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CREATION OF NOVEL CHIRAL SYNTHONS WITH ENZYMES AND APPLICATIONS TO NATURAL PRODUCT SYNTHESIS. 15.[1] EFFICIENT INTRODUCTION OF CHIRAL CENTERS INTO CYCLOHEXANE RING

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Abstract: The chiral half-ester **2** obtained by asymmetric hydrolysis of the symmetric diester **1** with pig liver esterase has been shown to be a versatile synthon for various chiral cyclohexane derivatives.

The stereocontrolled introduction of polyfunctional groups on cyclohexane ring has been well developed in recent years,[2] but the original synthons with the desired absolute configuration are not easily available for such a ring system from natural sources. Asymmetric Diels-Alder reactions using chiral auxiliary reagents[3] (intermolecular)or using chiral Z-diene[4] (intramolecular) have been extensively studied to afford some useful chiral cyclohexene derivatives. However, it may be much preferable to introduce chiral centers in a catalytic manner. We wish to report here an efficient methodology for the preparation of chiral cyclohexene derivatives from dimethyl cis-1,2-cyclohex-4-enedicarboxylate (**1**). Thus, as an extension of our chemicoenzymatic approach to biologically active natural product synthesis,[1] the symmetric unsaturated cis diester[5] **1** was treated with pig liver esterase (PLE) [**1** (508mg), PLE (440 units), 0.05M phosphate buffer solution (90ml, pH8.0), acetone (10ml), 30°C, 3h] to afford the chiral half-ester **2** in 98% chemical and 96% optical yields.[6,7] In accord with our previous findings,[1k] the presence of a double bond in the substate **1** seems to be essential for such remarkable high optical purity of the half-ester **2**, and it was indeed confirmed that the saturated cis-diester obtained by catalytic hydrogenation of **1** afforded the corresponding half-ester in 81% chemical and 75% optical yields. Then, the absolute structure of **2** was unambiguously verified by X-ray analysis of an iodolactone **8** derived from **2**. The iodolactone **8** was shown to be (1R,2R,4S,5S)-2-benzyloxycarbonylamino-4-iodo-7-oxo-6-oxabicyclo[3.2.1]octane.[8] Therefore, the absolute structure of **2** is assigned to 1-methyl hydrogen (1S,2R)-1,2-cyclohex-4-enedicarboxylate. Although the chiral half-ester **2** itself is a versatile synthon for the synthesis of various natural products, further enantioselective conversion of **2** to other potential intermediates for various aminocyclitols of fortimicin and the related pseudodisaccharide antibiotics[9] was carried out as shown in Scheme 1. Thus, the half ester **2** was treated with ethyl chloroformate in the presence

