ASYMMETRIC SYNTHESIS OF A PIPERAZINE ALKALOID[1]

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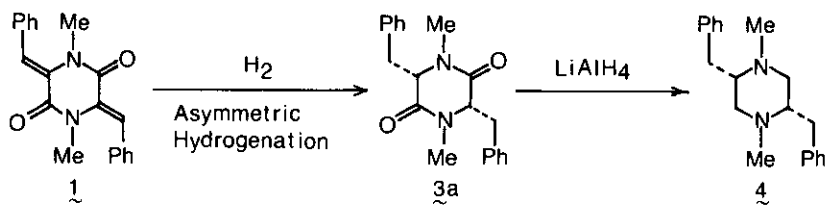
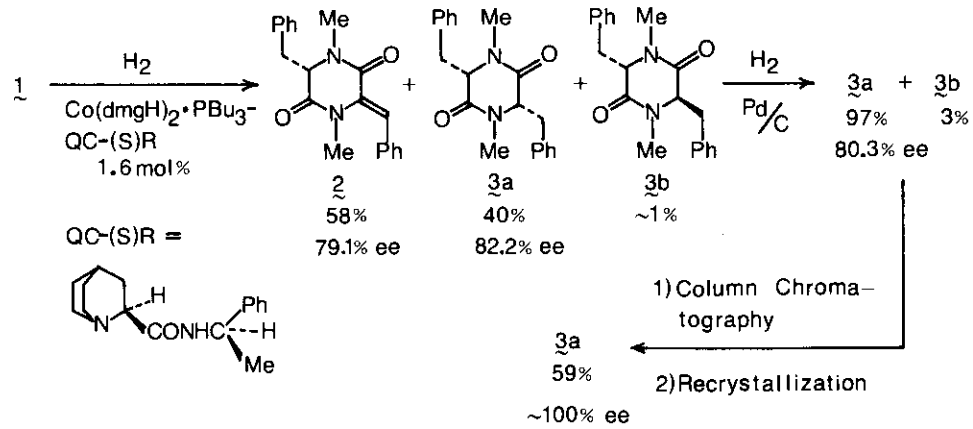
Abstract ——A piperazine alkaloid, (2S,5S)-2,5-dibenzyl-1,4-dimethylpiperazine, was synthesized by reduction of (3S,6S)-3,6-dibenzyl-1,4-dimethyl-2,5-piperazinedione which was prepared by a catalytic asymmetric hydrogenation of the corresponding 3,6-dibenzylidene derivative.

(2S,5S)-2,5-Dibenzyl-1,4-dimethylpiperazine (4) was isolated from Zanthoxylum arborescens Rose and synthesized from t-Boc-L-phenylalanine and L-phenylalanine methyl ester hydrochloride via four steps by Stermitz.[2]
We are interested in a pharmacological activity of such a simple alkaloid and the C_2 symmetric structure which is an important character as a bidentate ligand in a metal assisted asymmetric synthesis. This prompted us to synthesize the alkaloid in a large scale. From the practical point of view, Stermitz's method has some disadvantages: The starting materials are relatively expensive, the synthetic route is rather long, and the overall yield is low (33%). The low yield seems to be caused by partial epimerization or racemization in each step of the reaction path, especially in dimethylation of (3S,6S)-3,6-dibenzyl-2,5-piperazinedione with sodium hydride and methyl iodide in DMF at 40-50°C. We therefore planned to synthesize the alkaloid by the following route (Scheme 1).



Scheme 1

The starting material (1) was prepared from 2,5-piperazinedione by the condensation with bezaldehyde followed by dimethylation with dimethyl sulfate.[3] Hydrogenation of 1 was carried out by the catalytic system which was developed by us,[4] using $Co(dmgH)_2 \cdot PBu_3$-(S)-N[(R)-1-phenylethyl]-2-quinuclidinecarboxamide (dmgH = dimethylglyoximato, PBu_3 = tributylphosphine) (Scheme 2).



Scheme 2

Although the desired product (3a) was obtained in 40% yield (82.2% ee), the partially hydrogenated product (2) was also obtained in 58% yield (79.1% ee). This is due to rather low activity of the catalyst and to the inactivation of the catalyst before the complete conversion of 2 to 3a.[5] However, it was found that diastereoselective hydrogenation of the enantiomerically pure 2 over 10% palladium on charcoal (Pd/C) afforded the enantiomerically pure 3a (95%) and the meso compound (3b) (5%).[6] So, the reaction products (2+3a+3b) obtained in the asymmetric hydrogenation were hydrogenated over Pd/C to give 3a (97%; 80.3% ee) as a major product with a small amount (3%) of 3b. The product (3a) separated from 3b by column chromatography was recrystallized repeatedly to afford the enantiomerically pure 3a (59%). Since the yield of the hydrogenation over Pd/C was quantitative, the yield of the enantiomerically pure 3a based on 1 was 57%. The recrystallization procedures of 2 and 3a and a determination of their enantiomeric purities are described in the Experimental Section.

