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Red-Al Promoted Intramolecular Reductive Cleavage of Benzyl 4-Hydroxy-2-butenyl Ether Structures. A Concise Preparation of Polyol Chiral Building Blocks

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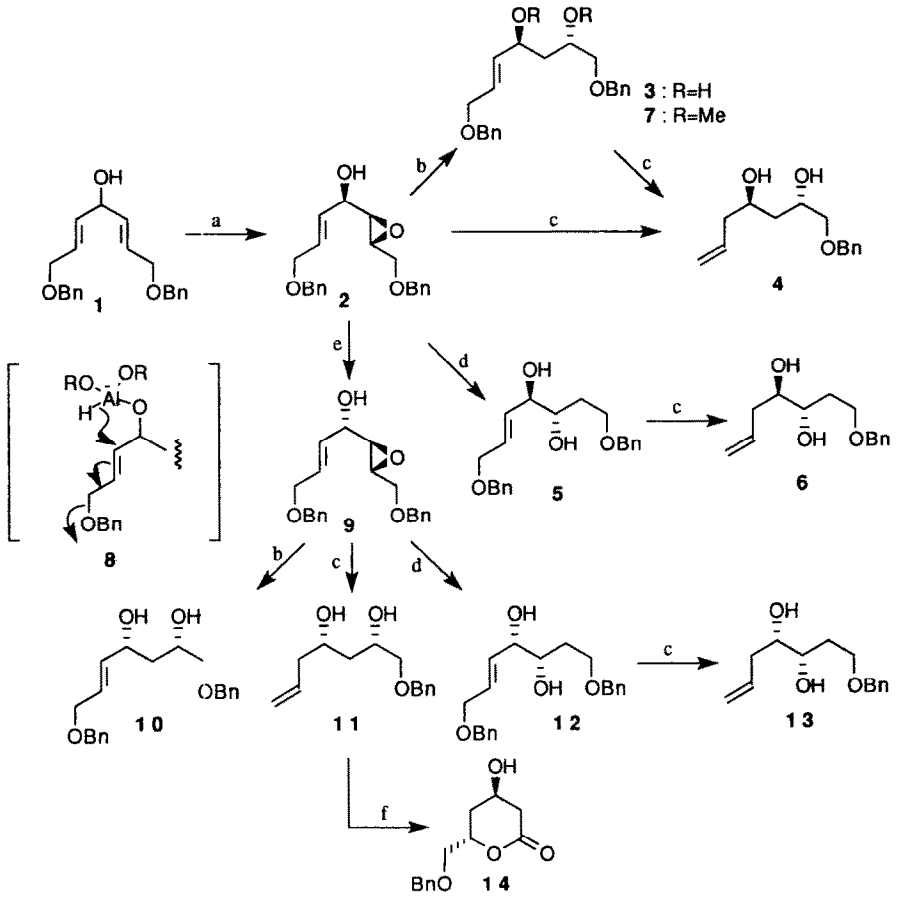
Abstract: A new concise and practical method for the preparation of polyol chiral building blocks has been developed based on the finding of unprecedented Red-Al promoted intramolecular reductive cleavage of benzyl 4-hydroxy-2-butenyl ether structures and the synthetic utility has been demonstrated by accomplishment of an expeditious synthesis of the compactin lactone derivative.

Functionalized diols of defined absolute stereochemistry are important chiral building blocks in the synthesis of various natural products including polyenemacrolide antibiotics. Much effort, therefore, has been devoted to developing an efficient method for the preparation of the subunits with 1,2- and, in particular, 1,3-diol functionalities.[2,3] We now report a new promising method for such purposes.

