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A CONVERGENT ENANTIOCONTROLLED ROUTE TO MEVALONOLACTONE AND VITAMIN E FROM (*S*)-*O*-BENZYLGLYCIDOL

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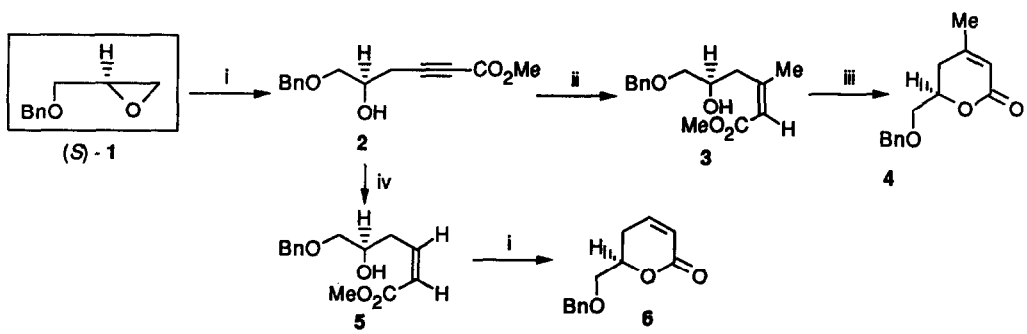
Summary: A convergent enantiocontrolled route to (+)- and (–)-mevalonolactones and vitamin E has been developed using (*S*)-*O*-benzylglycidol as the sole chiral block.

We report herein a convergent enantiocontrolled route to both enantiomers of mevalonolactone [(*R*)- and (*S*)-**14**][1] and natural vitamin E[2] (**41**) starting from (*S*)-*O*-benzylglycidol[3] (**1**) as the sole chiral building block.[4] The present study illustrates a particular advantage of utilizing a chiral glycerol unit for the construction of tertiary and quaternary centers in the target molecules.

Treatment of (*S*)-*O*-benzylglycidol (**1**) with methyl lithiopropiolate in the presence of $BF_3 \cdot Et_2O$[5] gave the 5-hydroxyhex-2-ynoate (**2**) (84%), $[\alpha]_D^{29}$ –14.7° (*c* 1.07, $CHCl_3$). This was treated with lithium dimethylcuprate to give the (*Z*)-5-hydroxy-3-methylhex-2-enoate (**3**), selectively,[6] which cyclized spontaneously to afford the α,β-unsaturated-δ-lactone[7] (**4**) (91%), $[\alpha]_D^{29}$ +120.9° (*c* 1.12, $CHCl_3$). On the other hand, hydrogenation of **2** yielded the *Z*-olefin (**5**) which gave the unsaturated δ-lactone[7] (**6**) (80% overall), $[\alpha]_D^{27}$ +115.1° (*c* 1.00, $CHCl_3$), after acid work-up (**Scheme 1**).



