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Enantioselective Synthesis of (*R*)- and (*S*)-2-Alkyl-1,4-butanediols *via* Enantiomerically Pure 3-Alkyl-5-(menthyloxy)butyrolactones

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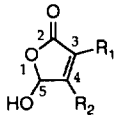
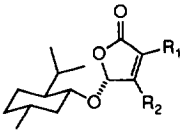
Abstract *: A general and practical synthesis of optically pure (R)- and (S)-2-ethyl, 2-propyl and 2-isopropyl-1,4-butanediols, 9a–c, has been accomplished from optically pure 5-(menthyloxy)butenolides in five steps in good yields.* Copyright © 1996 Elsevier Science Ltd

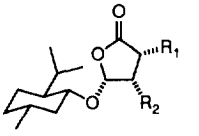
In connection with our ongoing project, we needed an efficient and practical way to prepare optically pure 2-alkyl substituted 1,4-butanediols in large quantities. Literature survey revealed that there have been only few reports for the synthesis of optically pure 2-methyl-1,4-butanediols **5**.[1-3] Feringa and co-workers reported two potentially practical methods for enantioselective synthesis of diols **5a** and **5b**, both of which involved the use of optically pure 5-(*l*-menthyloxy)butenolides **2a–c**. In the first reaction, the diols were synthesized by stereoselective hydrogenation of 3- or 4-methyl substituted butenolides **2b** and **2c** followed by LAH reduction of butyrolactones **3b** and **3c**.[2] In the second reaction, the conjugate addition of lithium anion of tris(methylthio)methane to unsubstituted butenolide **2a** followed by desulfurization of the adduct **4** and LAH reduction afforded optically pure diol **5a**.[3] Based on these two reports, we envisioned that the general synthesis of optically pure 2-alkyl substituted 1,4-butanediols would be feasible if we can prepare enantiomerically pure 3- or 4-alkyl mono-substituted 5-(menthyloxy)butenolides or come up with appropriate carboanion equivalent for conjugate addition. It was well documented that optically pure 5-(*l*-menthyloxy)butenolides **2a–c** were prepared from 5-hydroxybutenolides **1a–c** in 36–50 % yields by condensation with *l*-menthol followed by repeated crystallization-epimerization process.[2] However, in our case the attempt to obtain optically pure 4-ethyl, 4-propyl or 4-isopropyl-5-(*l*-menthyloxy)butenolides **2d–f** from readily available recemic 4-alkyl-5-hydroxybutenolides **1d–f**[4] was not successful since both of two diastereomers were too much soluble (petroleum ether, *n*-hexane, pentane, *etc.*) for selective crystallization. As for the second approach, a series of experiments including



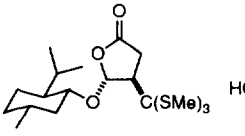
1a:R_1=R_2=H
1b:R_1=Me, R_2=H
1c:R_1=H, R_2=Me
1d:R_1=H, R_2=Et
1e:R_1=H, R_2=*n*-Pr
1f:R_1=H, R_2=*i*-Pr



2a:R_1=R_2=H
2b:R_1=Me, R_2=H
2c:R_1=H, R_2=Me
2d:R_1=H, R_2=Et
2e:R_1=H, R_2=*n*-Pr
2f:R_1=H, R_2=*i*-Pr



3a:R_1=R_2=H
3b:R_1=Me, R_2=H
3c:R_1=H, R_2=Me



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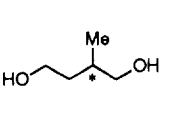
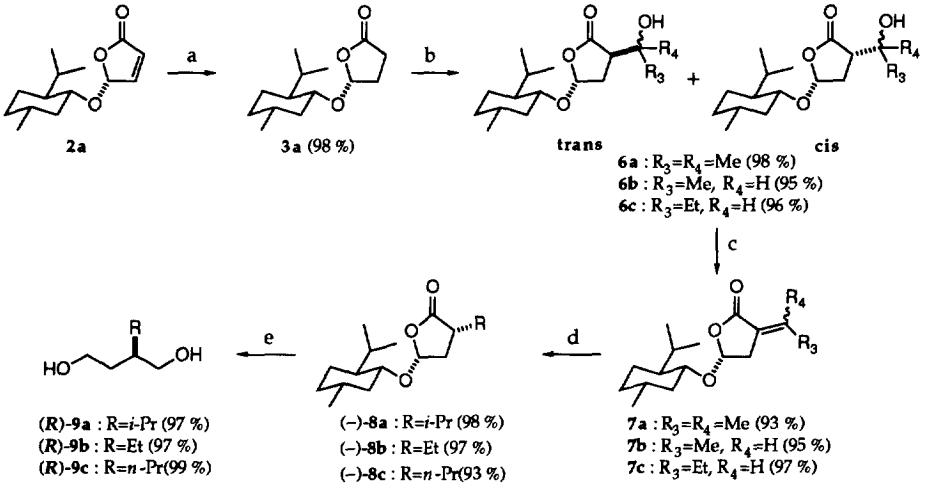


5a:(*R*)
5b:(*S*)

copper or manganese(II) mediated conjugate additions of organometallic compounds[5] to **2a** turned out to be unfruitful. On the basis of these observations, we finally concluded that both of these two methods could not be extended to the synthesis of optically pure 1,4-butanediols with other alkyl substituents at C-2 than methyl group.

