

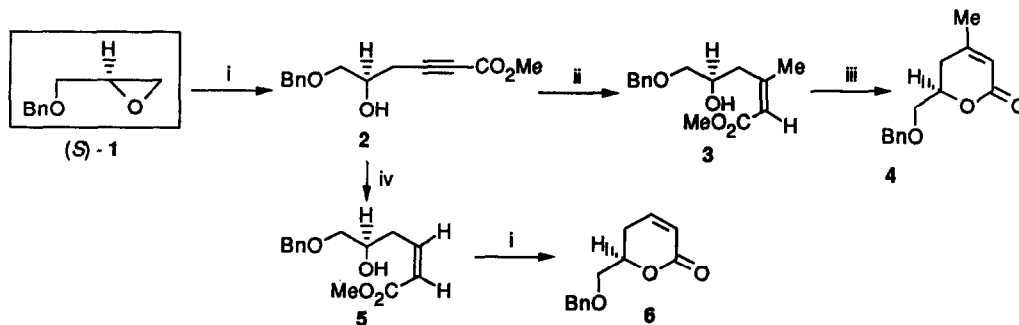
A CONVERGENT ENANTIOCONTROLLED ROUTE TO MEVALONOLACTONE AND VITAMIN E FROM (S)-O-BENZYLGLYCIDOL

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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 E² (**41**) starting from (S)-O-benzylglycidol³ (**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 BF₃·Et₂O⁵ gave the 5-hydroxyhex-2-ynoate (**2**) (84%), [α]_D²⁹ -14.7° (c 1.07, CHCl₃). 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 -lactone⁷ (**4**) (91%), [α]_D²⁹ +120.9° (c 1.12, CHCl₃). On the other hand, hydrogenation of **2** yielded the Z-olefin (**5**) which gave the unsaturated δ -lactone⁷ (**6**) (80% overall), [α]_D²⁷ +115.1° (c 1.00, CHCl₃), after acid work-up (Scheme 1).

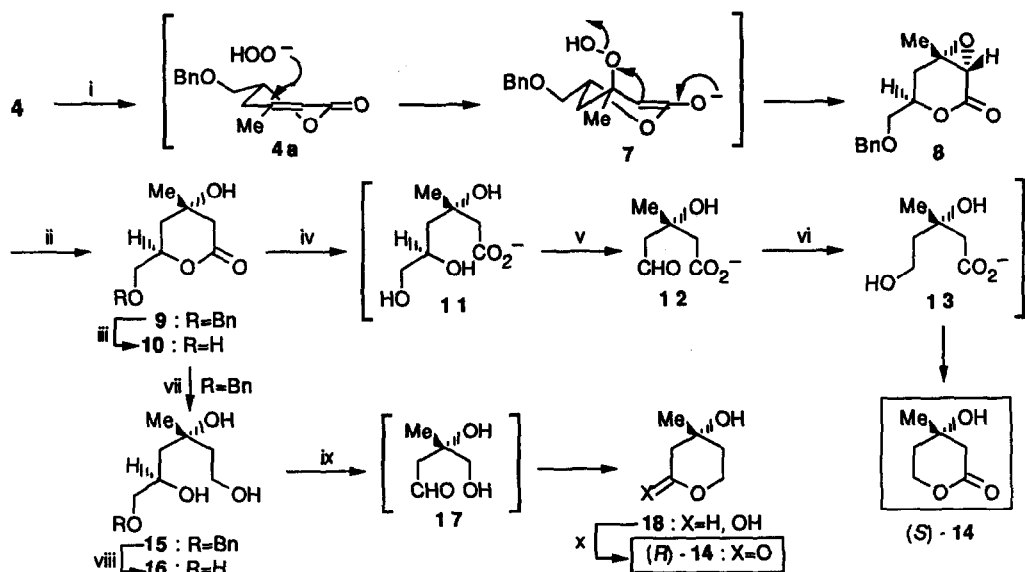


Conditions: i) methyl propiolate, ⁿBuLi, BF₃·OEt₂, THF, -90 °C; ii) Me₂CuLi, THF, -70 °C; iii) aq. NH₄Cl; iv) H₂, Lindlar catalyst, benzene, quinoline (cat.); v) PPTS, benzene, reflux.

