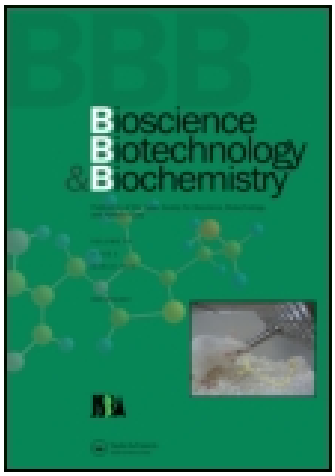

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Asymmetric Trans-esterification of meso-2,5-Dibromoadipate and Synthesis of Optically Active cis-2,5-Disubstituted Pyrrolidines

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Asymmetric Trans-esterification of *meso*-2,5-Dibromoadipate and Synthesis of Optically Active *cis*-2,5-Disubstituted Pyrrolidines

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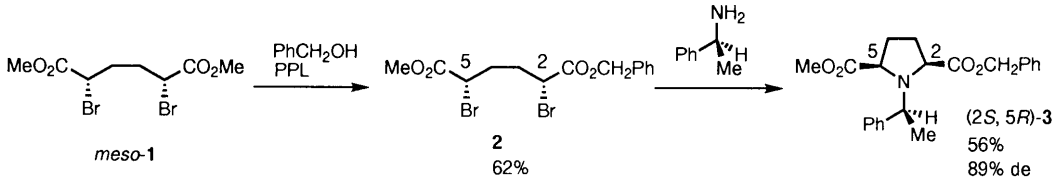
Asymmetric trans-esterification of *meso*-2,5-dibromoadipate to (−)-benzyl methyl 2,5-dibromoadipate by lipase with subsequent chemical reactions afforded optically active *cis*-2,5-disubstituted pyrrolidines. An equivalent asymmetric transformation was performed by selectively hydrolyzing a *cis*-2,5-disubstituted pyrrolidine having a chiral *N*-substituent.

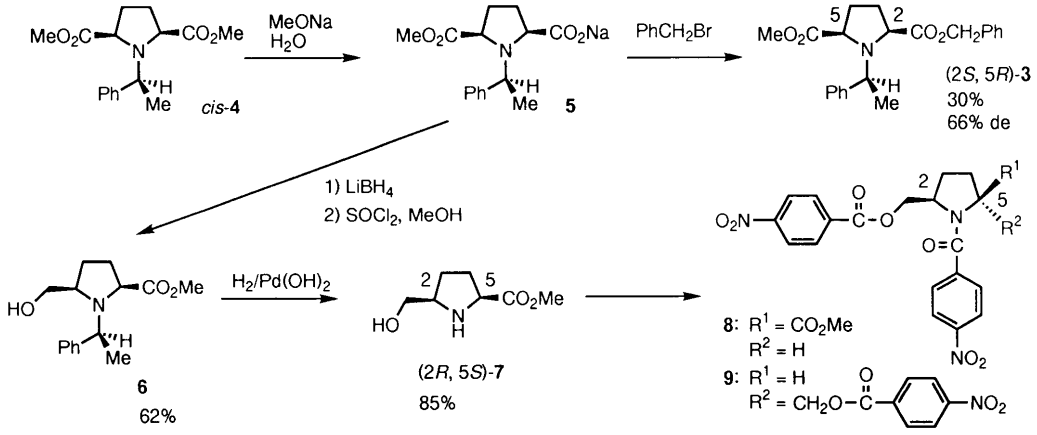
Optically active *cis*-2,5-disubstituted pyrrolidines have attracted much attention because this moiety is found in naturally occurring alkaloids which display significant biological activity[1]; for example, monomorine I, a trail pheromone of the pharaoh ant.[2] Pyrrolidine bearing appropriately functionalized substituents serves as a useful chiral building block for these compounds.[3] We now describe the synthesis of (2*S*,5*R*)-2-benzyloxycarbonyl-5-methoxycarbonyl-1-[(*S*)-1-phenylethyl]pyrrolidine (**3**) by an asymmetric trans-esterification of *meso*-2,5-dibromoadipate (**1**)[4] mediated by lipase.[5]

