ASYMMETRIC SYNTHESIS OF A PIPERAZINE ALKALOID[1]

Seiji Takeuchi[*], Yoshiaki Ohgo, and Norikazu Miyoshi

Niigata College of Pharmacy, 5-13-2 Kamishin'ei-cho,

Niigata 950-21, Japan

Chung-gi Shin and Yasuchika Yonezawa

Laboratory of Organic Chemistry, Kanagawa University,

Kanagawaku, Yokohama 221, Japan

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 synthe-
size the alkaloid in a large scale. From the practical point of view, Ster-
mitz'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 racemiza-
tion 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).
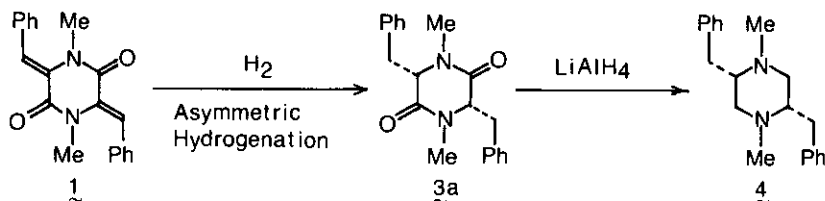
Scheme 1

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)$_2$·PBu$_3$-(S)-N[(R)-1-phenylethyl]-2-quinuclidinecarboxamide (dmgH = dimethylglyoximato, PBu$_3$ = tributylphosphine) (Scheme 2).
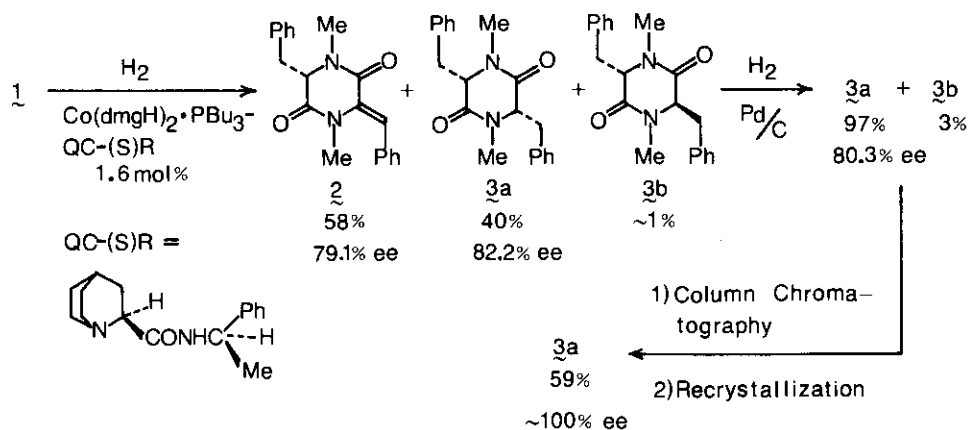
Scheme 2

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 enantiomer-
ically 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 enantio-
merically 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)$_2$·PBu$_3$-QC-(S)R and diastereoselective
hydrogenation of the product over Pd/C.   The catalyst was prepared from CoCl$_2$·
6H$_2$O (0.25 g, 1.05 mmol), dimethylglyoxime (0.24 g, 1.05 mmol), tributylphos-
phine (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 atmos-
pheric 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 elu-
ate) to give 9.6 g of pure 3a : $[\alpha]_D^{20}$ -125.1°(c=1.008, CHCl$_3$)(80.3% ee).   Anoth-
er 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) mix-
ture.   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 recrystal-

lized 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, $PhCH_2$), 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 puri-

fied 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 nee-

dles: $[\alpha]_D^{24}$ +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$_2$CH), 2.75 (2H, dd, J=9.4 Hz, J=12.8 Hz, PhCH$_2$), 2.98 (2H, dd, J=3.3 Hz, J=12.8 Hz, PhCH$_2$), 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, PhCH$_2$), 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$_2$SO$_4$. 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) ([α]$_D^{24}$ +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 [α]$_D^{24}$ +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 [α]$_D^{24}$ +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.

REFERENCES AND NOTES

1. Asymmetric Reactions XVI.

2. J. A. Grina and F. R. Stermitz, Tetrahedron Lett., 1981, 22, 5257.

3. For the preparation and stereochemistry of 3,6-disubstituted 2,5-piperazine-dione including 1, see: C.-gi Shin, Heterocycles, 1983, 20, 1407

4. S. Takeuchi and Y. Ohgo, Bull. Chem. Soc. Jpn., 1984, 57, 1920; Idem, ibid., 1987, 60, 1449.

5. The hydrogenation rate for 1 by the catalyst was rather fast and one of the two olefinic double bonds had been completely hydrogenated after 1 day.

6. N. Izumiya, S. Lee, T. Kanmera, and H. Aoyagi, J. Am. Chem. Soc., 1977, 99, 8346; T. Kanmera, S. Lee, H. Aoyagi, and N. Izumiya, Tetrahedron Lett., 1979, 46, 4483: Izumiya and coworkers have reported the diastereoselective hydroge-nation of 3-alkylidene-6-(S)-alkyl-2,5-piperazinedione over palladium black in up to 99% de and proposed a mechanism in which the olefinic double bond of the substrate is adsorbed on the catalyst surface from the less bulky face (re face) of the molecule and then catalytic hydrogenation takes place to give (3S,6S)-dialkyl-2,5-piperazinedione. Accordingly, the diastereoselect-ive catalytic hydrogenation of 2 over Pd/C should proceed in the same mecha-nism.

7. W. Radding, B. Donzel, N. Ueyama, and M. Goodman, J. Am. Chem. Soc., 1980, 102, 5999.