Tunable C_2-Chiral 1,2-Diols. Syntheses of 1,4-Bis-Alkoxybutane-2*S*,3*S*-diols

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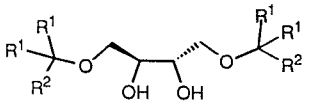
Abstract: Tunable C_2-chiral 1,4-dialkoxy-2,3-butanediols are synthesized from the reactions of the corresponding bisacetals **2** with Grignard reagents or with $LiAlH_4$-$AlCl_3$.

C_2-Chiral diols demonstrate an enormous variety of fascinating applications in asymmetric synthesis.[1,2] Ingenious and practical approaches have been made by the variation of the steric environment around the diol moiety to meet different reaction needs.[3] Since the existing methods occasionally require multistep to modify the diol ligand, there is a demand to develop a simple procedure which can furnish the desired diols having a wide range of structural variety. We now wish to report a convenient method for the regioselective synthesis of various tunable C_2-chiral 1,2-diols **1**.



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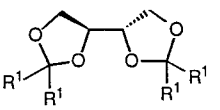

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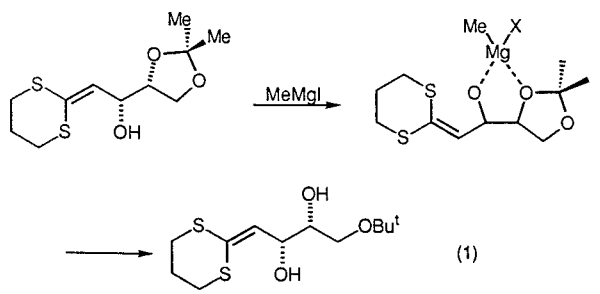
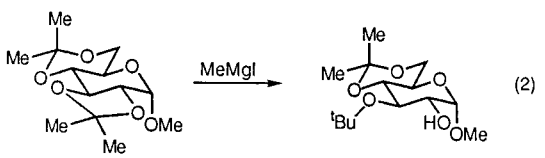
The strategy was based on our recent discovery on the regioselective alkylative ring opening of acetals with MeMgI to give the corresponding *tert*-alkoxyalcohol derivatives (eq 1).[4] The reaction is particular useful in the synthesis of various monosaccharide derivatives having only one free hydroxy group (eq 2).[4b] The idea of



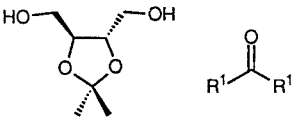
(1)



(2)

this approach relies on the possible formation of a chelation intermediate between the magnesium ion and the oxygen atoms. We felt that the reaction of 2*S*,3*S*-bisacetal **2** with the Grignard reagent would provoke a regioselective synthesis of 2*S*,3*S*-**1**. Bisacetals **2** were readily obtained from the reaction of 2*S*,3*S*-**3**[5] with ketone **4** in the presence of a catalytic amount of TsOH. Treatment of **2** with different kinds of the Grignard reagent (3-4 equivalents) in refluxing benzene afforded 1,4-bis-*tert*-alkoxybutane-2*S*,3*S*-diols **1** in good yield.[6] No other regioisomers were detected from these reactions. The results are summarized in Table 1.

As can be seen from Table 1, the size of the *tert*-alkoxy substituent can easily be tuned by varying the ketone reagent **4** or by changing the Grignard reagent. It is noteworthy that both primary and secondary Grignard reagents underwent the reaction smoothly. The regioselective formation of **1** from **2** is due to the formation of the



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4 **a** R^1 = Me

b R^1 = Et

c R^1R^1 = -$(CH_2)_4$-

d R^1R^1 = -$(CH_2)_5$-

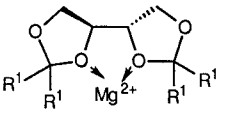

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Table 1. Reaction of **2** with Grignard reagents

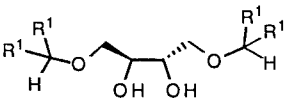
2	R^1	R^2	**1** (%yield)	$[\alpha]_D^{30}$
a	Me	Me	**a** (89)	+4.8
a	Me	Et	**b** (77)	+5.4
a	Me	i-Pr	**c** (64)	+5.5
a	Me	$PhCH_2$	**d** (60)	+2.5
b	Et	Me	**e** (85)	+1.7
c[a]	-$(CH_2)_4$-	Me	**f** (70)	+2.1
d[b]	-$(CH_2)_5$-	Me	**g** (70)	+1.5

[a] R^1R^1 = -$(CH_2)_4$-; [b] R^1R^1 = -$(CH_2)_5$-

chelation complex **5** with magnesium which results in the selective cleavage of the C-O bonds in **2**.

