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Efficient Stereocontrol of a Quaternary Chiral Center in the Cyclohexene Systems. Potential Chiral Synthons for Vitamin D and Related Compounds by Enzymatic Approach[1)]

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Abstract: *Cyclohexene derivatives, 8 ~ 11, fused to γ-lactone with angular methyl are efficiently prepared in an enantio-, stereo- and regioselective manner from the chiral monoester 1.*

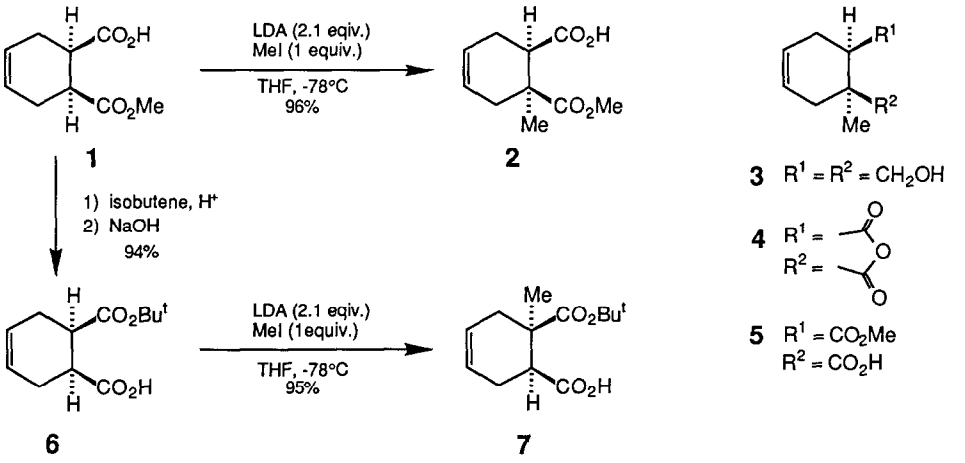
The stereocontrol of a quaternary chiral carbon center is one of the important subjects in asymmetric synthesis, and indeed some efficient methodologies have been developed by employing chiral enolate[2)] or chiral electrophile[3)]. Corey has recently described the acylation of the chiral enolate derived from dimenthyl (*R,R*)-*trans*-1,2-cyclohex-4-enedicarboxylate, which was successfully applied to the enantioselective synthesis of bilobalide[4)]. This prompted us to report our results utilizing the chiral monoester **1**, 1-methyl hydrogen (1*S*,2*R*)-1,2-cyclohex-4-enedicarboxylate. The chiral monoester **1** is now available in multi hundred gram scale by the PLE-mediated hydrolysis of the corresponding symmetric diester[5)]. We have demonstrated the usefulness of **1** as a versatile chiral synthon by synthesizing fortamine[6)], an aminocyclitol moiety of fortimicin A, and thienamycin[7)].

We report here the efficient conversion of the monoester **1** into the both enantiomers of the methylated bicyclic lactones **8** and **9** having methyl group at the angular position, which are considered as valuable starting materials for the synthesis of vitamin D and related compounds[8)].

We first examined to introduce the methyl group at C-1 of the chiral monoester **1**. Thus, **1** was treated with LDA (2.1 equiv) and HMPT (2.1 equiv) in THF at -78°C, and the resulting dianion was then reacted with methyl iodide (1 equiv) at -78°C for 20 min to afford the methylated monoester **2**[9)] in 96% yield. The stereochemistry of **2** was determined by converting to the diol **3** [$LiAlH_4$], and comparison of **3** with the authentic sample (racemic) prepared from racemic-**4**.

In a separate experiment, the chiral monoester **1** was transformed to the *t*-butyl monoester **6**[5)], regarded as a formal enantiomer conversion. The *t*-butyl monoester **6** was then reacted with LDA and methyl iodide in the same manner as for **1** to obtain the methylated product **7**[9)] in 95% yield.

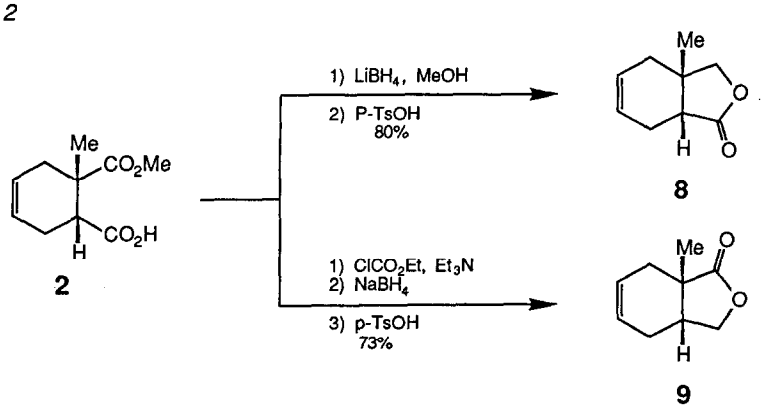
Scheme 1



The efficiency and the stereoselectivity are excellent, and the formation of the trans isomer was not detected at all in any methylation step. Although the ester groups are different in **2** and **7**, these derivatives are enantiomeric in a stereochemical point of view, and we could thus establish the enantioselective route to the both enantiomers. Enantiomerically pure **2** has previously been obtained by resolution of the racemic **2**[10] with cinchonidine[8b], and applied for the synthesis of decalin and hydrindan derivatives.

