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A Facile Synthesis of Optically Active C_2-Symmetric 2,5-Disubstituted Pyrrolidines and other β,β'-Dihydroxyamines

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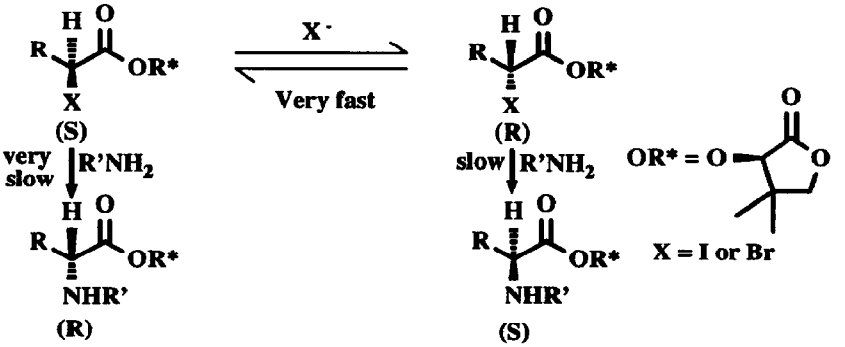
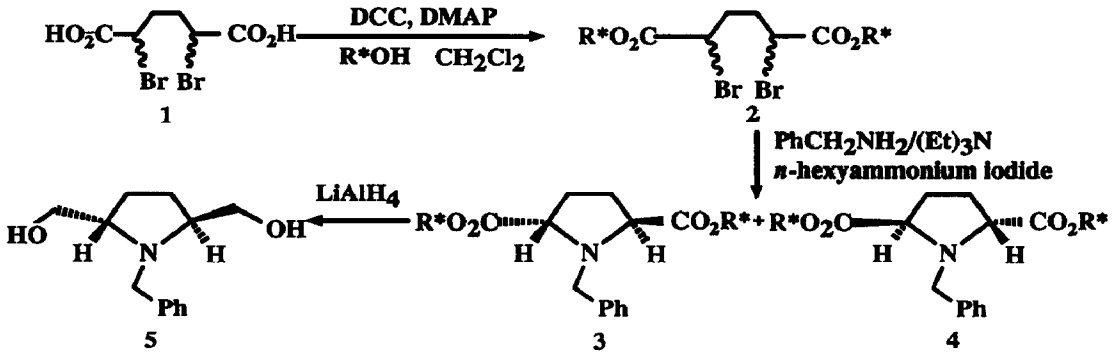
Abstract: *2,5-Dibromoadipic acid has been converted into the di-(R)-pantolactone ester of (S,S)-pyyrolidine-2,5-dicarboxylic acid in two steps. This compound serves as a precursor to C_2-symmetric 2,5-disubstituted pyrrolidines. The synthesis of linear C_2-symmetric β,β'-dihydroxyamines starting with α-bromophenylacetic acid and (S)-phenylglycine ethyl ester is also reported.*

We have recently reported that reaction of (R)-pantolactone esters of racemic α-halocarboxylic acids with primary or secondary amines furnished up to 75% yield one of the two possible diastereomeric α-amino esters.[1] The greater than 50% yield of one diastereomer is due to epimerization of the slower reacting α-halo ester into the faster reacting isomer by the halide released as a result of the displacement. This epimerization can also be effected by addition of catalytic amounts of soluble tetra-alkylammonium iodides.