It is known that acetals can also undergo reductive cleavage with $LiAlH_4$-$AlCl_3$.[7] The regioselectivity of this ring opening reaction has not been explored. It is well documented that aluminum can also form chelation complexes with heteroatoms.[8,9] Accordingly, similar to **5**, complexation with the aluminum reagent would be anticipated when bisacetals **2** are employed. Reductive cleavage of the acetal moiety in **2** would lead to 1,4-bis-*sec*-alkoxybutane-2,3-diol **6**. Indeed, bis-ketals 2*S*,3*S*-**2** were allowed to react with $LiAlH_4$ in the presence of a catalytic amount $AlCl_3$ in refluxing toluene afforded 2*S*,3*S*-**6**.[10]

Again, no other regioisomeric diols (e.g. **7**) were obtained from these reactions. Representative examples are tabulated in Table 2.



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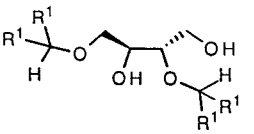

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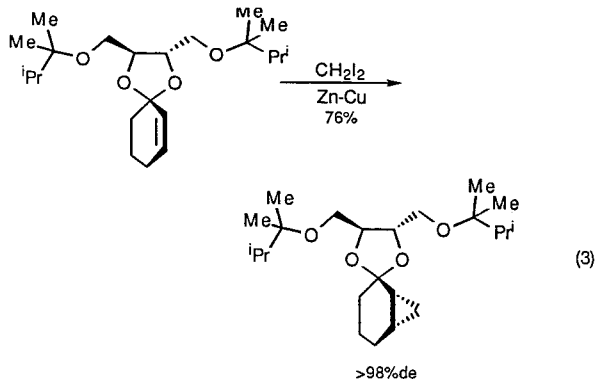
Table 2. Reduction of **2** with $LiAlH_4$-$AlCl_3$

2	R^1	**6** (%yield)	$[\alpha]_D^{25}$
a	Me	**a** (58)	-1.4
b	Et	**b** (77)	-0.4
c[a]	-$(CH_2)_4$-	**c** (64)	-0.7
d[b]	-$(CH_2)_5$-	**d** (60)	-1.6

[a] R^1R^1 = -$(CH_2)_4$-; [b] R^1R^1 = -$(CH_2)_5$-

In order to test the importance of chelation on the regioselectivity of the ring opening reaction, a sterically hindered bisketal **2e** (R^1 = i-Pr) was subjected to $LiAlH_4$-$AlCl_3$ reduction. In addition to the desired **6e** (R^1 = i-Pr, 30%), the other regioisomer **7e** (R^1 = i-Pr) was also obtained in 30% yield. Since the corresponding aluminum analogue of the intermediate complex **5** (R^1 = i-Pr and Mg is replaced by an aluminum species) would be highly congested, the reductive ring opening reaction becomes unselective. In other words, competitive coordination of the aluminum reagent with the terminal oxygen atom will result in the cleavage of the less hindered C-O bond leading to **7e**.[4a]

In summary, we have depicted an unprecedented chelation approach for the synthesis of various tunable C_2-chiral 1,4-dialkoxy-2,3-butanediols **1** and **6**. These diols might demonstrate certain unique properties to serve as an auxiliary in asymmetric synthesis. First, the size of the alkoxy substituents can be tuned. Second, the oxygen atom in the alkoxy substituent can act as an additional ligand for complexation with the metallic species which might result in the enhancement of the stereoselectivity of the reaction. We have briefly demonstrated this viewpoint by studying the diastereoselective cyclopropanation of the corresponding cyclic enone acetals (eq 3).[11] Further extension of employing these diol ligands in asymmetric synthesis is in progress in our laboratory.



(3)