Upon exposure to 30% hydrogen peroxide in methanolic 6N-NaOH, **4** afforded the epoxide (**8**) (70%), [α]_D²⁹ -21.9° (c 1.02, CHCl₃), 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(triisopropoxy)borate generated in the same flask^{7,9} to afford the β -hydroxylactone (**9**) (90%), [α]_D²⁸ -3.28° (c 1.02, CHCl₃). After catalytic debenzoylation of **9**, the resulting diol (**10**), [α]_D²⁸ +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), $[\alpha]_D^{27} +22.3^\circ$ (*c* 1.07, EtOH), [lit.^{1a} $[\alpha]_D +22.8^\circ$ (*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%), $[\alpha]_D^{27} +8.44^\circ$ (*c* 1.09, MeOH). Upon sequential debenzylation, periodate cleavage, and Jones oxidation, 15 furnished natural (*R*)-mevalonolactone [(*R*)-14] (79% overall), $[\alpha]_D^{28} -21.8^\circ$ (*c* 1.10, EtOH) [lit.^{1a} $[\alpha]_D -23.0^\circ$ (*c* 6.0, EtOH)] via 16, 17, and 18 (Scheme 2).

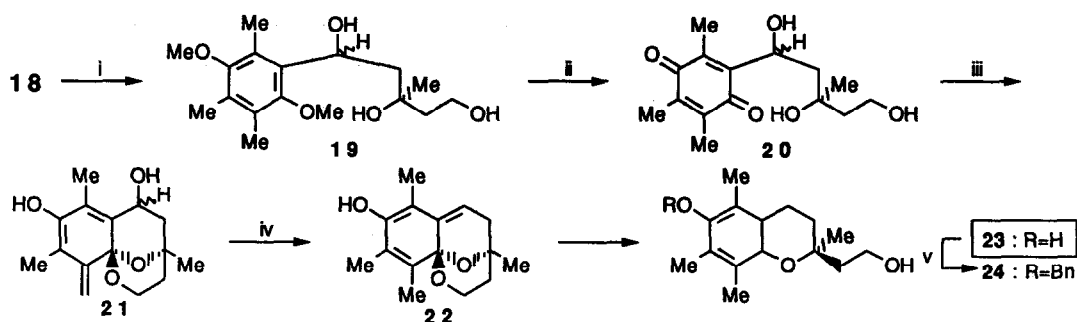


Scheme 2

Conditions: i) 30% H_2O_2 , 6N NaOH, MeOH; ii) PhSePh , NaBH_4 , $\text{CH}_3\text{CO}_2\text{H}$, $i\text{PrOH}$; iii) H_2 , $\text{Pd}(\text{OH})_2\text{-C}$ (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 , $\text{Pd}(\text{OH})_2\text{-C}$, MeOH; ix) HIO_4 , H_2O ; x) H_2SO_4 , CrO_3 .

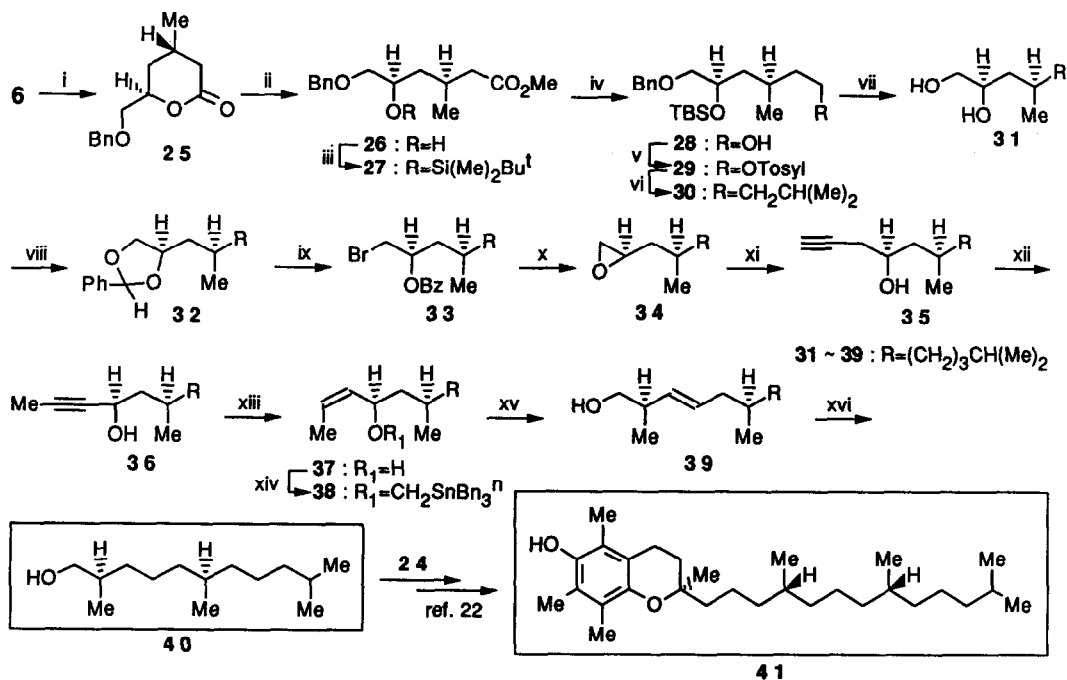
In order to construct vitamin E (41), synthesis of the chroman moiety (23), to which the vitamin owes most of its activity,¹⁰ was first carried out using the lactol intermediate (18) above. Reaction of 18 with an excess 2,5-dimethoxy-3,4,6-trimethylphenylmagnesium bromide (9 equiv.) afforded the triol (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 chromanethanol¹⁴ (23) (70% overall), $[\alpha]_D^{29} -4.06^\circ$ (*c* 0.7, MeOH), mp $137 - 138^\circ\text{C}$ (lit.¹⁴ mp $136.5 - 137.5^\circ\text{C}$), via trienol¹³ (22). Finally, 23 was converted into the benzyl ether^{15,16} (24) (80%), $[\alpha]_D^{29} -15.99^\circ$ (*c* 1.15, CHCl_3) [lit.¹⁵: $[\alpha]_D^{25} -16.21^\circ$ (*c* 2.03, CHCl_3)], mp $57 - 58^\circ\text{C}$ [lit.¹⁵: $55 - 56^\circ\text{C}$] (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%), $[\alpha]_D^{25} -33.33^\circ$ (*c* 1.01, CHCl_3), with complete anti-stereoselection. On methanolysis followed by the protection,



