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Diastereodivergent Synthesis of Optically Active *trans*- and *cis*-6-Benzyloxymethyl-4-hydroxytetrahydro-2-pyrones *via* 3-Hydroxyalkenyl Phenyl Sulfides

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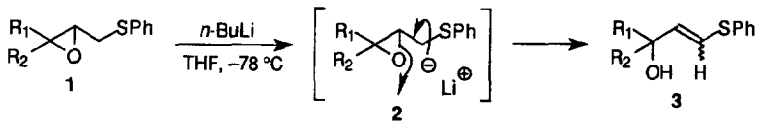
Abstract: A diastereodivergent synthesis of optically active *trans*- and *cis*-6-benzyloxymethyl-4-hydroxytetrahydro-2-pyrones has been developed *via* 3-hydroxyalkenyl phenyl sulfides by employing base-induced cleavage of the glycidyl phenyl sulfide functionality as the key step.

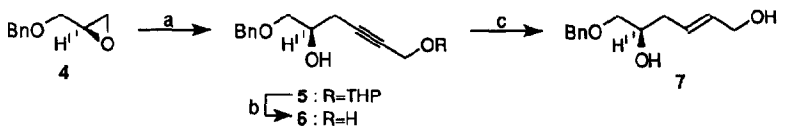
Because two 1,3-secondary oxygen functionalities are present on the chiral δ-lactone ring together with a 6-hydroxymethyl group, both of the *trans*- and *cis*-6-hydroxymethyl-4-hydroxytetrahydro-2-pyrone systems would become extremely useful building blocks in the synthesis of a wide variety of polyketide natural products as well as other polyoxygenated natural products if they were readily accessible.[1] We wish to report a new procedure for a diastereodivergent construction of these systems based on the base-induced epoxide cleavage reaction starting from the common chiral starting material. We have recently reported that glycidyl phenyl sulfides (**1**) undergo a facile cleavage reaction of the epoxide bond on exposure to *n*-butyllithium at low temperature to afford 3-hydroxyalkenyl phenyl sulfides (**3**) in excellent yields *via* transient formation of carbanion intermediates[2] (**2**) (**Scheme 1**). Since the 3-hydroxyalkenyl phenyl sulfide system may be regarded as a masked aldol, we have incorporated this functionality into the C_1-C_3 moiety of the *cis*- and *trans*-6-benzyloxymethyl-4-hydroxytetrahydro-2-pyrone systems.



Scheme 1

We first prepared the common optically active allylic alcohol (**7**) starting from readily accessible optically pure (*S*)-*O*-benzylglycidol[3] (**4**) (>98% e.e.). Thus, (*S*)-**4** was treated with the lithium acetylide generated *in situ* from propargyl tetrahydropyranyl ether (**5**) in the presence of boron trifluoride[4] to give the secondary alcohol (**5**) as a mixture of epimers. This was refluxed in methanol in the presence of pyridinium *p*-toluenesulfonate (PPTS)[5] for 6 h to afford the 1,5-diol (**6**), $[\alpha]_D^{29}$ –6.79 (*c* 1.1, $CHCl_3$), in 83.4% overall yield from **4**. Upon treatment with lithium aluminum hydride in tetrahydrofuran[6] (THF) at reflux, **6** furnished the *E*-allyl alcohol (**7**), $[\alpha]_D^{29}$ –2.65 (*c* 1.0, $CHCl_3$), selectively, in 85.7% yield (**Scheme 2**).

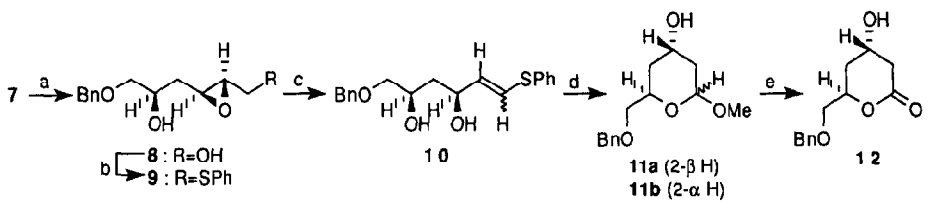
To construct *trans*-6-benzyloxymethyl-4-hydroxytetrahydro-2-pyrone (**12**), we oxidized the allyl alcohol (**7**) by employing the Katsuki-Sharpless asymmetric epoxidation reaction[7] under the stoichiometric conditions in the presence of diisopropyl (L)-tartrate to give the 2*S*,3*S*-epoxide (**8**), $[\alpha]_D^{29}$ –21.26 (*c* 1.11, $CHCl_3$), in 82.8% yield as a single product. Exposure of **8** to two equivalents of diphenyl disulfide and tri-*n*-butylphosphine in pyridine[8] at 0 °C allowed chemoselective substitution of the primary hydroxy group[9] to give