In the presence of porcine pancreas lipase (PPL), *meso*-**1** was trans-esterified with benzyl alcohol to yield (−)-benzyl methyl 2,5-dibromoadipate (**2**) in a 62% yield (Scheme 1). By the action of (*S*)-1-phenylethylamine, (−)-**2** was converted to pyrrolidine **3** in a 56% yield. The diastereomeric excess (de) of **3** was assessed to be 89% by ^{1}H-NMR with monitoring of the methoxy group. The absolute configuration of **3** was determined to be 2*S*,5*R*, which will be described later. This fact indicates that (−)-**2** had the 2*R*,5*S* configuration and that the ester group adjacent to the chiral center of *R*-configuration in *meso*-**1** preferentially reacted. Amano PS, *Pseudomonas* sp. lipase, promoted the trans-esterification more quickly, and **3** having 65% de was yielded. The reaction with *Candida cylindracea* lipase (CCL) was very sluggish, and the selectivity was also moderate (52% de). A product having the same configuration as that of PPL was obtained in both cases.

Starting from *cis*-**4**,[6] an equivalent asymmetric transformation was also performed by a chemical method (Scheme 2). Selective hydrolysis of *cis*-**4** with sodium methoxide and water in methanol afforded mono-sodium salt **5**, which was converted to diester **3** having 66% de in an overall yield of 30% from *cis*-**4**. The major isomer of **3** thus obtained was proved to be identical with that yielded through the enzymatic trans-esterification by a comparison of the ^{1}H and ^{13}C-NMR spectra. The 2*S*,5*R* configuration was assigned to the major isomer of **3** as followed. Selective reduction of the ester group in **5** by lithium borohydride and subsequent esterification with thionyl chloride and



Scheme 1.



Scheme 2.

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Abbreviations: PPL, porcine pancreas lipase; CCL, *Candida cylindracea* lipase; de, diastereomeric excess.

Table UV and CD Spectra for **8** and **9**

	UV (MeOH)		CD (MeOH) $[\theta]$ (deg·cm^{-2}·dmol)		
	λ_{max} (nm)	ε (M^{-1}·cm^{-1})	269 nm	252 nm	241 nm
(2*R*,5*S*)-**8**	258	4.8×10^4	4.6×10^4	0	-4.1×10^4
(2*R*,5*R*)-**9**	260	2.0×10^4	2.8×10^3	0	-5.8×10^3

methanol gave hydroxy ester **6** in an overall yield of 62% from *cis*-**4**. Hydrogenolysis of **6** yielded (−)-2-hydroxymethyl-5-methoxycarbonylpyrrolidine (**7**) in an 85% yield. The absolute configuration of (−)-**7** was deduced to be 2*R*,5*S* by comparing the CD spectrum of its bis-*p*-nitrobenzoyl derivative **8** with that of tris-*p*-nitrobenzoyl derivative **9** of (2*R*,5*R*)-2,5-bis(hydroxymethyl)pyrrolidine.[6,7] The CD spectra showed the same inversion of sign around the UV absorption of the *p*-nitrobenzoyl group (Table), which indicates the same spatial orientation of the *O*-benzoyl group toward the *N*-benzoyl group in **8** and **9**.

The present trans-esterification method for *meso*-diester **1** with high selectivity encouraged us to undertake the optical resolution of methyl 2-bromopropionate and methyl 2-bromobutyrate with lipase. Trans-esterification with benzyl alcohol was promoted with PPL, CCL, and Amano PS, but the enantio-selectivity[8] was low to moderate ($E = 1.1$–7.5). However, the *R*-enantiomers preferentially reacted, which agrees with the stereo-chemical bias observed in the reaction of *meso*-**1**.

Experimental

Instruments. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a JEOL EX-270 (at 270 MHz for ^{1}H, and at 68 MHz for ^{13}C). *J* Values are given in Hz. Optical rotation was measured with a Perkin-Elmer R-241 polarimeter (with a 1 dm cell). Mass spectra were recorded with a JEOL JMS DX-300. CD spectra were measured with a JASCO J-600.