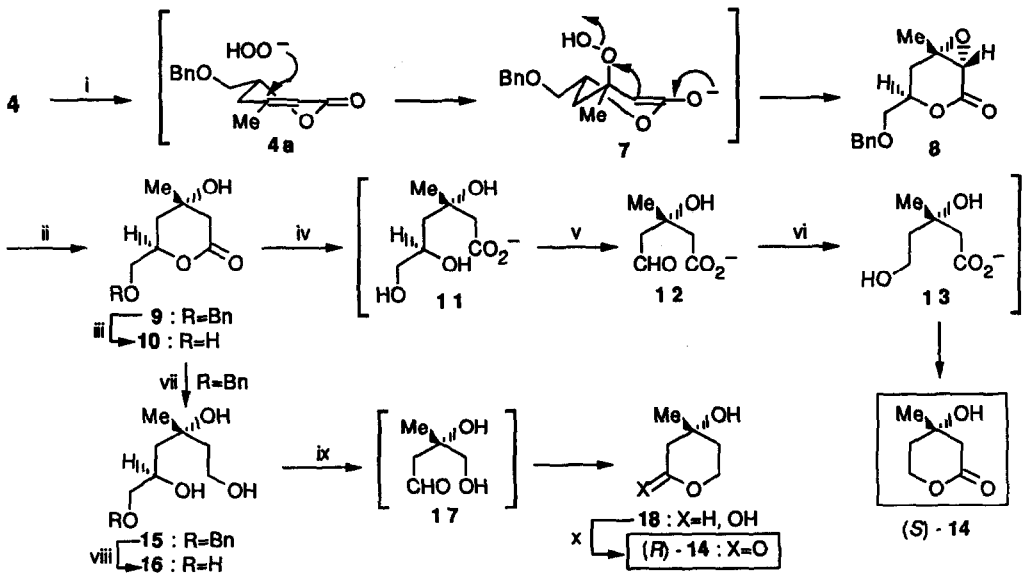
Scheme 1

Conditions: i) methyl propiolate, ^nBuLi, $BF_3 \cdot OEt_2$, THF, –90 °C; ii) Me_2CuLi, THF, –70 °C; iii) aq. NH4Cl; iv) H_2, Lindlar catalyst, benzene, quinoline (cat.); v) PPTS, benzene, reflux.

Upon exposure to 30% hydrogen peroxide in methanolic 6N-NaOH, **4** afforded the epoxide (**8**) (70%), $[\alpha]_D^{29}$ –21.9° (*c* 1.02, $CHCl_3$), as a single epimer after acid work-up. Remarkable stereoselectivity observed may be due to the favorable stereoelectronic effect of the α,β-unsaturated-δ-lactone system (**4a**) as shown.[8] Cleavage of the epoxide moiety could be neatly carried out regioselectively by treating **8** with sodium phenylseleno(triisopropyloxy)borate generated in the same flask[7,9] to afford the β-hydroxylactone (**9**) (90%), $[\alpha]_D^{28}$ –3.28° (*c* 1.02, $CHCl_3$). After catalytic debenzylation of **9**, the resulting diol (**10**), $[\alpha]_D^{28}$ +3.54° (*c* 1.13, MeOH), was sequentially saponified, cleaved, and reduced in the same flask to give unnatural (*S*)-mevalono-

lactone [(*S*)-**14**] (90% overall), $[\alpha]_D^{27}$ +22.3° (*c* 1.07, EtOH), [lit.[1a] $[\alpha]_D$ +22.8° (*c* 1.0, EtOH)], after acid work-up.

The same intermediate (**9**), on the other hand, was first reduced with $LiAlH_4$ to give the triol (**15**) (~100%), $[\alpha]_D^{27}$ +8.44° (*c* 1.09, MeOH). Upon sequential debenzylation, periodate cleavage, and Jones oxidation, **15** furnished natural (*R*)-mevalonolactone [(*R*)-**14**] (79% overall), $[\alpha]_D^{28}$ −21.8° (*c* 1.10, EtOH) [lit.[1a] $[\alpha]_D$ −23.0° (*c* 6.0, EtOH)] via **16**, **17**, and **18** (**Scheme 2**).

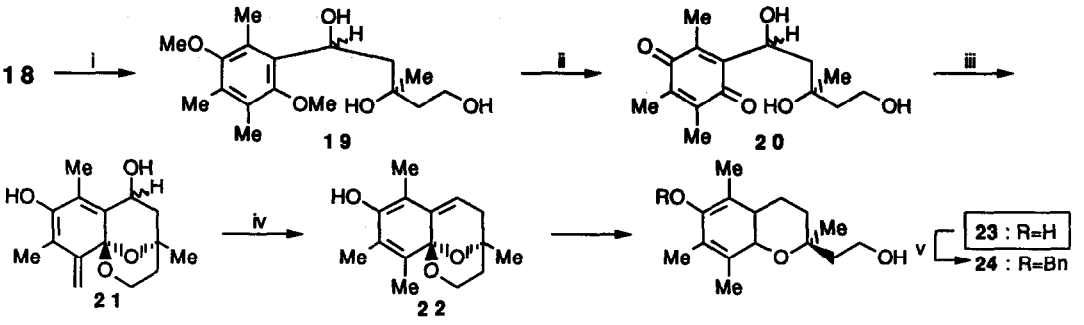


Scheme 2

Conditions: i) 30% H_2O_2, 6N NaOH, MeOH; ii) PhSeSePh, $NaBH_4$, CH_3CO_2H, ^iPrOH; iii) H_2, $Pd(OH)_2$-C (20%), MeOH; iv) 20% aq. NaOH; v) CO_2 gas then $NaIO_4$; vi) $NaBH_4$ then HCl; vii) $LiAlH_4$, THF; viii) H_2, $Pd(OH)_2$-C, MeOH; ix) HIO_4, H_2O; x) H_2SO_4, CrO_3.

