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키랄 보조제로서의 C_2-대칭성 피롤리딘 아미드의 합성과 광학 순도 결정

문 홍 식* · 고 동 수†

*제일제당 종합연구소, 동덕여자대학교 응용화학과
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Synthesis and Determination of Optical Purity of C_2-Symmetric Pyrrolidine Amides as Chiral Auxiliaries

Hong-sik Moon* and Dongsoo Koh†

*CheilJedang Corporation R & D Center, Kyonggi-Do 467-810, Korea
Department of Applied Chemistry, Dongduk Women's University, Seoul 136-714, Korea
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요 약: 쉽게 얻을 수 있는 1,2:5,6-di-*O*-isopropylidene-D-mannitol (1)로부터 C_2-대칭성 피롤리딘 아미드 (8)을 합성하였다. 벤질 아민과 dimesylated hexitol (4)를 고리화 반응 시키면 트랜스 형태의 C_2-대칭성 피롤리딘 아민 (5)가 주생성물로 얻어지나, 이와 함께 이성질화가 일어나 시스 이성질체인 화합물 (6)도 생성된다. 피롤리딘 아민 (5, 6)을 탈보호된 아민 (7)을 거쳐 아미드 (8, 9)로 변형시켜 이를 순수한 형태로 분리하고, 이 C_2-대칭성 피롤리딘 아미드 (8)의 광학 순도를 측정하기 위해 Mosher 유도체 (13, 14)를 합성하였다. ^{1}H 과 ^{19}F NMR 실험으로 Mosher 유도체 (13, 14)가 단일 물질임이 밝혀졌고, 이로서 피롤리딘 아미드 (8)이 광학적으로 순수한 화합물임을 확인하였다.

Abstract: Optically pure C_2-symmetric pyrrolidine amides (8) were synthesized from readily available 1,2:5,6-di-*O*-isopropylidene-D-mannitol (1). Cyclization of dimesylated hexitol (4) with benzyl amine gave an inseparable mixture of C_2-symmetric pyrrolidine amine derivative (5) as a major product, concurring with its *cis* isomer (6) as a minor product. The pyrrolidine amines (5, 6) were converted to separable pyrrolidine amides (8, 9) *via* free amine (7). Optical purity of desired C_2-symmetric pyrrolidine amide (8a) was determined with its Mosher derivatives (13, 14) by their ^{1}H and ^{19}F NMR spectra.

Key words: *C_2-Symmetric Pyrrolidine, Mosher Derivatives, Optical Purity*

1. Introduction

Pyrrolidines that are stereospecifically substituted at 2- and 5-position have attracted interest for chiral auxiliaries as well as naturally occurring amines called alkaloids[1]. Especially, optically active trans-2,5-disubstituted pyrrolidine amides with C_2-symmetry are very useful as chiral auxiliaries in asymmetric alkylation, Diels-Alder reaction, diastereoselective organometallics addition, and enantioselective lactonization[2]. For these reasons, a number of stereoselective synthetic methods for the optically active pyrrolidines have been reported during the last decade. However, optically pure pyrrolidines were usually obtained *via* a resolution[3] of corresponding racemates. Only a few examples of stereoselective synthetic route utilizing optically active starting materials[4] have been reported. As a part of strategy of reagent-controlled asymmetric synthesis, we have been interested in developing new C_2-symmetric pyrrolidine amides with bulky substituents at 2,5-position. Sterically bulky *t*-butyldimethylsilyl group protection at 2,5-positionpyrrolidine provides possibility in increased stereoselectivity of chiral pyrrolidine as a chiral auxiliary. Furthermore *t*-butyldimethylsilyl group protection furnishes facile deprotection of silyl group. In this paper, we wish to describe the synthesis of optically pure C_2-symmetric pyrrolidine amides and determination of their optical purity.