(−)-*1-Benzyl 6-methyl (2R,5S)-2,5-dibromoadipate* (**2**). A mixture of *meso*-**1** (3.3 g, 10 mmol), benzyl alcohol (4.3 g, 40 mmol), PPL (13.2 g, Sigma, type II), molecular sieves 4A (6.6 g), and diisopropyl ether (100 ml) was stirred at room temperature for 18 d. The lipase was filtered was filtered off and washed with ether (20 ml), and the combined filtrate and washings were evaported. The residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexane) to afford **2** (2.53 g, 62%) as a colorless oil: $[\alpha]_D^{20}$ −6.4° (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 1.97–2.42 (m, 4H), 3.78 (s, 3H), 4.19–4.33 (m, 2H), 5.21 (s, 2H), 7.34 (s, 5H); ^{13}C-NMR ($CDCl_3$) δ: 32.4 (2 peaks), 44.2, 44.4, 53.1, 67.8, 128.3, 128.6 (2 peaks), 134.9, 168.9, 169.6; MS *m/z*: 408 (M^+), 327, 311, 279, 221 (100), 191, 169, 141, 107; HRMS *m/z* (M^+): calcd. for $C_{14}H_{16}Br_2O_4$, 405.9414, 407.9394, 409.9376; found, 405.9425, 407.9370, 409.9383.

(2*S*,5*R*)-*2-Benzyloxycarbonyl-5-methoxycarbonyl-1-*[(*S*)-*1-phenylethyl*]*pyrrolidine* (**3**). A mixture of **2** (2.5 g, 6.2 mmol), (*S*)-1-phenylethylamine (0.97 g, 7.0 mmol), K_2CO_3 (1.1 g, 8.0 mmol), benzene (7 ml), and water (7 ml) was stirred at 50°C for 5 d. The mixture was extracted with EtOAc (10 ml × 3), and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated. The residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexane) to afford *cis*-**3** (1.3 g, 56%) as a colorless oil: $[\alpha]_D^{20}$ −7.0° (*c* 1.0, $CHCl_3$); 89% de; ^{1}H-NMR ($CDCl_3$) δ: 1.38 (d, $J = 7.0$, 3H), 1.86–2.16 (m, 4H), 3.57 (s, 0.165 H, OCH_3 of 2*R*,5*S*-isomer), 3.58 (s, 2.835H, OCH_3 of 2*S*,5*R*-isomer), 3.60–3.76 (m, 2H), 4.08 (q, $J = 7.0$, 1H), 5.05 (s, 2H), 7.15–7.43 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ: 18.7, 29.5 (2 peaks), 51.5, 60.3, 62.8, 63.3, 66.0, 126.8, 127.0, 127.8, 127.9 (2 peaks), 128.0, 136.0, 142.5, 174.1, 175.0; MS *m/z*: 367 (M^+), 352, 308, 232, 204, 128, 105 (100); HRMS *m/z* (M^+): calcd. for $C_{22}H_{25}NO_4$, 367.1785; found, 367.1795.

(−)-*2-Hydroxymethyl-5-methoxycarbonyl-1-*[(*S*)-*1-phenylethyl*]*pyrrolidine* (**6**). To a mixture of sodium hydride (320 mg, 60%, 8.0 mmol) that had earlier been washed with hexane (5 ml × 3), methanol (2 ml), and water (0.14 ml), a solution of **4** (2.2 g, 7.6 mmol) in methanol (5 ml) was added while ice-cooling. After stirring at −10°C for 2 d, the mixture was evaporated to yield sodium salt **5** (2.6 g). To a suspension of **5** (2.0 g) in ethanol (60 ml), $NaBH_4$ (860 mg, 23 mmol) and LiCl (970 mg, 23 mmol) were added. After stirring at 50°C for 25 h, the mixture was evaporated, and the residue was suspended in methanol (20 ml). Thionyl chloride (4.9 g, 41 mmol) was added to the mixture while ice-cooling, and the mixture was then refluxed for 24 h and evaporated. The residue was treated with a solution of K_2CO_3 (1.38 g, 10 mmol) in water (10 ml) and extracted with EtOAc (20 ml × 3). The combined extracts were washed with saturated NaCl (20 ml), dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (silica gel, 30% EtOAc in hexane) to yield **6** (950 mg, 62% from **4**) as a colorless oil: $[\alpha]_D^{20}$ −9.5° (*c* 7.8, $CHCl_3$); 66% de; ^{1}H-NMR ($CDCl_3$) δ: 1.39 (d, $J = 6.8$, 3H), 1.77–2.10 (m, 4H), 3.25–3.40 (m, 2H), 3.51 (s, 2.489H, OCH_3 of 2*R*,5*S*-isomer), 3.63 (s, 0.511H, OCH_3 of 2*S*,5*R*-isomer), 3.66–3.74 (m, 2H), 4.03 (q, $J = 7.0$, 1H), 7.17–7.36 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ: 15.6, 28.2, 30.9, 51.6, 58.8, 61.5, 62.9, 63.0, 127.0, 127.7, 128.4, 142.9, 176.9; MS *m/z*: 263 (M^+), 248, 232, 204, 128, 105 (100); HRMS *m/z* (M^+): calcd. for $C_{15}H_{21}NO_3$, 263.1520; found, 263.1543.