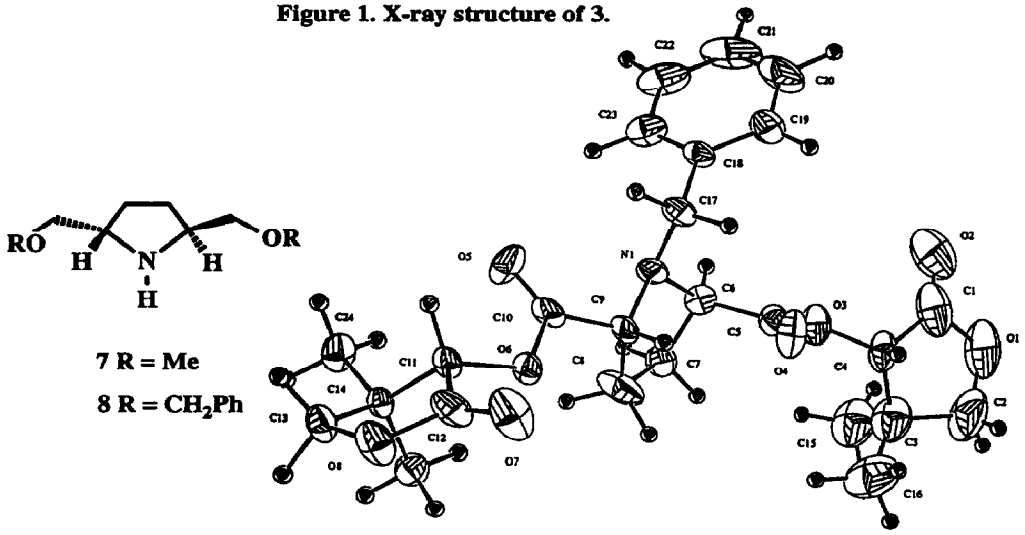
Application of the above methodology has enabled us to prepare the di-(R)-pantolactone ester of (S,S)-pyrrolidine-2,5-dicarboxylic acid **3** in two steps in 27% overall yield starting with 2,5-dibromoadipic acid **1**. Thus, reaction of **1** with (R)-pantolactone in the presence of DCC (2.1 eq) and DMAP (0.2 eq) in CH_2Cl_2 for 18 h furnished 77% of **2** as a mixture of diastereomers. When **2** was stirred with benzylamine (1.1 eq), *n*-hexylammonium iodide (0.4 eq) and triethylamine (2.1 eq) in THF for 48 h, a 7:3 mixtures of the trans- and cis-fused pyrrolidines were formed. Chromatography (Hexanes/EtOAc 4:1) of the reaction mixtures furnished an 8:1 mixture of (S,S)- and (R,R)-pyrrolidines **3** and **4** in 51% yield.[2] Recrystallization of the mixture from hexanes/ethyl acetate gave 35% yield (from **2**) of **3**.[3] The absolute configuration was established as (2S, 5S) by single crystal X-ray structure determination (Fig.1). Reduction of **4** with $LiAlH_4$ in THF afforded the C_2-symmetric diol **5** in an unoptimized yield of 55%.[4]



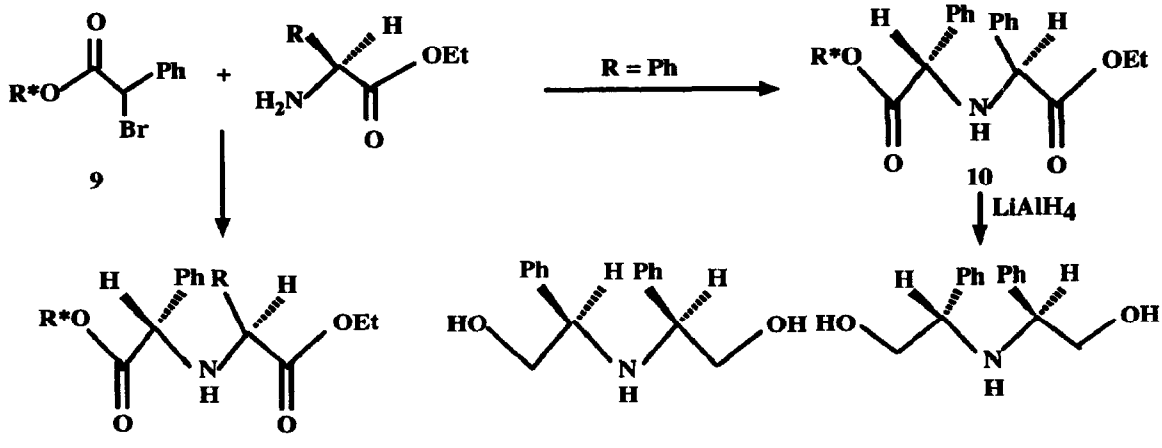
Optically active pyrrolidine-trans-2,5-dicarboxylic acids **6** were first prepared by Katsuki via resolution.[5] This procedure was improved by Ghosez.[6] Yamamoto also used a resolution step to prepare **7**.[7] Synthesis of optically active **7** and **8** have recently be reported starting with (S)-O-benzylglycidol (8 steps)[8] and D-mannitol (8 steps);[9] **6** has recently been prepared from N-BOC pyroglutamate ethyl ester.[10] The present synthesis offers the advantage of conciseness and high selectivity for one of the enantiomers in the pyrrolidine ring forming reactions.