Conditions: i) 2,5-dimethoxy-3,4,6-trimethylphenylmagnesium bromide, THF, 0 °C; ii) CAN, aq. CH₃CN (1:1); iii) 2N-H₂SO₄, dioxane, reflux; iv) H₂, Pd(OH)₂-C, MeOH, cat. CHCl₃; v) BnCl, K₂CO₃, DMF.

25 afforded the silyl ether (27) (76% overall), $[\alpha]_D^{30} +8.84^\circ$ (*c* 1.00, CHCl₃), via the seco-ester (26). Reduction of 27 with LiAlH₄, followed by tosylation of the resulting alcohol (28), $[\alpha]_D^{31} +5.49^\circ$ (*c* 1.03, CHCl₃), gave the tosylate (29), $[\alpha]_D^{27} +8.08^\circ$ (*c* 1.06, CHCl₃), which was treated with isobutylmagnesium bromide in the presence of copper(I) iodide to give the coupling product (30) (92% overall), $[\alpha]_D^{29} +9.63^\circ$ (*c* 1.22, CHCl₃). Hydrogenolysis of 30 in methanol containing



Conditions: i) MeLi, CuI, Et₂O, 0 °C; ii) K₂CO₃, MeOH; iii) TBDMSCl, imidazole, DMF; iv) LiAlH₄, THF; v) TsCl, Et₃N, CH₂Cl₂; vi) ⁱBuMgBr, CuI(cat.), THF, -30 °C; vii) H₂, Pd(OH)₂-C (20%), MeOH, CHCl₃ (cat); viii) TsOH (cat.), benzene, reflux; ix) NBS, CCl₄; x) NaOH, THF-MeOH (5:1); xi) LiC≡CH+H₂NCH₂CH₂NH₂, DMSO; xii) ^tBuOK, DMSO; xiii) H₂, Lindlar catalyst, benzene, quinoline (cat.); xiv) KH, ⁿBu₃SnCH₂l, THF; xv) ⁿBuLi, THF, -70 → -20 °C; xvi) H₂, Pd-C (10%), AcOEt.

a trace of chloroform was proceeded with spontaneous desilylation to give the diol (**31**) (95%), $[\alpha]_D^{31} +9.33^\circ$ (*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**), $[\alpha]_D^{29} +13.45^\circ$ (*c* 1.57, CHCl_3), via the bromobenzoate (**33**).^{3b} Treatment of **34** with lithium acetylide gave the terminal acetylene (**35**), $[\alpha]_D^{28} +5.52^\circ$ (*c* 1.09, CHCl_3), which on exposure to potassium *tert.* butoxide in DMSO¹⁷ brought about the migration¹⁷ to afford the internal acetylene¹⁸ (**36**), $[\alpha]_D^{27} +10.36^\circ$ (*c* 2.92, CHCl_3) [lit.¹⁸: $[\alpha]_D^{25} +10.52^\circ$ (*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**), $[\alpha]_D^{25} +19.95^\circ$ (*c* 3.22, CHCl_3) [lit.¹⁸: $[\alpha]_D^{25} +19.65^\circ$ (*c* 5.01, CHCl_3)], with tri-*n*-butylstanylmethyl iodide¹⁹ afforded the stannyl ether (**38**) (70% overall), $[\alpha]_D^{28} +1.77^\circ$ (*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%), $[\alpha]_D^{29} +21.85^\circ$ (*c* 1.12, hexane), which was hydrogenated to give the known alcohol²¹ (**40**) (80%), $[\alpha]_D^{27} +8.78^\circ$ (*c* 1.2, hexane) [lit.²⁰: $[\alpha]_D^{25} +9.36^\circ$ (*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

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- 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%).
- 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%).
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