In this communication, a general and practical synthesis of optically pure (*R*)- and (*S*)-2-ethyl, 2-propyl and 2-isopropyl-1,4-butanediols is described. Our approach involves the aldol reaction, elimination of aldol adducts, stereoselective hydrogenation of *exo*-butenolides and LAH reduction of enantiomerically pure 3-alkyl-5-(menthyloxy)butyrolactones as shown in Scheme 1.

Scheme 1[a]



[a](a) H_2 (50 psi), 10 % Pd/C, Et_3N (0.1 equiv.), EtOAc, rt, 16 h; (b) LDA (1.2 equiv.), THF, –78 °C, 30 min, then R_3COR_4 (1.2 equiv. for **6a**, 4.0 equiv. for **6b** or 2.0 equiv. for **6c**), –78 °C, 1 h; (c) MsCl (2.0–3.0 equiv.), Et_3N (5.0 equiv.), 1,2-dichloroethane, 0 °C, 30 min, then rt, 2 h, then reflux, 5 h; (d) H_2 (50 psi), 10 % Pd/C, Et_3N (0.1 equiv.), EtOH, rt, 2 h for **7a**, 5 h for **7b** or 50 °C, 40 h for **7c**; (e) $LiAlH_4$ (2.0 equiv.), THF, reflux, 2 h.

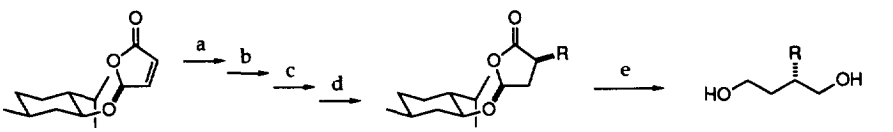
Synthesis began with 5-(*R*)-(*l*-menthyloxy)butenolide **2a** which was prepared in an improved yield of 68 % by modifyng the published procedures.[2,6,7] Butenolide **2a** was hydrogenated under a Parr condition in ethyl acetate/triethylamine to give butyrolactone **3a** in almost quantitative yield. Lithiation of butyrolactone **3a** with LDA (1.2 equiv., 30 min at –78 °C, THF) followed by trapping of the enolate (1 h at –78 °C) with acetone (1.2 equiv.), acetaldehyde (4.0 equiv.) or propionaldehyde (2.0 equiv.) afforded the corresponding aldol products **6a–c** in excellent yields (>95 %). As expected, all the possible diastereomers were produced in the aldol reactions and the ratios of diastereomeric mixtures were obtained from ^1H NMR spectra in benzene-d_6. NMR analysis showed that diastereoselectivities ranged from 4.7:1 (**6a**, acetone), 2.2:1 (**6b**, acetaldehyde) to 1.4:1 (**6c**, propionaldehyde) favoring the sterically less hindered *trans* isomers which have the absolute configuration of (*R*) at C-3 center. Diastereomeric mixtures of aldol products were treated with methanesulfonyl chloride (2.0–3.0 equiv.) and triethylamine (5.0 equiv.) in 1,2-dichloroethane for 30 min at 0 °C and then for 2 h at room temperature. Refluxing of the resulting reaction mixture for 5 h afforded elimination products **7a–c** in excellent yields (93–97 %). It is especially noteworthy that the butyrolactone with *exo*-double bond was isolated as the sole product in this elimination reaction and no trace of *endo* isomer

was observed in all cases. Note also that two geometrical isomers about the *exo*-double bond were formed in the E:Z ratios of 3.1:1 and 3.9:1 from **6b** and **6c**, respectively. With these *exo*-butenolides in hand, we tried to convert the *exo* compounds **7a–c** to *endo* isomers prior to hydrogenation but it was not possible under the treatment with DBU in refluxing solvents such as dichloromethane, acetonitrile and 1,2-dichloroethane. These observations strongly indicate that the *exo*-butenolides are *the themodynamic* products.