Derivatives of **5** such as **6** and **7** are of considerable interest as C_2-symmetric chiral auxiliaries[11] since their carboxamide enolates show remarkable stereochemical control in alkylations,[5,12a-c] acylations,[12d] aldol[12e] and Wittig rearrangement reactions.[12f] These auxiliaries have also been used to control the stereochemical outcome of Diels-Alder cycloadditions[12g] and halolactonizations.[12h]

Figure 1. X-ray structure of 3.



Non-cyclic C_2-symmetric β,β'-dihydroxyamines can also be produced via this methodology. Thus, reaction of **9**, prepared from racemic α-bromophenylacetic acid with (S)-phenylglycine ethyl ester afforded the diester **10** (RSS:RRS ratio=18:1) in 80% isolated yield.[13] Reduction with $LiAlH_4$ gave the (S,S)-amino diol **11**, $[\alpha]^{22}_D$ +133.5° (c 1.4, CH_2Cl_2).[14] Similar treatment of **9** with (R)-phenylglycine ethyl ester resulted in 70% of the (RSR) diastereomer of **10**; reduction gave the meso diol **12** $[\alpha]^{22}_D$ 0° (c 0.85, CH_2Cl_2).

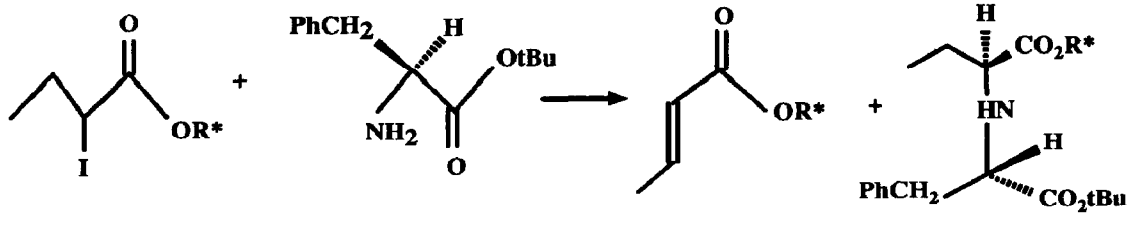


Reaction of **9** with other optically active α-amino esters gave a series of amino diesters **13** in similar and even higher diastereomer ratios. These results are summarized below.

Amino ester	Isolated Yield (%)	Diastereomer Ratio (RSS:RRS)
(S)-Glycine ethyl ester	70	12:1
(S)-Phenylalanine methyl ester	60	9:1
(S)- Phenylalanine t-butyl ester	77	27:1
(S)-Proline methyl ester	74	10:1
(S)- Proline t-butyl ester	90	8:1

The reduction products derived from **13** no longer have C_2 symmetry. Nevertheless, they show that a variety of optically active β,β'-dihydroxyamines can be prepared by this methodology. Hydrolysis of **13** leads to optically active compounds consisting of two α-amino acids which share the one nitrogen atom present in the molecule. Such compounds are structurally related to the octopines and nopalines which are implicated in crown gall tumors in higher plants.[15] Other related structures have been identified as inhibitors of angiotensin-converting enzyme as well as thermolysin[16]; they are also components of peptide antibiotics.[17]

Initial experiments indicate that displacement of bromide or iodide ion by α-amino esters from non-aromatic analogs of **9** is accompanied by significant amounts of elimination product. However, the diastereomer enrichment is still in the >15:1 range.