In order to construct vitamin E (**41**), synthesis of the chroman moiety (**23**), to which the vitamin owes most of its activity,[10] was first carried out using the lactol intermediate (**18**) above. Reaction of **18** with an excess 2,5-dimethoxy-3,4,6-trimethylphenylmagnesium bromide (9 equiv.) afforded the triol (**19**), quantitatively, as a mixture of two epimers (ca. 1:1). Treatment of **19** with an excess cerium(IV) ammonium nitrate (CAN) (6 equiv.) afforded the benzoquinone (**20**) (63%). Acid catalyzed cyclization of **19** in refluxing dioxane occurred in an unprecedented way to give the trienediol (**21**) which on hydrogenation furnished the chromanethanol[14] (**23**) (70% overall), $[\alpha]_D^{29}$ −4.06° (*c* 0.7, MeOH), mp 137 – 138 °C (lit.[14] mp 136.5 – 137.5 °C), via trienol[13] (**22**). Finally, **23** was converted into the benzyl ether[15,16] (**24**) (80%), $[\alpha]_D^{29}$ −15.99° (*c* 1.15, $CHCl_3$) [lit.[15]: $[\alpha]_D^{25}$ −16.21° (*c* 2.03, $CHCl_3$)], mp 57 – 58 °C [lit.[15]: 55 – 56 °C] (**Scheme 3**).

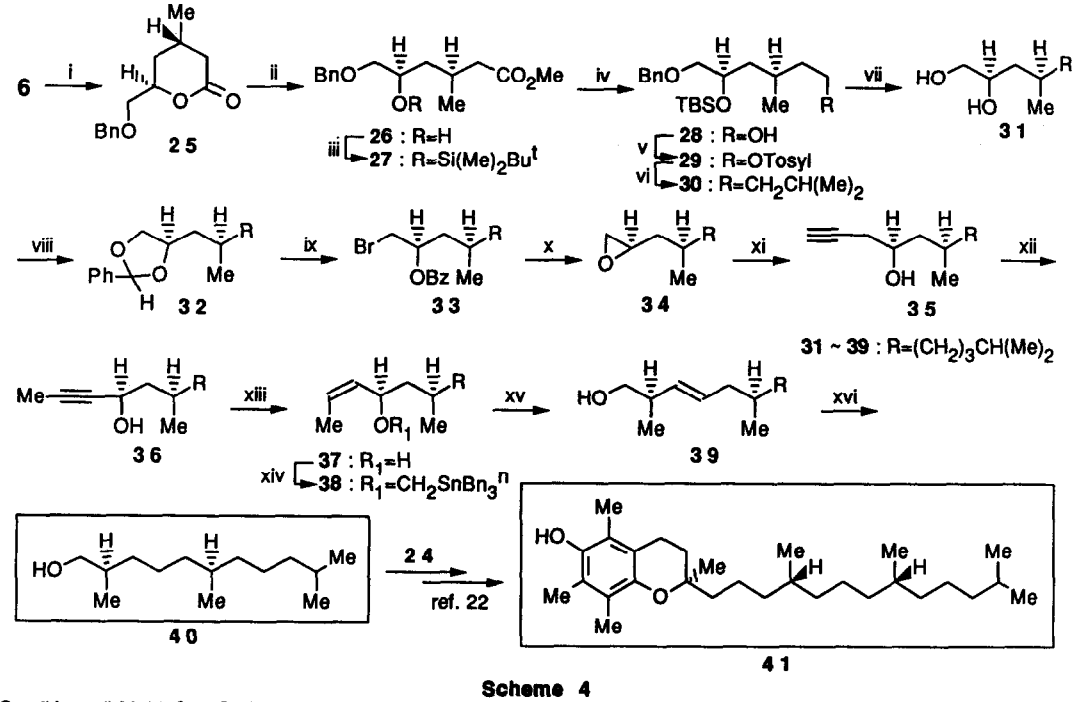
For the construction of the side chain moiety (**40**) of vitamin E (**41**) the δ-lactone (**6**) was first treated with lithium dimethylcuprate to give the secondary methyl lactone (**25**) (74%), $[\alpha]_D^{25}$ −33.33° (*c* 1.01, $CHCl_3$), with complete anti-stereoselection. On methanolysis followed by the protection,



Scheme 3

Conditions: i) 2,5-dimethoxy-3,4,6-trimethylphenylmagnesium bromide, THF, 0 °C; ii) CAN, aq. CH_3CN (1:1); iii) 2N-H_2SO_4, dioxane, reflux; iv) H_2, $Pd(OH)_2$-C, MeOH, cat. $CHCl_3$; v) BnCl, K_2CO_3, DMF.