Finally, the enantiomerically pure 3a was reduced with lithium aluminum hydride by a modified method of Stermitz's[2] to give 4 in good yield (84%). The determination of the enantiomeric purity of 4 by ^{1}H-nmr spectrum in the presence of dibenzoyl-(+)-tartaric acid demonstrated that the product (4) was higher than 98%

ee and recrystallization of the product (4) from hexane afforded the enantiomerically pure 4.

Consequently, the alkaloid was synthesized efficiently from the readily availble starting material in 48% total yield.

EXPERIMENTAL

The melting points were determined by a Yanagimoto micro-melting point apparatus and are uncorrected. The structures of 2, 3a[7], 3b[7], and 4[2] were elucidated by ^{1}H- and ^{13}C-nmr spectra: JEOL-FX200. Enantiomeric purity of 3a was determined by optical rotation (Perkin Elmer 241 polarimeter) based on that of the enantiomerically pure 3a and was confirmed by ^{1}H-nmr spectrum in the presence of tris(3-trifluoroacetyl-d-camphorato)europium(III) in $CDCl_3$: the methine protons of the enantiomers were separated completely. Enantiomeric purity of 2 was determined by hplc using chiral column (Chiralcel OB', DAICEL CHEMICAL INDUSTRY LTD.) and hexane/2-propanol (9:1) as eluate: the enantiomers were separated completely.

Asymmetric hydrogenation of 1 with $Co(dmgH)_2 \cdot PBu_3$-QC-(S)R and diastereoselective hydrogenation of the product over Pd/C. The catalyst was prepared from $CoCl_2 \cdot 6H_2O$ (0.25 g, 1.05 mmol), dimethylglyoxime (0.24 g, 1.05 mmol), tributylphosphine (0.29 ml, 1.07 mmol), QC-(S)R (1.62 g, 6.3 mmol), and QC-(S)R·HCl (0.31 g, 1.05 mmol) by the procedure described in the previous papers.[4] Into this catalyst a benzene (116 ml) solution of 1 (20 g, 62.8 mmol) was injected and hydrogenation was carried out under atmospheric pressure of hydrogen at room temperature for 7 days (1.98 l of hydrogen was absorbed). The reaction mixture was worked up as usual[4] and a half of the crude oily product was hydrogenated in ethanol (450 ml) and ethyl acetate (50 ml) over 2.0 g of 10% Pd/C under atmospheric pressure of hydrogen at room temperature overnight. After filtration, the filtrate was concentrated in vacuo to give 9.9 g of crystalline material in which 3a (97%) and 3b (3%) were observed in ^{1}H-nmr spectrum. The product was purified by column chromatography (Wakogel C-300, 150 g; ethyl acetate as eluate) to give 9.6 g of pure 3a : $[\alpha]_D^{20}$ -125.1°(c=1.008, $CHCl_3$)(80.3% ee). Another half of the crude oily product was adsorbed on a silica gel column (Wakogel C-300, 100 g) and eluted by benzene and then benzene-ethyl acetate (10:1) mixture. Thus, 5.8 g of 2 (58%, 79.1% ee) and 4.0 g of 3a (40%, $[\alpha]_D^{20}$ -128.1° (c=1.010, $CHCl_3$), 82.2% ee) were obtained.

Recrystallization of the products 2 and 3a. Recrystallization of the product (3a) from ethyl acetate gave fine needles of low optical rotation ($[\alpha]_D$ 0° ~ -18°). The filtrate was concentrated and the crystalline residue was recrystallized from ethyl acetate and petroleum ether to give plates covered with a small amount of fine needles. The fine needles were separated from the plates by decantation with gentle swirling and the plates were recrystallized 2-3 times from ethyl acetete and petroleum ether to afford prisms: $[\alpha]_D^{21}$ -155.8°(c=1.011, $CHCl_3$), mp 151.5-152.0°C. This optical rotation was the highest value which unchanged by further recrystallizations and the ^{1}H-nmr spectrum of the sample in the presence of the chiral shift reagent showed that there was no detectable (3R,6R)-enantiomer. Concentration of the mother liquor and recrystallization of the residue from ethyl acetete and petroleum ether afforded prisms having the same optical rotation. Thus, recrystallization of the product (3a) (9.5 g) obtained by the asymmetric hydrogenation followed by the diastereoselective hydrogenation afforded 5.61 g (59%) of 3a: $[\alpha]_D^{20}$ -155.6°~-155.7°(c=1.005, $CHCl_3$). Similarly, recrystallization of the product (2) from the same solvents as those in the case of 3a afforded enantiomerically pure material, the purity of which was confirmed by hplc using Chiralcel OB': $[\alpha]_D^{20}$ -837.8°(c=1.004, $CHCl_3$), mp 109.0-110.5°C. ^{1}H-Nmr ($CDCl_3$) δ: 2.78 (3H, s, 1-Me), 2.95 (3H, s, 4-Me), 3.21 (2H, ddd, J=4.8 Hz, J=6.3 Hz, J=13.9 Hz, $PhC\underline{H}_2$), 4.29 (1H, dd, J=4.8Hz, J=6.3 Hz, $PhCH_2C\underline{H}$), 6.98 (1H, s, $PhC\underline{H}$=), 7.36-6.98 (10H, m, Ph). Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.78; H, 6.28; N, 8.77.