† 주 저자 (e-mail: dskoh@www.dongduk.ac.kr)

2. Experiment

2.1 General Methods

Infrared spectra were recorded on a Beckman IR/32 FT-IR spectrometer. Magnetic resonance spectra (^{1}H at 300 MHz; ^{13}C at 75 MHz) were obtained on a Bruker ARX instrument and were reported in ppm (δ units). Specific rotations were measured on a Jasco DIP 370 digital polarimeter. Capillary gas chromatographic analyses were carried out using a Hewlett-Packard 5890 GC instrument equipped with a β-cyclodextrin on OV-1701 (30 m × 0.25 μm) column, SE-54 (30 m × 0.25 μm) and DB 210 (30 m × 0.25 μm) fused silica capillary columns. Mass spectra were obtained with a Varian 3400/ARC-I on the ITD. Analytical thin layer chromatography was performed by using precoated silica gel 60 F_{254} plates and the silica gel used

for flash column chromatography was from Merck (230-400 mesh, 60 Å). HPLC analyses were performed on a Waters 600E instrument equipped with a Waters R401 refractometer and Waters 440 UV detector, using a DNBPG chiral column.

2.2 Synthesis of C_2-symmetric pyrrolidine amides (8)

2.2.1. Synthesis of 1,6-di-*t*-butyl-dimethylsilyl-3,4-dideoxy-D-*threo*-hexitol (3)

A mixture of 3,4-dideoxy-*threo*-hexitol (2) (6.2 g, 41.3 mmole) and imidazole (5.78 g, 85 mmole) in 100 mL of distilled DMF was stirred for 10 min at room temperature. A solution of *t*-butyldimethylsilyl chloride (12.8 g, 85 mmole) in 30 mL of distilled DMF was added to the mixture at 0 ℃. The reaction mixture was warmed to room temperture and stirred for 18 hr. After stirring, 25 mL of ice-water was added to the reaction mixture and then acidified with 20% HCl until pH is 5-6. The resulting solution was extracted with two 100 mL portions of ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ and water. This organic solution was dried, concentrated and purified by column chromatography (ethyl acetate : n-hexane = 1 : 3, v/v). After separation, pure product was obtained as a white powder (5.58 g, 86%): m.p. 68-70 ℃; IR (neat) 3403, 2931, 2857, 1188 cm^{-1} ; ^1H NMR (300 MHz, chloroform-*d*) δ 3.68-3.65 (m, 2H), 3.62-3.57 (dd, *J*=9.6, 3.9 Hz, 2H), 3.46-3.40 (dd, *J*=9.6, 7.2 Hz, 2H), 1.60-1.54 (m, 4H), 0.88 (s, 18H), 0.06 (s, 12H); ^{13}C NMR(75 MHz, chloroform-*d*) δ 71.7, 67.2, 29.1, 25.8, 18.2, -5.3.

2.2.2. Synthesis of 1,6-di-*t*-butyl-dimethylsilyl-2,5-dimesyl-3,4-dideoxy-D-*threo*-hexitol (4)

A solution of 1,6-di-*t*-butydimethyl-silyl-3,4-dideoxy-hexitol (3) (10 g, 26.4 mmole), triethylamine (5.56 g, 55 mmole), and dimethylaminopyridine (0.75 g, 6.1 mmole) in 100 mL of dichloromethane was stirred for 30 min at 0 ℃ under nitrogen atmosphere. Freshly distilled methanesulfonyl chloride (6.3 g, 55 mmole) was added to the above solution at 0 ℃ under nitrogen. This reaction mixture was stirred for 4 hr at 0 ℃ and then 50 mL of ice-water was added to the mixture. The resulting solution was concentrated to a volume of about 50-60 mL and then acidified to pH 6-7 by addition of cold 20% HCl. The aqueous phase was extracted with two 70 mL portions of dichlormethane. The combined organic layers were washed with fresh water, dried ($MgSO_4$), and filtered. The filtrate was concentrated and the residue was purified by column chromatography (ethyl acetate : n-hexane = 1 : 1, v/v). After separation, a pure product was obtained as a slightly yellow oil (13.98 g, 99%): IR (neat) 2955, 2855, 1466, 1257, 1095, 841 cm^{-1}; ^1H NMR (300 MHz, chloroform-*d*) δ 4.76-4.71 (m, 2H), 3.73-3.71 (d, *J*=5.1 Hz, 4H), 3.04 (s, 6H), 1.79-1.78 (m, 4H), 0.88 (s, 18H), 0.07 (s, 12H); ^{13}H NMR (75 MHz, chloroform-*d*) δ 83.1, 65, 38.5, 26.3, 25.8, 18.3, -5.5.