25 afforded the silyl ether (**27**) (76% overall), $[\alpha]_D^{30}$ +8.84° (*c* 1.00, $CHCl_3$), via the seco-ester (**26**). Reduction of **27** with $LiAlH_4$, followed by tosylation of the resulting alcohol (**28**), $[\alpha]_D^{31}$ +5.49° (*c* 1.03, $CHCl_3$), gave the tosylate (**29**), $[\alpha]_D^{27}$ +8.08° (*c* 1.06, $CHCl_3$), which was treated with isobutylmagnesium bromide in the presence of copper(I) iodide to give the coupling product (**30**) (92% overall), $[\alpha]_D^{29}$ +9.63° (*c* 1.22, $CHCl_3$). Hydrogenolysis of **30** in methanol containing



Scheme 4

Conditions: i) MeLi, CuI, Et_2O, 0 °C; ii) K_2CO_3, MeOH; iii) TBDMSCl, imidazole, DMF; iv) $LiAlH_4$, THF; v) TsCl, Et_3N, CH_2Cl_2; iv) ^iBuMgBr, CuI(cat.), THF, –30 °C; vii) H_2, $Pd(OH)_2$-C (20%), MeOH, $CHCl_3$ (cat); viii) TsOH (cat.), benzene, reflux; ix) NBS, CCl_4; x) NaOH, THF-MeOH (5:1); xi) $LiC{\equiv}CH{\cdot}H_2NCH_2CH_2NH_2$, DMSO; xii) ^tBuOK, DMSO; xiii) H_2, Lindlar catalyst, benzene, quinoline (cat.); xiv) KH, $^nBu_3SnCH_2I$, THF; xv) ^nBuLi, THF, –70 → –20 °C; xvi) H_2, Pd-C (10%), AcOEt.

a trace of chloroform was proceeded with spontaneous desilylation to give the diol (**31**) (95%), $[\alpha]_D^{31}$ +9.33° (*c* 1.10, $CHCl_3$). After benzylidenation of **31**, the resulting acetal (**32**) was treated sequentially with NBS and sodium hydroxide to give the epoxide (**34**), $[\alpha]_D^{29}$ +13.45° (*c* 1.57, $CHCl_3$), via the bromobenzoate (**33**).[3b] Treatment of **34** with lithium acetylide gave the terminal acetylene (**35**), $[\alpha]_D^{28}$ +5.52° (*c* 1.09, $CHCl_3$), which on exposure to potassium *tert.* butoxide in DMSO[17] brought about the migration[17] to afford the internal acetylene[18] (**36**), $[\alpha]_D^{27}$ +10.36° (*c* 2.92, $CHCl_3$) [lit.[18]: $[\alpha]_D^{25}$ +10.52° (*c* 3.32, $CHCl_3$)]. Overall yield of **36** from **31** was 53.4%. Hydrogenation of **36**, followed by treating the resulting *Z*-alcohol (**37**), $[\alpha]_D^{25}$ +19.95° (*c* 3.22, $CHCl_3$) [lit.[18]: $[\alpha]_D^{25}$ +19.65° (*c* 5.01, $CHCl_3$)], with tri-*n*-butylstanylmethyl iodide[19] afforded the stannyl ether (**38**) (70% overall), $[\alpha]_D^{28}$ +1.77° (*c* 2.32, hexane). When **38** was exposed to *n*-butyllithium a smooth [2,3]-Wittig rearrangement occurred to furnish the homo-allylic alcohol (**39**) (77%), $[\alpha]_D^{29}$ +21.85° (*c* 1.12, hexane), which was hydrogenated to give the known alcohol[21] (**40**) (80%), $[\alpha]_D^{27}$ +8.78° (*c* 1.2, hexane) [lit.[20]: $[\alpha]_D^{25}$ +9.36° (*c* 2.02, hexane)] (**Scheme 4**).

Since synthesis of vitamin E (**41**) by assemblage of the chroman moiety (**24**) and the side chain moiety (**40**) has already been established,[22] the present procedure utilizing the sole chiral building block (**1**) constitutes a formal enantiocontrolled synthesis of the vitamin (**41**).