In the course of a search[4] for the synthetic utility of chiral epoxy alcohols derived from σ-symmetrical divinylcarbinols[4,5] by the Katsuki-Sharpless asymmetric epoxidation,[6] we have recently found that Red-Al reduction[7] of the epoxy alcohol **2** always produces a mixture of two 1,3-diols **3** and **4** and the ratio of these isomers varies with the reaction temperature. Careful examination of this reduction allowed us to find out the conditions where each of the 1,3-diols were obtained selectively. Thus, upon reduction of **2**,[8] easily prepared from **1** (82%),[5b,9] using Red-Al (10 equiv.) in toluene at –30 °C, highly regioselective reaction[10] took place to produce the diol **3**,[11] $[\alpha]_D^{30}$ +1.5° (*c* 0.998, $CHCl_3$), $[\alpha]_D^{26}$ –3.1° (*c* 1.024, MeOH), almost exclusively in 77% yield. On the other hand, reduction of **2** with Red-Al (3 equiv.) in boiling toluene[12] brought about concomitant loss of the benzyloxy group to give the diol **4**, $[\alpha]_D^{30}$ –9.9° (*c* 1.506, $CHCl_3$), as the sole product in 81% yield. The diol **3** was found to be converted to **4** quantitatively by further Red-Al reduction under the refluxing conditions. For comparison with these results, we also undertook DIBAH reduction of **2** in toluene. In this case, the reductive cleavage of the allyl benzyl ether moiety did not occur even at 110 °C, although reduction of the epoxy alcohol moiety proceeded with high regioselectivity at 0 °C to give the 1,2-diol **5** (82%), $[\alpha]_D^{30}$ +11.0° (*c* 1.416, $CHCl_3$), along with 1,3-diol **4** (6%). Upon reduction with Red-Al (3 equiv.) in boiling toluene, the 1,2-diol **5** also underwent the reductive cleavage of the benzyloxy group to give the diol **6**, $[\alpha]_D^{29}$ +15.2° (*c* 1.144, $CHCl_3$), in 61% yield. It is worthy of note that the methyl ether **7** derived from **3** turned out to be very stable in Red-Al reduction under refluxing conditions and no reaction took place even after 3 h. These results suggest that the cleavage of the benzyloxy group proceeds through an intramolecular reductive process as in **8**.

Having developed a new method for the preparation of chiral building blocks with 1,2- and 1,3-*anti*-diol functionalities, we then investigated inversion of the C-4 asymmetric center of **2** required for the synthesis of

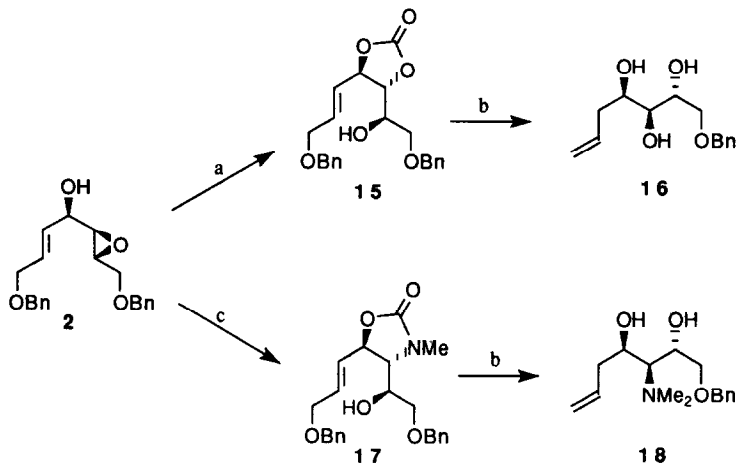
the corresponding *syn* series of diols. Although the Mitsunobu reaction under the standard conditions[13] led to unsatisfactory results, the epoxy alcohol **2** was successfully inverted to the epoxy alcohol **9**, $[\alpha]_D^{30}$ +5.2° (*c* 1.028, $CHCl_3$), in 76 % yield by the modified Mitsunobu reaction[14] followed by base catalyzed methanolysis.[15] The epoxy alcohol **9** thus obtained was then converted to four *syn*-diols **10** (89%), $[\alpha]_D^{30}$ +0.6° (*c* 1.144, $CHCl_3$), $[\alpha]_D^{30}$ –7.0° (*c* 1.004, MeOH), **11**[16] (81%), $[\alpha]_D^{30}$ +3.5° (*c* 1.002, $CHCl_3$), **12** (86%), $[\alpha]_D^{29}$ +0.3° (*c* 1.162, $CHCl_3$), $[\alpha]_D^{30}$ –20.8° (*c* 1.076, MeOH), and **13** (68%), $[\alpha]_D^{30}$ +1.6° (*c* 1.042, $CHCl_3$), in the same manner as described above for the preparation of the corresponding *anti*-isomers. The synthetic utility of the present method was exhibited, for example, by conversion of **11** into the compactin lactone **14**, $[\alpha]_D^{30}$ +8.7° (*c* 1.662, $CHCl_3$) [lit.[17] $[\alpha]_D^{30}$ +6.59° (*c* 1.032, $CHCl_3$)], a key subunit of HMG-CoA reductase inhibitors represented by compactin,[18] by successive Lemieux-Johnson oxidation and Fetizon oxidation (73% overall yield).[19]