To a suspension of **5** (560 mg) in DMF (5 ml), benzyl bromide (1.7 g, 10 mmol) was added. After stirring at room temperature for 24 h, the mixture was diluted with water (50 ml) and extracted with EtOAc (20 ml × 3). The combined extracts were washed with saturated NaCl (20 ml), dried (Na_2SO_4), and evaporated. The residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexane) to afford *cis*-**3** (160 mg, 30% from **4**) of 66% de by ^{1}H-NMR monitoring of OCH_3.

(2*R*,5*R*)-*2-Hydroxymethyl-5-methoxycarbonylpyrrolidine* (**7**). A mixture of **6** (260 mg, 1.0 mmol), 26% palladium hydroxide on carbon (260 mg), and MeOH (10 ml) was shaken under a hydrogen atmosphere (5 atm) for 3 h. After filtration, the filtrate was evaporated to give **7** (135 mg, 85%) as a colorless oil: $[\alpha]_D^{20}$ −21.1° (*c* 1.2, MeOH); ^{1}H-NMR ($CDCl_3$) δ: 1.62–2.21 (m, 4H), 3.43–4.00 (m, 6H), 3.74 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ: 27.0, 30.2, 52.3, 59.4, 60.1, 64.3, 175.6; MS *m/z*: 159 (M^+), 142, 128 (100); HRMS *m/z* (M^+): calcd. for $C_7H_{13}NO_3$, 159.0900; found, 159.0858.

Bis-p-nitrobenzoyl derivative **8**. To a mixture of **7** (120 mg, 0.75 mmol), 4-dimethylaminopyridine (180 mg, 1.5 mmol), Et_3N (230 mg, 2.3 mmol), and CH_2Cl_2 (2 ml), *p*-nitrobenzoyl chloride (320 mg, 1.8 mmol) was added while ice-cooling. After being stirred at room temperature for 15 h, the mixture was diluted with EtOAc (50 ml), sequentially washed with 1 M HCl (20 ml × 3), saturated $NaHCO_3$ (20 ml × 2), and saturated NaCl (20 ml), and then dried (Na_2SO_4). After evaporation, the residue was purified by preparative thin-layer chromatography (silica gel, 50% EtOAc in hexane) to give **8** (180 mg, 52%) as a pale yellow solid: $[\alpha]_D^{20}$ −19.2° (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$ at 60°C) δ: 1.96–2.22 (m, 4H), 3.69 (s, 3H), 4.25–4.80 (m, 4H), 7.58–7.64 (m, 2H), 8.16–8.34 (m, 6H); ^{13}C-NMR ($CDCl_3$ at 60°C) δ: 27.4, 29.0, 52.5, 57.5, 61.5, 65.8, 123.4, 123.8, 127.8, 130.8, 135.4, 142.2, 148.8, 150.8, 164.4, 168.6, 172.2; MS *m/z*: 457 (M^+), 437, 398, 290, 277, 150 (100); HRMS *m/z* (M^+): calcd. for $C_{21}H_{19}N_3O_9$, 457.1122; found, 457.1143.

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