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(6) **1a** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (s, 18 H), 3.03 (d, *J* = 4.8 Hz, 2 H), 3.48 (dd, *J* = 9.2, 5.3 Hz, 2 H), 3.52 (dd, *J* = 9.2, 4.7 Hz, 2 H), 3.73-3.81 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.4, 64.1, 70.9, 73.4 **1b** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, *J* = 7.5 Hz, 6 H), 1.12 (s, 12 H), 1.48 (q, *J* = 7.5 Hz, 4 H), 3.02 (d, *J* = 4.1 Hz, 2 H), 3.44 (dd, *J* = 9.1, 5.2 Hz, 2 H), 3.48 (dd, *J* = 9.1, 4.9 Hz, 2 H), 3.74 - 3.81 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.19, 24.9, 32.7, 63.6, 71.0, 75.5; 1c ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (d, *J* = 6.8 Hz, 12 H), 1.07 (s, 12 H), 1.77 (septet, *J* = 6.8 Hz, 2 H), 3.00 (d, *J* = 4.8 Hz, 2 H), 3.44 (dd, *J* = 9.0, 5.1 Hz, 2 H), 3.49 (dd, *J* = 9.0, 4.8 Hz, 2 H), 3.72-3.79 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.4, 22.0, 35.7, 63.1, 71.0, 76.6; 1d ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (s, 6 H), 1.16 (s, 6 H), 2.77 (s, 4 H), 2.81 (d, *J* = 4.2 Hz, 2 H), 3.52 (dd, *J* = 9.0, 5.6 Hz, 2 H), 3.57 (dd, *J* = 9.0, 4.8 Hz, 2 H), 3.72-3.83 (m, 2 H), 7.15-7.30 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.0, 25.1, 47.4, 63.5, 70.9, 75.7, 126.2, 127.9, 130.5, 138.0; **1e** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, *J* = 7.4 Hz, 12 H), 1.05 (s, 6 H), 1.44 (q, *J* = 7.4 Hz, 4 H), 1.45 (q, *J* = 7.4 Hz, 4 H), 3.06 (d, *J* = 4.9 Hz, 2 H), 3.40 (dd, *J* = 8.9, 5.1 Hz, 2 H), 3.45 (dd, *J* = 8.9, 4.8 Hz, 2 Hz, 2 H), 3.74-3.82 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.8, 22.0, 27.4, 29.7, 63.1, 71.0, 77.4; **1f** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (s, 6 H), 1.35-1.85 (m, 16 H), 3.01 (d, *J* = 4.8 Hz, 2 H), 3.44 (dd, *J* = 9.6, 5.0 Hz, 2 H), 3.48 (dd, *J* = 9.6, 4.8 Hz, 2 H), 3.73-3.78 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.3, 23.8, 37.8, 38.0, 64.6, 70.9, 84.9; **1g** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12 (s, 6 H), 1.17-1.70 (m, 20 H), 3.12 (d, *J* = 4.8 Hz, 2 H), 3.46 (dd, *J* = 9.1, 4.9 Hz, 2 H), 3.52 (dd, *J* = 9.1, 4.8 Hz, 2 H), 3.81-3.87 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.1, 24.6, 25.6, 36.2, 36.3, 62.9, 71.0, 74.0.

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(10) **6a** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15(d, J = 6.1 Hz, 12H), 2.91(d, J = 4.6 Hz, 2H), 3.44-3.66(m, 6H), 3.72-3.85(m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.0, 70.2, 70.8, 72.4; **6b** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.86 (t, *J*=7.4 Hz, 12 H), 1.48 (m, 8 H), 2.92 (d,*J* = 4.8 Hz, 2 H), 3.15 (quint, J=5.8 Hz, 2 H), 3.53 (dd, *J*= 6.3, 3.6 Hz, 2 H), 3.58 (dd, *J*= 6.3, 3.2 Hz, 2 H), 3.72-3.88 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.5, 25.7, 70.7, 70.8, 82.7; **6c** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39-1.84 (m, 16 H), 2.88 (d, *J* = 4.6 Hz, 2 H), 3.43-3.62 (m, 4 H), 3.70-3.85 (m, 2 H), 3.85-4.00 (m, 2 H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 24.5, 30.2, 71.4, 71.5, 82.7; **6d** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.08-1.93 (m, 28 H), 1.77-1.84 (m, 2 H), 2.65 (t, *J* = 5.7 Hz, 2 H), 3.02 (d, *J* = 4.7 Hz, 2 H), 3.57 (dd, *J*= 8.9, 4.7 Hz, 2 H), 3.61 (dd, *J* = 8.9, 3.8 Hz, 2 H), 3.72-3.88 (m, 2 H); 3.77-3.86 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.9, 25.7, 32.0, 70.0, 70.8, 78.2. **6e** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.77-0.96 (m, 24 H), 1.77-1.86 (m, 4 H), 2.65 (t, *J* = 5.7 Hz, 2 H), 3.02 (d, *J* = 4.7 Hz, 2 H), 3.59-3.71 (m, 4 H), 3.77-3.86 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.5, 17.7, 20.1, 20.2, 30.6, 70.8, 75.4, 90.8. **7e**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82-0.99 (m, 24 H), 1.73-1.92 (m, 4 H), 2.74 (t, *J* = 5.6 Hz, 1 H), 2.78 (d, *J* = 3.8 Hz, 1H, OH), 2.90 (dd, *J* = 5.7, 7.0 Hz, 1 H, OH), 3.02 (t, *J* = 4.8 Hz, 1 H), 3.51-3.59 (m, 1 H), 3.61-3.77 (m, 4 H), 3.87-3.98 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.7, 17.8, 18.5, 18.7, 20.1, 20.2, 20.3, 20.4, 30.1, 30.5, 30.6, 30.7, 61.7, 71.9, 74.0, 79.1, 87.4, 91.7.

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