of triethylamine, and then the reaction mixture was treated with sodium azide. The resulting azide solution was subjected to thermal rearrangement in benzene and treated with benzylalcohol in the presence of p-TsOH (catalytic). After work-up and column chromatography on silica gel afforded a colorless solid **3** in 91% yield, mp 50-51°C, $[\alpha]_D^{25}$+21.33 (c 1.00, $CHCl_3$), Rf 0.37 (ether-hexane=1:1). The cis aminocarboxylate **3** was converted to the trans-isomer **4** in 72% yield by treatment with sodium methoxide in MeOH for 6h under reflux, [**4**: mp 57-57.5°C, $[\alpha]_D^{25}$-33.5° (c 1.00, $CHCl_3$), Rf 0.29 (ether-hexane=1:1)]. Next, the enantiomer conversion characteristic of our chemicoenzymatic strategy was investigated. The half-ester **2** was treated with isobutene in methylene chloride in the presence of conc. H_2SO_4 (catalytic) at room temperature for 6 days. After workup, the condensed residue was subjected to alkaline hydrolysis with NaOH (1.5eq) in aqueous methanol at room temperature for 18h, affording t-butyl half-ester **5** in 82% yield [**5**, mp 80-81°C, $[\alpha]_D^{20}$+ 7.68 (c 2.00, $CHCl_3$), Rf 0.42 (ether-hexane=1:1)]. The carboxyl group of **5** was carefully converted to the amino group with retention of configuration through Curtius rearrangement. Thus, the t-butyl half-ester **5** was treated with ethyl chloroformate at -25°C in acetone and with sodium azide at -10°. The mixture was stirred for 1h at room temperature. After workup and removal of the solvent, the residue was dissolved in xylene and the solution was heated to 140°C for 50 min and the resulting isocyanate was directly converted to a methyl urethane **6** by adding methanol and p-TsOH (catalytic) [**6**, 89% yield, oil, $[\alpha]_D^{20}$-19.5° (c 1.07, $CHCl_3$), Rf 0.46 (ether-hexane=1:1)]. The cis-isomer **6** was isomerized more stable trans-isomer **7** with potassium t-butoxide in t-butanol at room temperature for 80 min. After workup and column chromatography on silica gel afforded crystalline trans-isomer **7** in 76% yield, [mp 57-58.5°C, $[\alpha]_D^{20}$+27.6° (c 1.01, $CHCl_3$), Rf 0.36 (ether-hexane=1:1)]. The trans relationship of **4** and **7** was well demonstrated by ^1H NMR. Finally, the iodolactone **8** was prepared from **4** in completely stereocontrolled manner. The methyl ester of **4** was quantitatively hydrolyzed with NaOH (5.3eq) in aqueous methanol at room temperature to afford the free acid, [mp 108.5-109.5°C, $[\alpha]_D^{25}$-36.3° (c 1.00, $CHCl_3$)]. The free acid was subjected to conventional iodolactonization[2] to afford crystalline **8** in 84% yield [**8**, mp 116-117°C, $[\alpha]_D^{20}$-15.4° (c 1.00, $CHCl_3$), Rf 0.25 (ether-hexane =1:1)]. The key features of the present methodology include the following: (1) the remarkably high optical purity of **2** illustrates the potential of an enzymatic process in organic synthesis; (2) enantioselective conversion of the chiral half-ester **2** to potential intermediates **3** ~ **8** has been carried out smoothly and scaling up to 10 to 100g presents no problem; (3) stereocontrolled introduction of polyfunctional groups on cyclohexane ring has opened a new avenue to natural product synthesis.[10,11]

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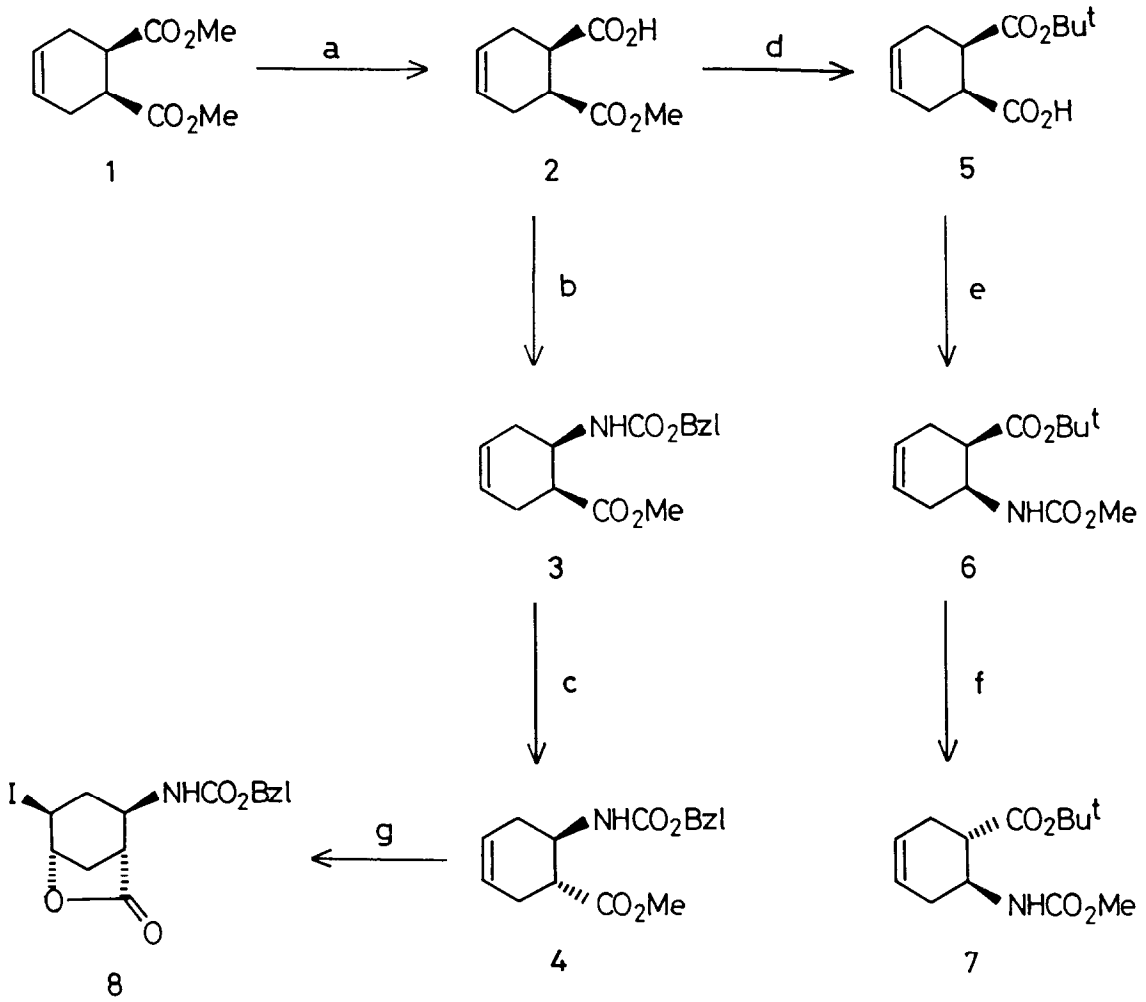
Scheme I