2.2.3. Synthesis of N-benzyl-*trans* and *cis*-bis[(*t*-butyldimethylsilyl) oxymethyl] pyrrolidine (5,6)

A mixture of the mesylated hexitol (4) (13.7 g, 25.6 mmole) and benzyl amine (98 g, 914 mmole) was heated at 100~110 ℃ for 4 hr. The rest of solvent (benzyl amine) was distilled off at reduced pressure and the residue was dissolved in 100 mL of ethyl acetate. The organic solution was washed with 10% HCl, saturated $NaHCO_3$, and saturated NaCl solution successively. The organic layer was dried, concentrated, and separated by flash column chromatography (ethyl acetate : n-hexane = 1 : 20, v/v). After purification, an inseparable mixture of *trans*- and *cis*- product (5, 6) was obtained as a colorless oil (10.05 g, 87%). For major *trans* isomer: ^1H NMR (300 MHz, chloroform-*d*) δ 7.4-7.3 (m, 5H), 4.12-4.07 (d, *J*=14.7 Hz, 1H), 3.97-3.92 (d, *J*=14.4 Hz, 1H), 3.55-3.53 (d, *J*=5.1 Hz, 4H), 3.16-3.14 (m, 2H), 2.04-2.02 (m, 2H), 1.75-1.69 (m, 2H), 0.29 (s, 18H), 0.03-0.01 (d, *J*=6 Hz, 12H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 141.2, 128.09, 128.07, 126.4, 64.9, 62.6, 52.8, 27.1, 25.9, 18.2, -5.39. Capillary G.C. analysis: chirasil-L-valine on OV-1701 column (0.25 mm x 30 mm), 165 ℃ isothermal, pressure H_2 at 7.7 psi; R_t(*cis*) = 33.075, R_t(*trans*) = 39.103; HRMS (FAB) calcd for $[C_{25}H_{47}NO_2Si_2+H]$: 450.3223, found: 450.3231.

2.2.4. Synthesis of *trans*- and *cis*-bis[(*t*-butyldimethylsilyl) oxymethyl]pyrrolidine(7)

To a solution of N-benzyl pyrrolidine mixture (5, 6) (9.6 g, 21.3 mmole) in 120 mL of dry methanol was added 1.12 g of 20% $Pd(OH)_2/C$ in one portion. The mixture was hydrogenated under 1 atm hydrogen and the reaction was monitored by TLC. After completion of the reaction, the catalyst was removed by filtration through Celite and was washed with 30 mL of methanol. The filtrate was evaporated and the residue was dissolved with two 150 mL portions of ethyl acetate. The resulting organic solution was washed with water. After drying over $MgSO_4$, solvent was evaporated to afford debenzylated product (7) as a colorless oil (7.5 g, 97.8%): IR (neat) 2957, 2858, 1471, 1255, 1093, 837 cm^{-1}. For major *trans* isomer: ^1H NMR (300 MHz, chloroform-d) δ 3.43-3.40 (dd, *J*=6.0, 5.7 Hz, 4H), 3.23-3.19 (m, 2H), 2.30 (s, 1H), 1.83-1.72 (m,2H), 1.41-1.32 (m, 2H), 0.82 (s, 18H), 0.01 (s, 12H); ^{13}C NMR (75 MHz, chloroform-d) δ 66.3, 68.7, 27.2, 25.8, 18.1, -5.4. HRMS (FAB); calcd for $[C_{18}H_{41}NO_2Si_2+H]$: 360.2754, found: 360.2746.