In the meantime, we investigated the possibility of using *exo*-butenolides **7a–c** for hydrogenation. The *exo*-butenolide **7a** was first reduced under a Parr hydrogenation condition (ethanol, 10 % Pd/C, 50 psi of H_2) in the presence of some triethylamine (0.1 equiv.) at room temperature for 24 h. Gratifyingly, hydrogenation of **7a** proceeded with complete stereocontrol to give enantiomerically pure 3-isopropyl-5-(*l*-menthyloxy)butyrolactone **8a** in 98 % yield. A single diastereomer was observed in the ^{1}H NMR and ^{13}C NMR spectra of the hydrogenation product. The *cis* relationship between the isopropyl group at the C-3 position in **8a** and the menthyloxy substituent was deduced from the fact that the hydrogenation of optically pure C-5 substituted *exo*-butenolide has been known to occur from the opposite side of the sterically demanding C-5 group to afford predominantly *cis*-3,5-disubstituted butyrolactone.[8] Two other *exo*-butenolides **7b** and **7c** were hydrogenated also in completely stereoselective manner to give the corresponding optically pure 3-ethyl- and 3-propyl-5-(*l*-menthyloxy)butyrolactones **8b** and **8c** in 93–97 % yields. The NMR spectra (^{1}H and ^{13}C) of the hydrogenation products showed only a single diastereomer and this has been further proved by the following direct alkylation study. The reaction of enolate derived from butyrolactone **3a** with ethyl iodide yielded a mixture of two diastereomers which were readily separable by flash column chromatography on silica gel. A careful comparison of each diastereomer's spectra clearly tells that the hydrogenation product **8b** is indeed a single isomer. It is interesting to observe that the rate of hydrogenation was somewhat dependent on the substitution in **7a–c**; i.e., it took only about 2 h at room temperature for **7a**, 5 h at room temperature for **7b** and 40 h even at 50 °C for **7c**. Finally, the LAH reduction (2.0 equiv., THF, reflux) of the butyrolactones **8a–c** afforded enantiomerically pure (*R*)-2-alkyl-1,4-butanediols **9a–c** in >97 % yields.

Since Feringa and co-workers have already proved[3] that the stereochemical integrity was completely maintained during LAH reduction of enantiomerically pure 3- or 4-methyl-5-(*l*-menthyloxy)butyrolactones **3b**, **3c** and the optical purities of the resulting diols were >98 % ee, there is no doubt on the fact that the diols (*R*)-**9a**, (*R*)-**9b** and (*R*)-**9c** are enantiomerically pure. In the same manner, other enantiomers, (*S*)-2-alkyl-1,4-butanediols (*S*)-**9a–c** were also synthesized by starting with 5-(*S*)-(*d*-menthyloxy)butenolide[2] as shown in scheme 2.

Scheme 2[a]



(+)-**8a** : R=*i*-Pr
(+)-**8b** : R=Et
(+)-**8c** : R=*n*-Pr

(*S*)-**9a** : R=*i*-Pr (97 %)
(*S*)-**9b** : R=Et (96 %)
(*S*)-**9c** : R=*n*-Pr(99 %)

[a] See footnote of Scheme 1.

In conclusion, we have reported a quite efficient and practical route to the synthesis of optically pure 3-alkyl-5-(menthyloxy)butyrolactones, (+)- and (–)-**8a–c**[9], and 2-alkyl-1,4-butanediols, (*R*)- and (*S*)-**9a–c**[9]. This approach could be easily scaled up and the optically pure diols have been prepared in 0.15 mole scale.