References and Notes

1. Recent enantiocontrolled syntheses, see: (a) S. Takano, M. Morimoto, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 82 (1984); (b) F. Bonadie, G. Rossi, and C. Bonini, *Tetrahedron Lett.*, **25**, 5431 (1984); S. V. Frye and E. L. Eliel, *J. Org. Chem.*, **50**, 3402 (1985); K. Mori and K. Okada, *Tetrahedron*, **41**, 557 (1985).
2. A recent example, see: S. Inoue, H. Ikeda, S. Sato, K. Horie, T. Ota, O. Miyamoto, and K. Sato, *J. Org. Chem.*, **52**, 5497 (1987) and references cited therein.
3. (a) S. Takano, K. Seya, E. Goto, M. Hirama, and K. Ogasawara, *Synthesis*, 116 (1983); (b) S. Takano, M. Akiyama, and K. Ogasawara, *ibid.*, 503 (1985).
4. A review on the utilization of chiral *O*-benzylglycidol in natural product synthesis, see: S. Takano and K. Ogasawara, *J. Syn. Org. Chem. Jpn.*, **47**, 813 (1989).
5. S. P. Munt and E. J. Thomas, *J. Chem. Soc., Chem. Commun.*, 480 (1989).
6. Cf. E. J. Corey and J. A. Katzenellenbogen, *J. Am. Chem. Soc.*, **91**, 1851 (1969); J. B. Sidall, M. Biskup, and J. H. Fried, *ibid.*, **91**, 1853 (1969).
7. Cf. S. Takano, Y. Shimazaki, Y. Sekiguchi, and K. Ogasawara, *Synthesis*, 539 (1989).
8. P. Deslongchamps, "Stereoelectronic Effects in Organic Chemistry," p. 209, Pergamon, Oxford, 1983.
9. M. Miyashita, T. Suzuki, and A. Yoshikoshi, *Tetrahedron Lett.*, **28**, 4293 (1987); M. Miyashita, M. Hoshino, T.
10. Cf. E. Niki, *J. Syn. Org. Chem. Jpn.*, **47**, 902 (1989).
11. R. Barner and M. Schmid, *Helv. Chim. Acta*, **62**, 2384 (1979).
12. Compound **12**: ir ($CHCl_3$) ν 3350 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 1.39 (s, 3H), 1.6 – 1.9 (m, 4H), 2.12 (s, 3H), 2.18 (s, 3H), 2.90 (br.s, 1H exchangeable with D_2O), 3.3 – 3.8 (m, 2H), 4.7 – 5.0 (m, 3H), 7.0 (br.s, 1H exchangeable with D_2O); m/z 264 (M^+), 201 (100%).
13. Compound **13**: ir ($CHCl_3$) ν 3350 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 1.40 (s, 3H), 1.6 – 1.8 (m, 4H), 2.12 (s, 3H), 2.18 (s, 3H), 2.22 (s, 3H), 3.20 – 3.75 (m, 2H), 4.25 (br.s, exchangeable with D_2O), 5.05 (m, 1H); m/z 248 (M^+), 203 (100%).
14. N. Cohen, R. J. Lopresti, and G. Saucy, *J. Am. Chem. Soc.*, **101**, 6710 (1979).
15. N. Cohen, R. J. Lopresti, and C. Newkom, *J. Org. Chem.*, **46**, 2445 (1981).
16. Optical purity of **24** was estimated to be >98% e.e. by ^1H n.m.r. analysis (500 MHz) of its MTPA (both enantiomers) esters.
17. S. Takano, Y. Sekiguchi, N. Sato, and K. Ogasawara, *Synthesis*, 139 (1987).
18. The same compound has been obtained via resolution, see: K. -K. Chan, N. Cohen, J. P. DeNoble, A. C. Specian, Jr., and G. Saucy, *J. Org. Chem.*, **41**, 3497 (1978).
19. Cf. M. M. Midland and Y. C. Kwon, *Tetrahedron Lett.*, **26**, 5013 (1982).
20. J. W. Scott, F. T. Bizzarro, D. R. Parrish, and G. Saucy, *Helv. Chim. Acta*, **59**, 290 (1976).
21. Diastereoselectivity of the [2,3]-Wittig rearrangement process was estimated to be ≥90% d.e. by ^1H n.m.r. analysis (500 MHz) of MTPA (both enantiomers) esters of **40**.
22. N. Cohen, W. F. Eichel, R. J. Lopresti, C. Newkom, G. Saucy, *J. Org. Chem.*, **41**, 3505 (1976).

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