Scheme 2

Reagents and conditions: (a) ≡–CH_2–OTHP, *n*-BuLi, BF_3·OEt_2, THF, –78 °C. (b) PPTS, MeOH, reflux. (c) $LiAlH_4$, THF, reflux.

the phenyl sulfide (**9**), $[\alpha]_D^{29}$ +2.95 (*c* 1.0, $CHCl_3$), in 81.1% yield. The key base-induced cleavage reaction of **9** proceeded as expected though it did not exhibit stereoselectivity in the formation of the olefinic bond. Thus, upon exposure to three equivalents of *n*-butyllithium in THF at –78 °C, the sulfide (**9**) afforded the 3,5-dihydroxyalkenyl phenyl sulfide (**10**) in 80.6% yield as an inseparable 3:2 *E*/*Z*-mixture by cleavage of the epoxide bond. Treatment of **10** with mercury(II) acetate and mercury(II) oxide in methanol[10] allowed transformation of the vinyl sulfide bond into the acetal bond to furnish a mixture of two cyclic acetals (**11**) after reductive workup using sodium borohydride. Both of the epimers could be separated by silica gel column chromatography to give the α-methoxy epimer **11a**, $[\alpha]_D^{27}$ –81.01 (*c* 0.5, $CHCl_3$), and the β-methoxy epimer **11b**, $[\alpha]_D^{28}$ +56.91 (*c* 1.0, $CHCl_3$), in yields of 29.2 and 41.7%, respectively. Finally, the mixture was treated sequentially with 70% acetic acid and *N*-iodosuccinimide (NIS) and tetrabutylammonium iodide[11] to give *trans*-(4*S*,6*R*)-6-benzyloxymethyl-4-hydroxytetrahydro-2-pyrone (**12**), $[\alpha]_D^{29}$ –9.80 (*c* 0.6, $CHCl_3$) [lit.[12]: $[\alpha]_D^{29}$ +6.59 (*c* 1.03, $CHCl_3$) for the enantiomer], in 41% yield. The enantiomer of **12** is a structural unit of the HMG-CoA reductase inhibitors compactin and mevinolin and responsible for their physiological activity[13] (**Scheme 3**).

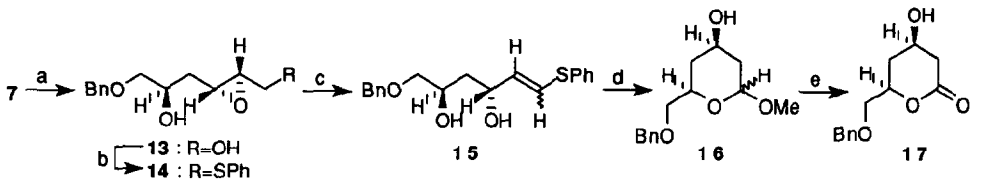


Scheme 3

Reagents and conditions: (a) (L)-DIPT, *t*-BuOOH, $(i\text{-PrO})_4Ti$, 4A sieves, –30 °C. (b) PhSSPh, *n*-Bu_3P, pyridine, 0 °C, 30 min. (c) *n*-BuLi (3 eq.), THF, –78 °C, 30 min. (d) $Hg(OAc)_2$, HgO, MeOH, –20 °C ~ room temp., 2 h then $NaBH_4$, –20 °C. (e) 70% AcOH, 50 °C, 6 h then NIS, *n*-Bu_4NI, CH_2Cl_2, room temp.

On the other hand, to construct the diastereomer *cis*-6-benzyloxymethyl-4-hydroxytetrahydro-2-pyrone (**17**), the allyl alcohol (**7**) was epoxidized enantioselectively in a similar manner as above by employing the Katsuki-Sharpless asymmetric epoxidation reaction in the presence of diisopropyl (D)-tartrate to give the 2*R*,3*R*-epoxide (**13**), $[\alpha]_D^{29}$ +30.93 (*c* 1.0, $CHCl_3$), in 73.5% yield as a single epimer. In a quite similar way, **13** was transformed into the sulfide (**14**), $[\alpha]_D^{29}$ +4.94 (*c* 1.2, $CHCl_3$), in 78.4%, which was then subjected to the key reaction using three equivalents of *n*-butyllithium to give the 3,5-dihydroxyalkenyl sulfide (**15**) in 71.6% yield as an inseparable 3:2 *E*/*Z*-mixture. Treatment of the mixture with the mercury salts as above furnished the cyclic acetal (**16**) in 71.6% yield as an inseparable mixture. Finally, on sequential hydrolysis and

oxidation, this mixture afforded single *cis*-(4*R*,6*R*)-6-benzyloxymethyl-4-hydroxytetrahydro-2-pyrone (**17**), $[\alpha]_D^{29}$ –18.71 (*c* 0.9, $CHCl_3$), in 43.2% yield (**Scheme 4**).