2.2.5. Synthesis of *trans*-(2*R*,5*R*)-1-(1'-oxo-propanyl)-bis[(*t*-butyldimethylsilyl)oxymethyl] pyrrolidine(8a)

To a solution of pyrrolidine (7) (2.0 g, 5.57 mmole) and triethylamine (0.56 g, 5.57 mmole) in 40 mL of distilled dichloromethane was added propionyl chloride (0.52 g, 5.61 mmole) at room temperature under nitrogen atmosphere. The reaction mixture was stirred and the reaction was monitored by TLC. After completion of the reaction (5 hr), the reaction mixture was washed with 10% HCl, sat'd $NaHCO_3$, sat'd NaCl solution respectively, and dried over $MgSO_4$. After evaporation, the residue was separated by flash column chromatography (ethyl acetate: n-hexane = 1 : 6, v/v R_f(*trans*) = 0.75, R_f(*cis*) = 0.55) to give the products of *trans*-isomer (8a, 2.22 g) and *cis*-isomer (9a, 0.06 g) (total 2.28 g, 99 %).

For *trans*-isomer (8a): IR (neat) 2953, 2856, 1647, 1464, 1288, 1099, 83 7cm^{-1}; ^1H NMR (300 MHz, chloroform-*d*) δ 4.10-4.04

(m, 1H), 3.87-3.81 (m, 1H), 3.75-3.67 (m, 2H), 3.56-3.51 (dd, J=10.2, 10.05 Hz, 1H), 3.39-3.33 (dd, J=9.9, 9.75 Hz, 1H), 2.37-2.29 (q, J=7.2 Hz, 2H), 2.18-2.04 (m, 1H), 1.97-1.85 (m, 3H), 1.19-1.14 (t, J=7.2 Hz, 3H), 0.87-0.85 (d, J= 5.4 Hz, 18H), 0.03-0.02 (d, J=3.2 Hz, 12H); ^{13}C NMR (75 MHz, chloroform-d) δ 172.9, 64.2, 62, 59.9, 58.9, 28, 26.6, 25.8, 24.9, 18.2, 18.1, 9.3, 5.4]; HRMS (FAB) Calcd for [$C_{21}H_{45}NO_3Si_2$+H]: 416.3016, found: 416.3011.

For *cis*-isomer (9a): ^{1}H NMR (300 MHz, chloroform-d) δ 4.06-3.99 (m, 1H), 3.89-3.82 (m, 1H), 3.74-3.73 (d, J=4.2 Hz, 2H), 3.50-3.46 (m, 2H), 2.38-2.30 (q, J=7.8 Hz, 2H), 1.98-1.85 (m, 3H), 1.82-1.75 (m, 1H), 1.14-1.08 (t, J=7.5 Hz, 3H), 0.87-0.85 (d, J=2.4 Hz, 18H), -0.08--0.11(d, J=3.2 Hz, 12H).]; ^{13}C NMR (75 MHz, chloroform-d) δ 173.4, 64.2, 63.1, 60.1, 59.3, 27.5, 26.8, 25.8, 24.9, 18.2, 18.1, 9.3, 5.5.

2.2.6 Synthesis of *trans*-(2*R*,5*R*)-1-(1′-oxo-4′-pentenyl)-bis[(*t*-butyldimethylsilyl)oxymethyl] pyrrolidine (8b)

To a solution of pyrrolidine (7) (313 mg, 0.87 mmole) and triethyl amine (98.7 mg, 0.97mmole) in 20 mL of dichloromethane was added 4-pentenoyl chloride (115 mg, 0.97 mmole). The same procedures were used as described in synthesis of (8a) and (9a). After purification, major *trans*-isomer (8b, 361.9 mg), and minor *cis*-isomer (9b, 10.1 mg) were obtained respectively (total 372 mg, 96.8%).

For *trans*-isomer (8b): IR (neat) 2954, 2929, 2857, 1643, 1409, 1255, 1099, 836 cm^{-1}; ^{1}H NMR (300 MHz, chloroform-d) δ 5.89-5.76 (m, 1H), 5.10-4.93 (m, 2H), 4.13-4.06 (m, 1H), 2.43-2.38 (s, 4H), 2.17-2.10 (m, 1H), 2.10-1.86 (m, 3H), 0.86-0.85(d, J=6 Hz, 18H), 0.03-0.02 (d, J=3 Hz, 12H); ^{13}C NMR (75 MHz, chloroform-d) δ 171.3, 137.3, 115, 64.2, 61.9, 59.4, 58.9, 34.2, 29.7, 26.6, 25.7, 24.8, 18.1, 18.0, 5.5.