References and Notes

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   (b) Poss, A. J.; Smyth, M. S. *Tetrahedron Lett.* **1987**, *28*, 5469.
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7. Reaction of **1a** (2.0 mole) with *l*-menthol (1.92 mole) in the presence of a catalytic amount of *p*-TsOH (10 mmole) in benzene (3 L) at reflux temperature for 20 h with azeotropic removal of H_2O using a Dean-Stark trap afforded a mixture of **2a** and its diastereomer in 90 % yield after vacuum distillation. Diastereomerically pure **2a** was obtained in 59 % yield after single crystallization with petroleum ether (4.5 L) at −20 °C. Epimerization of the mother liquor in the presence of a catalytic amount of *p*-TsOH followed by crystallization afforded an additional amount of diastereomerically pure **2a** (9 %).
8. Tomioka, K.; Mizuguchi, H.; Koga, K. *Chem. Pharm. Bull.* **1982**, *30*, 4304.
9. Physical and spectral data. (−)-**8a** : a colorless oil; $[\alpha]^{20}_D$ −189.5 ° (*c* 1.0, $CHCl_3$); IR (neat) 1388, 1456, 1775 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.65 (dd, *J* = 5.4, 5.2 Hz, 1 H), 3.54 (td, *J* = 10.8, 4.2 Hz, 1 H), 2.36–2.55 (m, 2 H), 2.08–2.26 (m, 3 H), 1.84–1.92 (m, 1 H), 1.62–1.69 (m, 2 H), 1.30–1.43 (m, 1 H), 1.18–1.28 (m, 1 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 0.96 (d, *J* = 7.2 Hz, 3 H), 0.93 (d, *J* = 7.2 Hz, 3 H), 0.88 (d, *J* = 7.2 Hz, 3 H), 0.79 (d, *J* = 6.9 Hz, 3 H), 0.70–1.00 (m, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 176.9, 99.0, 77.5, 47.8, 46.1, 39.9, 34.3, 31.4, 31.0, 28.6, 25.3, 23.0, 22.2, 20.9, 20.5, 18.7, 15.6. (+)-**8a** : $[\alpha]^{20}_D$ +189.7 ° (*c* 1.0, $CHCl_3$). (−)-**8b** : a white solid, mp 70.4–71.3 °C (hexane); $[\alpha]^{20}_D$ −188.3 ° (*c* 1.94, $CHCl_3$); IR (KBr) 1175, 1456, 1749 (C=O) cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 5.13 (dd, *J* = 5.7, 4.2 Hz, 1 H), 3.45 (td, *J* = 10.5, 4.2 Hz, 1 H), 2.30–2.44 (m, 1 H), 1.70–2.04 (m, 4 H), 1.36–1.54 (m, 4 H), 1.01–1.30 (m, 2 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H), 0.77 (t, *J* = 7.5 Hz, 3 H), 0.60–0.80 (m, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 178.0, 99.4, 77.4, 47.7, 41.2, 39.8, 34.3, 34.2, 31.4, 25.4, 24.6, 23.0, 22.2, 20.9, 15.5, 11.8. (+)-**8b** : $[\alpha]^{20}_D$ +187.6 ° (*c* 1.7, $CHCl_3$). (−)-**8c** : a white solid, mp 71.9–72.3 °C (hexane); $[\alpha]^{20}_D$ −178.5 ° (*c* 1.07, $CHCl_3$); IR (KBr) 1174, 1458, 1756 (C=O) cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 5.15 (dd, *J* = 5.7, 4.2 Hz, 1 H), 3.46 (td, *J* = 10.8, 4.2 Hz, 1 H), 2.32–2.42 (m, 1 H), 2.03–2.13 (m, 1 H), 1.75–1.89 (m, 3 H), 1.03–1.54 (m, 8 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H), 0.75 (t, *J* = 7.2 Hz, 3 H), 0.80–0.73 (m, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 178.2, 99.4, 77.4, 47.8, 39.8, 39.5, 34.7, 34.3, 33.5, 31.4, 25.4, 23.0, 22.3, 20.9, 20.7, 15.6, 13.7. (+)-**8c** : $[\alpha]^{20}_D$ +182.4 ° (*c* 1.02, $CHCl_3$). (*R*)-**9a** : a colorless oil; $[\alpha]^{20}_D$ −10.2 ° (*c* 1.0, MeOH); IR (neat) 1044, 1466, 3330 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.93 (br s, 2 H), 3.74–3.81 (m, 1 H), 3.66 (dd, *J* = 10.5, 3.6 Hz, 1 H), 3.56–3.64 (m, 1 H), 3.51 (dd, *J* = 10.5, 7.8 Hz, 1 H), 1.66–1.82 (m, 2 H), 1.41–1.61 (m, 2 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.88 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 64.7, 61.6, 45.4, 32.8, 29.6, 19.8, 19.3. (*S*)-**9a** : $[\alpha]^{20}_D$ +10.0 ° (*c* 1.0, MeOH). (*R*)-**9b** : a colorless oil; $[\alpha]^{20}_D$ −0.67 ° (*c* 3.88, MeOH); IR (neat) 1064, 1463, 3343 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.89 (br s, 2 H), 3.72–3.83 (m, 1 H), 3.58–3.66 (m, 2 H), 3.45 (dd, *J* = 10.6, 6.6 Hz, 1 H), 1.50–1.76 (m, 3 H), 1.20–1.44 (m, 2 H), 0.91 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 65.8, 60.9, 40.9, 35.3, 24.4, 11.4. (*S*)-**9b** : $[\alpha]^{20}_D$ +0.61 ° (*c* 3.76, MeOH). (*R*)-**9c** : a colorless oil; $[\alpha]^{20}_D$ −3.63 ° (*c* 2.12, MeOH); IR (neat) 1040, 1466, 3320 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (br s, 2 H), 3.72–3.78 (m, 1 H), 3.58–3.67 (m, 2 H), 3.44 (dd, *J* = 10.5, 6.9 Hz, 1 H), 1.52–1.72 (m, 3 H), 1.18–1.38 (m, 4 H), 0.90 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 66.1, 60.9, 39.1, 35.7, 34.0, 20.1, 14.3. (*S*)-**9c** : $[\alpha]^{20}_D$ +3.11 ° (*c* 3.18, MeOH).

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