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References and Notes

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1. Durst, T.; Koh. K, R.N, Ben. *Tetrahedron Lett.*, **1993**, *34*, 4476.
2. All new products described in this article were isolated by chromatography on silica gel or recrystallization, and show satisfactory analytical data (IR, NMR, ^{13}C and MS). All the diastereomeric ratios of the products were determined by examination of the crude reaction mixtures in $CDCl_3$ using ^1H NMR (300 MHz or 500 MHz)
3. **3** has the following physical data: Mp 147-148°C. $[\alpha]^{22}_D$ -61.7° (c 1.3, CH_2Cl_2). IR(CH_2Cl_2): 1751, 1796 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.10(s, 6H), 1.20(s, 6H), 1.90-2.10(m, 2H), 2.30-2.50(m, 2H), 3.83(d, 1H, J= 13.10 Hz), 3.90-3.97(m, 2H), 4.03(ABq, 4H, J= 9.04 Hz), 4.08(d, 1H, J= 13.10 Hz), 5.37(s, 2H), 7.11-7.50(m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.08(CH_3), 23.06(CH_3), 28.70(CH_2), 40.10(C), 53.67(CH_2), 63.01(CH), 75.10(CH), 76.14(CH_2), 127.35(CH), 128.41(CH), 129.10(CH), 137.85(C), 171.92(C), 172.85(C). EIMS *m/z*: 316(77), 91(100). CIMS *m/z*: 474(100, M+1), 316(77).
4. Physical data: $[\alpha]^{22}_D$ -36.2° (c 0.43, CH_2Cl_2). IR(CH_2Cl_2): 3373 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.60-2.10(m, 4H), 2.84(bs, 2H), 3.49(dd, 2H, J= 3.28, 11.01 Hz), 3.58(dd, 2H, J= 4.56, 11.01 Hz), 3.86(ABq, 2H, J= 13.92 Hz), 7.10-7.50(m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.47(CH_2), 52.25(CH_2), 62.28(CH_2), 62.95(CH), 127.79(CH), 128.80(CH), 129.11(CH), 139.62(C). EIMS *m/z*: 190(47), 91(100). CIMS *m/z*: 222(100, M+1), 204(82), 190(95).
5. Kawanami, Y.; Ito, Y.;Kitagawa,T.;Yaniguchi,Y.; Katsuki,T.; Yamaguchi, M. *Tetrahedron Lett.*, **1984**, *25*, 857.
6. Chen, L.Y.; Ghosez, L. *Tetrahedron Lett.*, **1990**, *31*, 4467.
7. Yamamoto, Y.; Hoshino, J.; Fujimoto, Y.; Ohmoto, J.; Sawada, S. *Synthesis*, **1993**, *3*, 298.
8. Takano, S.; Moriya, M. Iwabuchi, Y.; Ogasawara, K. *Tetrahedron Lett.*, **1989**, *30*, 3805.
9. Marzi, M.; Misiti, D. *Tetrahedron Lett.*, **1989**, *30*, 6075.
10. Ezpuerra, J.; Rubio, A.; Pedregal, C.; Sanz, G.; Rodriguez, J.H.; Garcia Ruano, J.L. *Tetrahedron Letters*, **1993**, *34*, 4989.
11. Whitesell, K.W. *Chem. Rev.*, **1989**, *89*, 1581.
12. a) Ikegtami, S.; Hayama, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.*,**1986**, *27*, 3403. b) Enomoto, M.; Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.*, **1985**, *26*, 1343. c) Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tett. Lett.*, **1986**, *27*, 2463. d) Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.*, **1984**, *25*, 6015. e) Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.*, **1985**, *26*, 5807. f) Uchikawa, M.; Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.*,**1986**, *27*, 4577. g) Gouverneur, V.; Ghosez, L. *Tetrahedron Lett.*, **1991**, *32*, 5349. h) Fuji, K.; Nodo, M.; Naniwa, Y.; Kawabata, T. *Tetrahedron Lett.*, **1990**, *31*, 3175.
13. **10** has the following physical data: $[\alpha]^{22}_D$ +1.1° (c 10.4, CH_2Cl_2). IR (CH_2Cl_2): 1072, 1168, 1691, 1745, 1797, 2912, 3347 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.60 (s, 3H), 1.00 (s, 3H), 1.21 (t, 3H, J= 8.70 Hz), 3.95 (q, 2H, J= 8.70 Hz), 4.05 (m, 2H), 4.12 (s, 1H), 4.45 (s, 1H), 5.26 (s, 1H), 7.42 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.84, 18.86, 22.55, 40.33, 61.21, 61.90, 62.05, 75.14, 75.83, 75.90, 127.71, 128.00, 128.26, 128.53, 128.73, 137.03, 137.09, 171.30, 171.90. CIMS *m/z*: 426 (100, M+1), 412 (12), 352 (55), 247 (30), 131 (22), 105 (24).
14. **11** has the following physical data: $[\alpha]^{22}_D$ +133.5° (c 1.4, CH_2Cl_2). IR (CH_2Cl_2): 1041, 1493, 2354, 2930, 3600 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.80 (bs, 3H), 3.50-3.80 (m, 6H), 7.10-7.40 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 60.73, 66.66, 127.14, 127.49, 128.39, 139.15. CIMS *m/z*: 258 (20, M+1), 240 (12), 226 (30), 102 (25).
15. Drummond, M. *Nature*, **1979**, *281*, 343.
16. Miyazawa, T.; Hiramatsu, S.; Yasuhiro, T.; Yamada, T.; Kuwata, S. *Bull. Chem. Soc. Jpn.*, **1985**, *58*, 1976.
17. Miyazawa, T. *Bull. Chem. Soc. Jpn.*, **1980**, *53*, 2555.

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