2.3 Determination of optical purity of C_2-symmetric pyrrolidine amides (8)

2.3.1. Synthesis of *trans*-(2*R*,5*R*)-1-(1′-oxo-propanyl)-bis-(hydroxymethyl)pyrrolidine (10)

A suspension of pyrrolidine amide (8a) (0.89 g, 2.16 mmole) and Amberlyst A-26 (F^- form, 4.29 g, 12.8 mmole; 3 mmole F/g) was stirred for 4 hr in 15 mL of boiling benzene. The benzene solution was then discarded and the resin was washed with methanol. The washing was evaporated to give practically pure desilylated product as a colorless oil in 72% yield (0.29 g): [α] = 29.99 (26 ℃, c = 1.75% in $CHCl_3$); IR (neat) 3369, 2956, 2882, 1615, 1428, 1050 cm^{-1}; ^{1}H NMR (300 MHz, chloroform-d) δ 4.76-4.73 (br, 1H), 4.27-4.17 (m, 1H), 3.99-3.95 (m, 1H), 3.73-3.67 (dd, J=11.4, 10.6 Hz, 1H), 3.61-3.47 (m, 3H), 3.21-3.20 (br, 1H), 2.46-2.38 (q, J=7.5 Hz, 2H), 2.18-1.95 (m, 3H), 1.72-1.67 (m, 1H), 1.17-1.12 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-d) δ 175.8, 67, 63.5, 61, 60.4, 28.2, 26.9, 26.4, 9.8; Capillary GC analysis: SE-54 on OV-1701 column (0.25 mm ×30 mm), 160 ℃ isothermal, pressure H_2 at 7.75 psi, R_t = 37.997; HRMS (FAB): calcd for [$C_9H_{17}NO_3$+H): 188.1286, found: 188.1278.

2.3.2. Synthesis of *trans*-(2*R*,5*R*)-1-(1′-oxo-propanyl)-bis[((2′*R*)-2′-methoxy-2′-phenyl-2′-trifluoromethylacetyl)oxymethyl] pyrrolidine (13)

A solution of hydroxymethyl pyrrolidene amide (10) (16.7 mg, 0.089mmole) dissolved in 2 mL of dichloromethane was added to a solution of (*R*)-(-)-2-methoxy-2-phenyl-2-trifluoromethylacetyl chloride (11) ((*R*)-MTPACl, 45 mg, 0.19 mmole), DMAP (23 mg, 0.19 mmole), and triethylamine (37 mg, 0.38 mmole) in 3 mL of distilled dichloromethane. The solution was stirred at room temperature and then refluxed until the diol (10) was consumed completely. After the reaction was complete, the mixture was cooled and washed with cold 1 M HCl, sat'd $NaHCO_3$, and sat'd NaCl successively. The organic layer was dried, concentrated and separated by column separation to give a product (13) as a colorless oil (42.7 mg, 77.6%). ^{1}H NMR (300 MHz, chloroform-d) δ 7.49-7.35 (m, 10H), 4.68-4.63 (dd, J=10.8, 10.5 Hz, 1H), 4.38-4.29 (dd, J=14.2, 9.6 Hz, 1H), 4.33-4.24 (m, 2H), 4.0-3.91 (m, 2H), 3.50 (s, 3H), 3.48 (s, 3H), 2.44-2.36 (m, 2H), 1.98-1.88 (m, 2H), 1.65-1.51 (m, 2H), 1.20-1.15(t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-d) δ 173.2, 166.5, 166.2, 132, 131.7, 129.8, 129.7, 128.6, 128.4, 127.2, 127, 65.8, 65.5, 55.8, 55.7, 55.4, 55.3, 27.8, 26.7, 25.5, 9.6.; ^{19}F NMR δ 107.27, 107.07.