Scheme 4

Reagents and conditions: (a) (D)-DIPT, *t*-BuOOH, $(i\text{-PrO})_4Ti$, 4A sieves, –30 °C. (b) PhSSPh, $n\text{-Bu}_3P$, pyridine, 0 °C, 30 min. (c) *n*-BuLi (3 eq.), THF, –78 °C, 30 min. (d) $Hg(OAc)_2$, HgO, MeOH, –20 °C ~ room temp., 2 h then $NaBH_4$, –20 °C. (e) 70% AcOH, 50 °C, 6 h then NIS, $n\text{-Bu}_4NI$, CH_2Cl_2, room temp.

In summary, a general method for the diastereodivergent preparation of optically active *cis*- and *trans*-6-benzyloxymethyl-4-hydroxytetrahydro-2-pyrones has been developed *via* 3,5-dihydroxyalkenyl phenyl sulfides by employing the base-induced cleavage of glycidyl phenyl sulfide functionality starting from readily accessible (*S*)-*O*-benzylglycidol. Although the present report describes the preparation of one enantiomeric forms, it can also be applicable to the synthesis of antipodal forms since (*R*)-*O*-benzylglycidol is also readily accessible.

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References and Notes

1. For example, Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. Ager, D. J.; East, M. B. *Tetrahedron* **1992**, *48*, 2803.
2. Takano, S.; Sugihara, Y.; Ogasawara, K. *Synlett* **1992**, 668. Takano, S.; Sugihara, Y.; Ogasawara, K. *Tetrahedron Lett.* **1993**, *34*, 845.
3. Synthetic utilities of optically active *O*-benzylglycidol: Takano, S.; Ogasawara, K. *J Syn. Org. Chem. Jpn.* **1987**, *45*, 1157; **1989**, *47*, 813. Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437. Takano, S. *J. Pharm. Soc. Jpn.* **1991**, *111*, 647.
4. Yamaguchi, M. 'Comprehensive Organic Synthesis,' Trost, B. M.; Schreiber, S. L. Eds. Pergamon, Oxford, 1991, Vol. 1, Chapter, 1 11. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 341.
5. Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.
6. Chanley, J. D.; Sobotka, H. *J. Am. Chem. Soc.* **1949**, *71*, 4140. Attenburrou, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094. Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245.
7. Johnson, R. A.; Sharpless, K. B. 'Comprehensive Organic Synthesis,' Trost, B. M. Ed. Pergamon, Oxford, 1991, Vol. 7, Chapter 3.2. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
8. Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409. Nakagawa, I.; Aki, T.; Hata, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1315.
9. Takano, S.; Goto, E.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 5567.

