THF lead cleanly to the desired diols **5** as shown in Scheme 3. The reaction proceeded smoothly at room temperature or for more hindered substrates at reflux and yielded the products in diastereomerically pure form (see Table 1).

Compared to the conventional addition of umpoled carbanions to aldehyde electrophiles[10] the described methodology exhibits a more stereoselective approach to 1,2-diols which bear a secondary and a tertiary center.[11] The preparation of the corresponding 1,2-diols by a stereospecific dihydroxylation is certainly possible, even in enantiomerically pure form.[12] However, this route

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Table 1. Ring Opening of Oxetanes 3 upon Deprotection and Subsequent Treatment with $LiAlH_4$ in THF

oxetane	R	t^a (h)	T	diol	yield^b (%)
3a	*i*-Pr	24	rt	**5a**	98
3b	Ph	48	rt	**5b**	99
3c	*t*-Bu	48	reflux	**5c**	75
3d	$CH(OMe)_2$	72	rt	**5d**	97
3e	$C(OCH_2)_2Me$	48	reflux	**5e**	69
3f	CMe_2CHCH_2	96	rt	**5f**	94

[a] Time required for complete conversion at the designated temperature. [b] Refers to isolated yield of analytically pure product.

requires a diastereoselective method for the carbonyl olefination of aldehydes which yields highly congested (*Z*)-alkenes and which therefore appears difficult to devise.

The overall yield of diastereomerically pure diol **5** for the three-step procedure, photocycloadditon, protective group removal, and reductive ring opening, ranges between 36 and 59% in the cases under scrutiny. Further studies are under way to extend the scope of hydroxyl-directed ring-opening reactions of oxetanes and will be reported in due course.

Experimental Section

General. For general remarks see ref 4. The oxetanes **3** were prepared as described previously.[3b] ^{13}C NMR multiplicities were obtained by DEPT experiments.

(1*RS*,2*SR*)-2,3-Dimethyl-1-phenyl-2-[(trimethylsilyl)oxy]-1-butanol (4a). The ring opening of oxetane **3a** with LTBA/BEt_3 in THP was carried out on a 1 mmol scale as previously described for **3b**.[3b] A total of 80 mg (30%) of **4a** were obtained as an oil after flash chromatography (cyclohexane−ethyl acetate = 97:3): R_f = 0.58 (CH/EtOAc = 75/25); ^1H NMR ($CDCl_3$) δ 0.04 (s, 9 H), 0.80 (d, J = 6.8 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 1.25 (s, 3 H), 1.73 (sept, J = 6.8 Hz, 1 H), 2.25 (s, b, 1 H), 4.60 (s, 1 H), 7.22−7.38 (m, 3 H), 7.39−7.42 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 2.5 (q), 17.7 (q), 18.1 (q), 19.0 (q), 34.7 (d), 79.3 (d), 80.9 (s), 127.4 (d), 127.6 (d), 128.3 (d), 141.5 (s). Anal. Calcd for $C_{15}H_{26}O_2Si$ (266.457): C, 67.62; H, 9.84. Found: C, 67.67; H, 9.94.

General Procedure for the Reductive Ring Opening with $LiAlH_4$. The oxetanols were obtained in quantitative yields from the corresponding oxetanes by treatment with K_2CO_3 in MeOH[9] and were used without further purification. To a suspension of 3 mmol $LiAlH_4$ (114 mg) in 2 mL of THF was added slowly a solution of 1 mmol crude oxetanol in 5 mL of THF at 0 °C. After complete addition the mixture was stirred for another hour at 0 °C and subsequently allowed to reach the temperature indicated in Table 1. Stirring was continued until the reaction was complete according to TLC (cf. Table 1). Workup was carried out according to the standard protocol.[13] The diols **5a** and **5b** proved to be analytically pure without further purification. The other products were purified by flash chromatography (cyclohexane−ethyl acetate mixture as eluent) or by recrystallization.

(1*RS*,2*SR*)-2,3-Dimethyl-1-phenylpropane-1,2-diol (5a): Yield 190 mg (98%) of a white solid with mp 125−126 °C (lit.[14] mp 124−125 °C); R_f = 0.22 (CH/EtOAc = 80/20); ^1H NMR ($CDCl_3$) δ 0.85 (d, J = 6.9 Hz, 3 H), 0.93 (d, J = 6.9 Hz, 3 H), 1.20 (s, 3 H), 1.52 (sept, J = 6.9 Hz, 1 H), 2.10 (s, b, 2 H), 4.60 (s, 1 H), 7.26−7.36 (m, 3 H), 7.39−7.43 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.8 (q), 17.8 (q), 19.1 (q), 33.3 (d), 77.0 (s), 78.4 (d), 127.8 (d), 127.9 (d), 128.1 (d), 140.9 (s). Anal. Calcd for $C_{12}H_{18}O_2$ (194.273): C, 74.19; H, 9.34. Found: C, 73.97; H, 9.26.