2.3.3. Synthesis of *trans*-(2*R*,5*R*)-1-(1′-oxo-propanyl)-bis-[((2′*S*)-2′-methoxy-2′-phenyl-2′-trifluoromethylacetyl) oxymethyl] pyrrolidine (14)

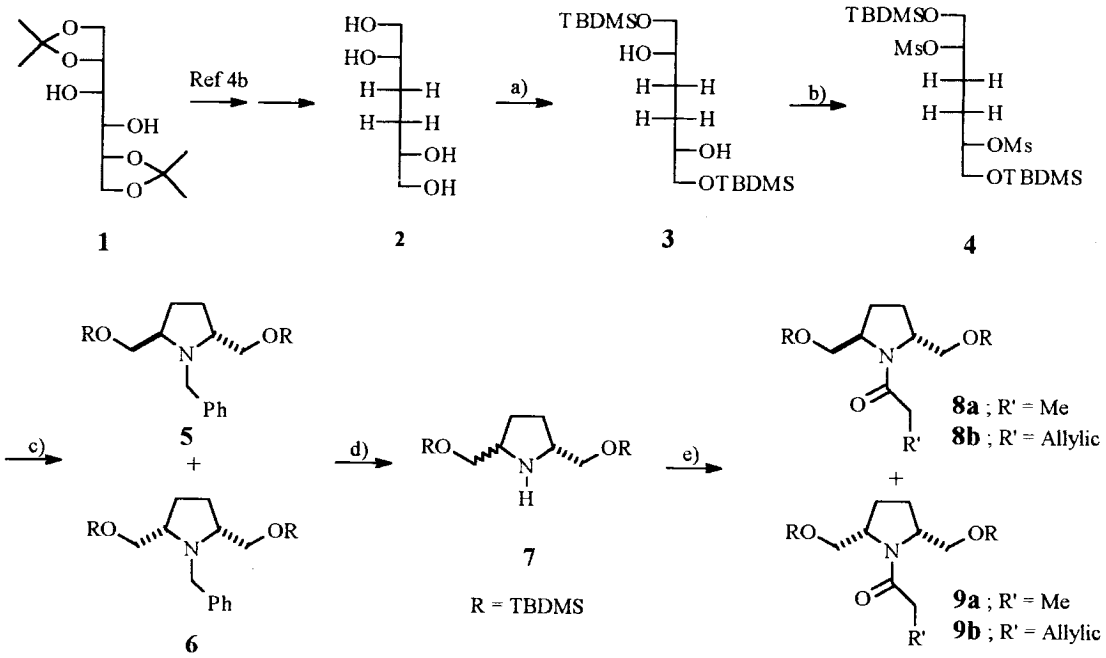
A solution of hydroxymethyl pyrrolidene amide (10) (19.9 mg, 0.106 mmole) dissolved in 2 mL of dichloromethane was added to a solution of (*S*)-(+)-2-methoxy-2-phenyl-2-trifluoromethylacetyl chloride (12) ((*S*)-MTPACl, 55 mg, 0.22 mmole), DMAP (27 mg, 0.22 mmole), and triethylamine (44 mg, 0.44 mmole) in 3 mL of distilled dichloromethane. The same procedures were used as described in the synthesis of (13). After purification, a desired product (14) was obtained as a colorless oil (48.5 mg, 73.9 %): ^{1}H NMR (300 MHz, chloroform-d) δ 7.36-7.32 (m, 10H), 4.70-4.64 (dd, J=11.4, 5.7 Hz, 1H), 4.27-4.20 (m, 3H), 4.05-3.98 (dd, J=11.1, 8.25 Hz, 1H), 3.82-3.79 (m, 1H), 3.51 (s, 3H), 3.50 (s, 3H), 2.37-2.15 (m, 2H), 2.01-1.87 (m, 2H), 1.72-1.64 (m, 2H), 1.13-1.08 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-d) δ 173.1, 166.4, 166.2, 132.3, 131.7, 129.8, 129.6, 128.5, 128.4, 127.1, 65.9, 65.3, 55.8, 55.7, 27.7, 27.1, 25.4, 9.4.; ^{19}F NMR δ 107.25, 107.18.