Preparation of 4. To a suspension of $LiAlH_4$ (0.820 g, 21.6 mmol) in THF (40 ml), a solution of 3a ($[\alpha]_D^{21}$ -155.8°(C=1.011, $CHCl_3$), 0.682 g, 2.12 mmol) in THF (20 ml) was added slowly at 0°C with stirring. Stirring was continued at 0°C for 5 h and then at room temperature overnight. After refluxing for 5 h, the reaction mixture was cooled to room temperature and poured into a 10% solution of potassium sodium tartrate (100 ml) at 0°C. The solution was extracted with methylene dichloride and the organic layer was washed with a saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (Wakogel C-300, ethyl acetate as eluate) to give 0.521 g (83.7%) of crystalline solid: $[\alpha]_D^{24}$ +120°(c=0.518, 99.5% ethanol), mp 129.0-131.2°C. Recrystallization of the product twice from hexane gave needles: $[\alpha]_D^{24}$ +122°(c=0.515, 99.5% ethanol), mp 129.5-131.3°C (lit.[2] $[\alpha]_D^{23}$ +118° (c=0.5, ethanol), mp 123.0-124.5°C). ^{1}H-Nmr ($CDCl_3$) δ: 2.22 (2H, dd, J=2.7 Hz,

J=11.0 Hz, N-CH_2), 2.35 (6H, s, N-Me), 2.49 (2H, dd, J=6.0 Hz, J=11.0 Hz, N-CH_2), 2.58 (2H, m, $PhCH_2C\underline{H}$), 2.75 (2H, dd, J=9.4 Hz, J=12.8 Hz, $PhC\underline{H}_2$), 2.98 (2H, dd, J=3.3 Hz, J=12.8 Hz, $PhC\underline{H}_2$), 7.18-7.36 (10H, m, Ph). ^{13}C-Nmr ($CDCl_3$, ppm): 33.1 (t, C-3 and C-6), 42.8 (q, N-Me), 55.5 (t, $PhC\underline{H}_2$), 62.8 (d, C-2 and C-5), 125.9 (d, Ph), 128.3 (d, Ph), 129.4 (d, Ph), 140.2 (s, C-1'). The ^{1}H- and ^{13}C-nmr spectra were identical with those of the natural product reported by Stermitz.[2]

Determination of the enantiomeric purity of 4. Equimolar amount of racemic (4) (20 mg) and dibenzoyl-(+)-tartaric acid (DBTA) monohydrate (25.6 mg) were dissolved in $CDCl_3$ (0.7 ml) and the solution was dried over Na_2SO_4. In the ^{1}H-nmr spectrum of the solution, the signals of N-Me and N-CH_2 were separated into two singlets (δ: 2.32, (2R,5R)-enantiomer; 2.37, (2S,5S)-enantiomer) and two doublets (δ: 2.56, (2R,5R)-enantiomer; 2.64, (2S,5S)-enantiomer), respectively. ^{1}H-Nmr spectra described below were similarly recorded in the presence of DBTA. The signals of N-Me and N-CH_2 corresponding to the (2R,5R)-enantiomer were not observed in the ^{1}H-nmr spectrum of the product (4) ($[\alpha]_D^{24}$ +120°(c=0.518, 99.5% ethanol)). However, it is impossible to confirm the absence of (2R,5R)-enantiomer in the product (4) because of the incomplete separation of signals corresponding to (2S,5S)- and (2R,5R)-enantiomers. Therefore, we carried out the following experiment using a mixture of racemic (4) (9.3 mg) and the product (4) (76.3 mg). The optical rotation of the mixture was $[\alpha]_D^{24}$ +109°(c=0.509, 99.5% ethanol). A small but distinct peak (δ: 2.32, N-Me) and a broad shoulder (δ: 2.56, N-CH_2) corresponding to (2R,5R)-enantiomer were observed in the ^{1}H-nmr spectrum of the mixture. Recrystallization of the mixture from hexane afforded needles, the ^{1}H-nmr spectrum of which showed no peak and shoulder of N-Me and N-CH_2 corresponding to (2R,5R)-enantiomer and the optical rotation of which was $[\alpha]_D^{24}$ +122°(c=0.522, 99.5% ethanol). The optical rotation unchanged by further recrystallization of the needles from hexane. These results demonstrates that the added racemate was removed by the recrystallization and an enantiomer enrichment took place, and strongly suggests that the crystals obtained by the recrystallization are enantiomerically pure.

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