(1*RS*,2*SR*)-1,2-Diphenylpropane-1,2-diol (5b): Yield 225 mg (99%) of a white solid with mp 102−104 °C (lit.[15] mp 103−104 °C); R_f = 0.28 (CH/EtOAc = 70/30); ^1H NMR ($CDCl_3$) δ 1.60 (s, 3 H), 2.55 (s, b, 2 H), 4.72 (s, 1 H), 6.99−7.02 (m, 2 H), 7.12−7.23 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 25.5 (q), 76.8 (s), 80.9 (d), 126.0 (d), 126.9 (d), 127.4 (d), 127.5 (d), 127.5 (d), 127.6 (d), 139.4 (s), 143.6 (s). Anal. Calcd for $C_{15}H_{16}O_2$ (228.290): C, 78.92; H, 7.06. Found: C, 78.96; H, 7.13.

(1*RS*,2*SR*)-1-Phenyl-2,3,3-trimethylbutane-1,2-diol (5c). After purification by flash chromatography (cyclohexane−ethyl acetate = 90:10) 156 mg (75%) of a white solid with mp 82−83 °C were obtained: R_f = 0.60 (CH/EtOAc = 50/50); ^1H NMR ($CDCl_3$) δ 1.05 (s, 9 H), 1.11 (s, 3 H), 4.89 (s, 1 H), 7.24−7.41 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.0 (q), 26.4 (q), 37.8 (s), 77.1 (s), 77.3 (d), 127.7 (d), 127.9 (d), 128.1 (d), 142.1 (s). Anal. Calcd for $C_{13}H_{20}O_2$ (208.300): C, 74.96; H, 9.68. Found: C, 75.01; H, 9.66.

(1*RS*,2*RS*)-3,3-Dimethoxy-2-methyl-1-phenylpropane-1,2-diol (5d). After purification by flash chromatography (cyclohexane−ethyl acetate = 70:30) 220 mg (97%) of a white solid with mp 70−71 °C were obtained: R_f = 0.53 (CH/EtOAc = 10/90); ^1H NMR ($CDCl_3$) δ 1.16 (s, 3 H), 3.47 (s, 3 H), 3.55 (s, 3 H), 4.03 (s, 1 H), 4.72 (s, 1 H), 7.25−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 17.8 (q), 57.5 (q), 58.7 (q), 75.8 (s), 76.8 (d), 109.7 (d), 127.5 (d), 127.7 (d), 127.8 (d), 139.8 (s). Anal. Calcd for $C_{12}H_{18}O_4$ (226.272): C, 63.70; H, 8.02. Found: C, 63.86; H, 8.09.

(1*RS*,2*RS*)-2-(2-Methyl-1,3-dioxolan-2-yl)-1-phenylpropane-1,2-diol (5e). After recrystallization from ethyl acetate 165 mg (69%) of a white solid with mp 123−124 °C were obtained: R_f = 0.45 (CH/EtOAc = 30/70); ^1H NMR ($CDCl_3$) δ 1.12 (s, 3 H), 1.48 (s, 3 H), 3.99−4.18 (m, 4 H), 4.96 (s, 1 H), 7.26−7.37 (m, 3 H), 7.43−7.47 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.4 (q), 19.3 (q), 64.8 (t), 65.5 (t), 76.0 (d), 76.7 (s), 113.2 (s), 127.4 (d), 127.5 (d), 128.1 (d), 139.7 (s). Anal. Calcd for $C_{13}H_{18}O_4$ (238.283): C, 65.53; H, 7.61. Found: C, 65.65; H, 7.58.

(1*RS*,2*SR*)-1-Phenyl-2,3,3-trimethyl-4-pentene-1,2-diol (5f). After purification by flash chromatography (cyclohexane−ethyl acetate = 92:8) 206 mg (94%) of a white solid with mp 63−64 °C were obtained: R_f = 0.67 (CH/EtOAc = 50/50); ^1H NMR ($CDCl_3$) δ 1.11 (s, 3 H), 1.13 (s, b, 1 H), 1.15 (s, 3 H), 1.22 (s, 3 H), 2.21 (s, b, 1 H), 5.09 (dd, J = 10.9 Hz, J = 1.4 Hz, 1 H), 5.14 (dd, J = 17.7 Hz, J = 1.4 Hz, 1 H), 6.21 (dd, J = 17.7 Hz, J = 10.9 Hz, 1 H), 7.24−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 17.8 (q), 21.9 (q), 23.5 (q), 44.0 (s), 76.7 (s), 77.3 (d), 112.7 (t), 127.6 (d), 127.8 (d), 128.1 (d), 141.1 (s), 146.6 (d). Anal. Calcd for $C_{14}H_{20}O_2$ (220.311): C, 76.33; H, 9.15. Found: C, 76.54; H, 9.20.

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Supporting Information Available: Further analytical data (NMR assignments, IR, MS) for compounds **4a** and **5a**−**5f** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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