a) PLE / pH 8.0 phosphate buffer-10% acetone

b) (1) $ClCO_2Et$ - Et_3N / acetone (2) NaN_3 (3) C_6H_6 reflux
(4) BzlOH - cat. p-TsOH / C_6H_6 reflux

c) NaOMe / MeOH reflux

d) (1) isobutene - cat. H_2SO_4 (2) NaOH / H_2O-MeOH

e) (1) $ClCO_2Et$-Et_3N / acetone (2) NaN_3 (3) xylene 140°C
(4) MeOH - cat. p-TsOH / xylene 45°C

f) t-BuOK / t-BuOH

g) (1) NaOH / H_2O-MeOH (2) I_2 - KI - $NaHCO_3$ / H_2O - CH_2Cl_2

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5. The anhydride commercially available was converted to **1** in excellent yields by treatment with $SOCl_2$ in MeOH.

6. Chromatographically pure material (**2**) showed almost the same optical rotation as the purified material, mp 65.5-66°C; $[\alpha]_D^{20}$ +2.52° (c 4.33, $CHCl_3$) and +15.8° (c 0.2, EtOH). The optical purity was determined by ^1H and ^{19}F-NMR to be 96%ee by using (-)-α-methoxy-α-trifluoromethylphenylacetyl derivative of the free amine obtained by catalytic hydrogenation of **4**: J.A.Dale, D.L.Dull, and H.S.Mosher, J. Org. Chem., **34**, 2543 (1969).

7. The results also give significant insights into the topography of the active site of PLE and our active site model will be published soon.

8. Crystal data of **8**: $C_{15}H_{16}NO_4I$ (MW=401.2), space group $P2_1$, a=22.029(11)Å, b=6.520(4), c=10.704(6), β=91.43(5)°, V=1536.9Å^3, Z=4(2 molecule/a.u.), D cal=1.735gcm^{-3}.

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10. All materials described here gave satisfactory elementary analysis and MS, IR, and NMR spectra consistent with their structures.

11. Our enzymatic step described here was first presented at the 27th Meeting of Kanto Branch of the Pharmaceutical Society of Japan, Tokyo, Nov. 19, 1983, but we learned that two groups independently obtained the half-ester **2** according to the same concept as ours but with different synthetic targets. (a) P.Mohr, N.Waespe-Savcevic, C.Tamm, K.Gawronska, and J.K. Gawronski, Hel. Chim. Acta, **66**, 2501 (1983): (b) H.-J.Gais and K.L.Lukas, Angew. Chem., **96**, 140 (1984).

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