10. Davidson, A. H.; Floyd, C. D.; Lewis, C. N.; Myers, P. L. *J. Chem. Soc., Chem Commun.* **1988**, 1417.
11. Hanessian, S.; Wong, H. -C.; Therien, M. *Synthesis* **1981**, 394. Lee, T. -J. *Tetrahedron Lett.* **1985**, *26*, 4995.
12. Takano, S.; Shimazaki, Y.; Sekiguchi, Y.; Ogasawara, K. *Synthesis* **1989**, 539.
13. For example, Endo, A. *J. Med. Chem.* **1985**, *28*, 401. Vega, L.; Grundy, S. *J. Med. Assoc.* **1987**, *257*, 33.
14. Physical data for the synthetic compounds: IR (cm^{-1}); ^{1}H-NMR (δ); High resolution MS (Calcd: Found). **5**: 3444; 7.33 (br s, 5H), 4.78 (m, 1H), 4.56 (s, 2H), 4.24 (m, 2H), 4.03-3.38 (m, 5H), 2.55-2.43 (m, 3H), 1.61 (m, 6H); $C_{18}H_{24}O_4$ (304.1675: 304.1699). **6**: 3376, 2286, 2224; 7.33 (br s, 5H), 4.55 (s, 2H), 4.20 (br s, 2H), 3.93 (m, 1H), 3.61-3.32 (m, 2H), 3.08 (br s, 1H), 2.68 (br s, 1H), 2.46 (dt, 2H, *J*=2.2 and 6.1 Hz); $C_{13}H_{16}O_3$ (220.1099: 220.1086. **7**: 3388, 1668; 7.33 (br s, 5H), 5.74-5.65 (m, 2H), 4.54 (s, 2H), 4.08 (br s, 2H), 3.92-3.74 (m, 1H), 3.50 (dd, 1H, *J*=3.4 and 9.5 Hz), 3.34 (dd, 1H, *J*=6.3 and 9.5 Hz), 2.52-2.12 (m, 4H); $C_{13}H_{18}O_3$ (M^+-H_2O) (204.1156: 204.1149). **8**: 3398; 7.31 (br s, 5H), 4.52 (s, 2H), 4.10-2.85 (m, 9H), 1.80-1.66 (m, 2H); $C_{13}H_{18}O_4$ (M^+) (238.1205: 238.1188). **9**: 3456; 7.48-7.19 (m, 10H), 4.52 (s, 2H), 4.02-3.74 (m, 1H), 3.52-3.26 (m, 2H), 3.03-2.78 (m, 4H), 2.47 (br s, 1H), 1.72-1.59 (m, 2H); $C_{19}H_{22}O_3S$ (M^+) (330.1290: 330.1278). **10**: 3404, 1582; 7.37-7.22 (m, 10H), 6.46 (br d, 0.64 x 1H, *J*=15.1 Hz), 6.28 (br d, 0.36 x 1H, *J*=9.5 Hz), 5.97-5.68 (m, 1H), 4.91 (m, 0.36 x 1H), 4.55 (s, 0.36 x 2H), 4.53 (s, 0.64 x 2H), 4.52 (m, 0.64 x 1H), 4.14 (m, 1H), 3.56-3.38 (m, 2H), 3.20 (br s, 1H), 2.99 (br s, 1H), 1.82-1.57 (m, 2H); $C_{19}H_{22}O_3S$ (330.1290: 330.1292). **11a**: 3528; 7.33 (br s, 5H), 4.91 (m, 1H), 4.60 (s, 2H), 4.36-4.01 (m, 2H), 3.66-3.38 (m, 3H), 3.41 (s, 3H), 1.92-1.64 (m, 4H); $C_{13}H_{16}O_3$ (M^+-CH_4O) (220.1099: 220.1086). **11b**: 3450; 7.33 (br s, 5H), 4.76 (dd, 1H, *J*=2.6 and 9.0 Hz), 4.59 (s, 2H), 4.40-3.99 (m, 3H), 3.59-3.51 (m, 2H), 3.51 (s, 3H), 1.90-1.53 (m, 4H); $C_{13}H_{16}O_3$ (M^+-CH_4O) (220.1099: 220.1111). **12**: 3436, 1713; 7.32 (br s, 5H), 4.84 (m, 1H), 4.56 (s, 2H), 4.36 (m, 1H), 3.71 (dd, 1H, *J*=3.9 and 10.7 Hz), 3.57 (dd, 1H, *J*=4.4 and 10.5 Hz), 2.81 (br s, 1H), 2.61 (m, 2H), 1.94 (m, 2H); $C_{13}H_{17}O_4$ (M^++H) (237.1127: 237.1128). **13**: 3398; 7.32 (br s, 5H), 4.54 (s, 2H), 4.27-2.79 (m, 8H), 2.51 (br s, 1H), 2.04-1.41 (m, 2H). **14**: 3462; 7.46-7.18 (m, 10H), 4.52 (s, 2H), 3.82 (m, 1H), 3.56-2.84 (m, 6H), 2.57 (br d, 1H), 1.90-1.47 (m, 2H); $C_{19}H_{22}O_3S$ (330.1290: 330.1264). **15**: 3396; 7.33 (br s, 10H), 6.48 (br d, 0.58 x 1H, *J*=15.1 Hz), 6.29 (br d, 0.42 x 1H, *J*=9.5 Hz), 5.97-5.75 (m, 1H), 4.89 (m, 0.42 x 1H), 4.57 and 4.55 (2 x s, 2H), 4.47 (m, 0.58 x 1H), 4.28-3.98 (m, 1H), 3.52-3.36 (m, 2H), 3.05-2.79 (m, 2H), 1.83-1.60 (m, 2H). **16**: 3418; 7.33 (br s, 5H), 4.90 (br d, 1H), 4.59 (s, 2H), 4.29-3.92 (m, 2H), 3.54-3.49 (m, 2H), 3.34 (s, 3H), 2.18-1.26 (m, 5H); $C_{14}H_{20}O_4$ (M^+) (252.1362: 252.1335). **17**: 3440, 1732; 7.32-7.29 (m, 5H), 4.59 (dd, 2H, *J*=12.2 Hz), 4.45 (dt, 1H, *J*=4.3 and 14.5 Hz), 4.23 (m, 1H), 3.66 (ddd, 2H, *J*=4.3 and 10.4 Hz), 2.85 (ddd, 1H, *J*=1.2, 5.5, and 17.1 Hz), 2.57 (br d, 1H), 2.51 (dd, 1H, *J*=7.3 and 17.1 Hz), 2.29 (ddt, 1H, *J*=1.2, 4.9, and 14.0 Hz), 1.81 (ddd, 1H, *J*=8.5, 9.7 and 14.0 Hz); $C_{13}H_{17}O_4$ (M^++H) (237.1127: 237.1107).