Scheme 1. (a) diisopropyl D-tartrate (9 mol%), $Ti(O^iPr)_4$ (7 mol%), ^{t}BuOOH (2 equiv.), 4A Molecular Sieves, CH_2Cl_2, –25 °C; (b) $NaH_2Al(OCH_2CH_2OCH_3)_2$ (Red-Al) (10 equiv.), toluene, –30 °C; (c) Red-Al (3 equiv.), toluene, reflux; (d) ^{i}Bu$_2$AlH (DIBAH) (5 equiv.), toluene, 0 °C; (e) diethyl azodicarboxylate (DEAD) (5 equiv.), Ph_3P (5 equiv.), *p*-$(NO_2)C_6H_4CO_2H$ (4.4 equiv.), toluene, –20 °C; (f) (i) OsO_4 (2 mol%), $NaIO_4$ (2 equiv.), 50% aq. THF, (ii) Ag_2CO_3-Celite, benzene, reflux.

In addition, it is important to note that the cyclic carbonate **15**[5b] (85%), $[\alpha]_D^{30}$ +30.3° (*c* 1.464, $CHCl_3$), and the cyclic carbamate **17** (72 %), $[\alpha]_D^{30}$ +28.6° (*c* 1.362, $CHCl_3$), easily available from **2**,[20] were also converted to the triol **16** (68 %), $[\alpha]_D^{28}$ +1.6° (*c* 0.870, $CHCl_3$), and the amino diols **18** (84 %), $[\alpha]_D^{28}$ +8.4° (*c* 1.380, $CHCl_3$), both of which are useful chiral building blocks possessing three contiguous asymmetric centers.

Since enantiomerically pure **2** is obtainable in either antipodal form by the catalytic asymmetric epoxidation of **1** using L-tartrate or D-tartrate, the present study also enables us to prepare the corresponding enantiomers of all compounds described here.



Scheme 2. (a) (i) PhNCO (2 equiv.), pyridine (5 equiv.), CH_2Cl_2, (ii) BF_3·Et_2O (1.4 equiv.), Et_2O, –20 °C; (b) Red-Al (5 equiv.), toluene, reflux; (c) NaH (2 equiv.), MeNCO (2 equiv.), THF, 0 °C.

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12. A typical procedure of Red-Al promoted intramolecular reductive cleavage of benzyl 4-hydroxy-2-butenyl ethers. To a stirred solution of **2** (1 mmol) in toluene (24 ml) at 0 °C under argon was added a solution of Red-Al in toluene (70% (w/v); 0.87 ml, 3 mmol), and the mixture was heated under reflux for 10 min. The reaction mixture was cooled in an ice bath, diluted with Et_2O, acidified with 1M HCl (pH 3), and filtered through Celite. The filtrate was washed with sat. NaCl and sat. $NaHCO_3$, dried over $MgSO_4$, evaporated *in vacuo*, and chromatographed on silica gel .
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