Furthermore, it should be mentioned here that our method can afford the monoester also in a regioselective manner, since the methylation occurs exclusively at the α to the alkoxycarbonyl group. This is in sharp contrast with the previous method. For example, the methanolysis of the anhydride (±)-**4** resulted in the formation of (±)-**2** and (±)-**5** in *ca* 1.6 : 1 ratio[8a].

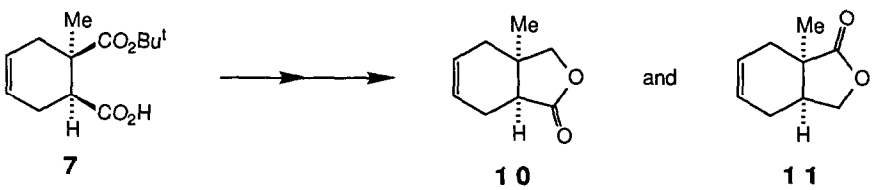
Scheme 2



Although the chiral monoesters **2** and **7** or even the corresponding diacids[11] are valuable starting materials, we further examined the conversion to the bicyclic γ-lactone derivatives. As shown in Scheme 2, the chemoselective reduction of **2** can be achieved very easily. Thus, the reaction of the monoester **2** with lithium borohydride and methanol in dimethoxyethane resulted in the reduction of the methoxycarbonyl group, and the subsequent treatment of the crude hydroxy acid with p-TsOH afforded the γ-lactone **8** in 80% yield. On the other hand, the reduction of the carboxyl group of **2** was carried out by the initial formation of the mixed anhydride, followed by the reduction with sodium borohydride [(i) $ClCO_2Et$, Et_3N / THF, 0°C; (ii) $NaBH_4$ / THF-H_2O, 0°C]. Acid treatment [catalytic p-TsOH / benzene, r.t.] of the hydroxy ester then afforded the isomeric γ-lactone **9** in 73% yield.

In the similar manner, the chiral monoester **7** was also converted to the enantiomeric γ-lactones **10** and **11** in overall 89% and 63% yields, respectively.

Scheme 3



These compounds with angular methyl group, **8** ~ **11**, and also the intermediates shown in the present study are useful starting materials for the variety of biologically significant compounds. Furthermore, the dianion derived from **1** or **6** can react with various electrophiles other than methyl iodide in principle to construct quaternary chiral carbon center having a variety of substituents.

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9. Typical data are as follows: **2** m.p. 98.0°C; $[\alpha]_D^{20}$ +7.1° (*c* 1.20, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 100MHz) δ 1.25 (s, 3H), 2.05 (br. d, *J*=17.0Hz, 1H), 2.36~2.90 (m, 3H), 2.99 (dd, *J*=3.4, 6.6Hz, 1H), 3.71 (s, 3H), 5.62 (br., 2H); ^{13}C-NMR ($CDCl_3$, 25MHz) ppm 24.1 (q), 24.8 (t), 31.3 (t), 41.4 (s), 44.5 (d), 52.1 (q), 123.0 (d), 125.2 (d), 177.6 (s), 179.8 (s); MS *m/e* 199 (M^++1), 198 (M^+), 181, 180, 167, 166, 153, 152, 139, 138, 137: **7** m.p. 106.0°C; $[\alpha]_D^{20}$ +5.6° (*c* 1.36, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 100MHz) δ 1.18 (s, 3H), 1.38 (s, 3H), 1.91 (br. d, *J*=16.6Hz, 1H), 2.37~2.94 (m, 4H), 5.55 (br., 2H); ^{13}C-NMR ($CDCl_3$, 25MHz) ppm 24.2 (q), 25.1 (t), 27.8 (qx3), 31.8 (t), 42.0 (s), 44.7 (d), 80.5 (s), 122.9 (d), 125.6 (d), 176.1 (s), 180.1 (s); MS *m/e* 241 (M^++1), 240 (M^+), 225, 223, 207, 196, 195, 194, 187, 186, 185, 184: **8** m.p. 71.0°C; $[\alpha]_D^{20}$ +96.3° (*c* 1.10, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.20 (s, 3H), 1.92 (br d, *J*=17.2Hz, 1H), 2.14 (br. d, *J*=16.8Hz, 1H), 2.27~2.39 (m, 2H), 2.57 (br. d, *J*=16.8Hz, 1H), 3.89 (d, *J*=8.4Hz, 1H), 3.99 (d, *J*=8.4Hz, 1H), 5.67 (br., 2H); ^{13}C-NMR ($CDCl_3$, 25MHz) ppm 21.0 (t), 22.3 (q), 31.4 (t), 37.0 (s), 43.8 (d), 77.8 (t), 123.8 (d), 124.1 (d), 178.7 (s); MS *m/e* 152 (M^+), 107: **9** m.p. 72.0°C; $[\alpha]_D^{20}$ +166° (*c* 0.89, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.27 (3H, s), 1.94~2.04 (m, 2H), 2.29~2.37 (m, 2H), 2.44 (br. ddt, *J*=1.8, 9.0, 7.2Hz, 1H), 3.90 (t, *J*=9.0Hz, 1H), 4.31 (dd, *J*=7.2, 9.0Hz, 1H), 5.74 (br., 2H); ^{13}C-NMR ($CDCl_3$, 25MHz) ppm 21.9 (q), 22.6 (t), 29.6 (t), 39.5 (d), 39.6 (s), 70.1 (t), 124.0 (d), 124.1 (d), 181.9 (s); MS *m/e* 152 (M^+), 137, 111, 107, 105: **10** $[\alpha]_D^{20}$ -90.6° (*c* 0.795, $CHCl_3$): **11** $[\alpha]_D^{20}$ -164° (*c* 1.20, $CHCl_3$).
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