3. Results and Discussion

3.1. Asymmetric synthesis of 2,5-disubstituted-C_2-symmetric pyrrolidine amides.

3,4-Dideoxy-D-*threo*-hexitol (2) was prepared from readily available 1,2; 5,6-di-*O*-isopropylidene-D-mannitol (1) in 4 steps by Marzi's method[4b]. The selective protection of the primary alcohols was carried out by treatment of hexitol (2) with 2 equivalent of *t*-butyldimethylsilyl chloride in DMF to give 1,6-bis(*t*-butyldimethylsilyl)-3,4-dideoxy-D-*threo*-hexitol (3) in 85.7% yield after chromatographic purification.

The partially protected hexitol (3) was treated with MsCl to give the completely protected hexitol (4) in 99% yield. By stirring a solution of mesylated hexitol (4) in benzylamine for 2~3 h at 90 ℃, the ring closed products, N-benzyl-2,5-bis



a) TBDMSCl, imidazole, DMF, 85.7%, b) MsCl, DMAP, Et_3N, CH_2Cl_2, 99%, c) $BnNH_2$, 120 ℃ 87.3%, d) H_2, $Pd(OH)_2/C$, EtOH, 97.8% e) R' = Me ; Propionyl chloride, Et_3N, CH_2Cl_2, 99% ; R' = $CH_2CH=CH_2$; 4-pentenoyl chloride, Et_3N, CH_2Cl_2, 96.8%.

Scheme 1. Synthesis of C_2 symmertric pyrrolidine amides (8) and their isomers (9).

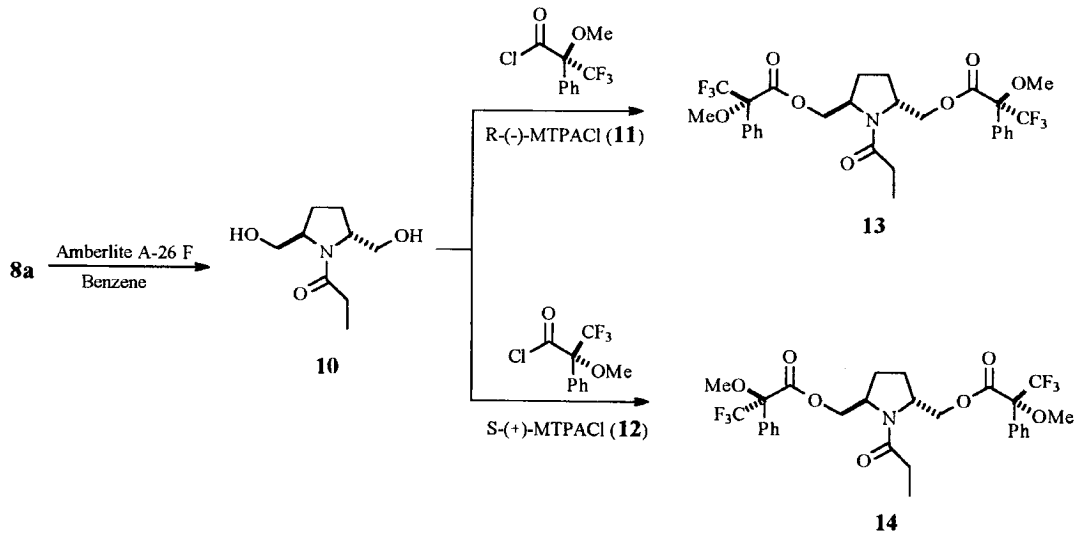
(*t*-butyldimethylsilyl)oxy pyrrolidines (5, 6) were obtained as an inseparable mixture of *trans* and *cis* isomer. GC analyses of pyrrolidines (5, 6) showed the ratio of *trans* : *cis* = 97.7 : 2.3. According to the literature[5], a direct nucleophilic substitution of primary amines with *racemic*-2,5-dibromoadipic ester gives a mixture of *cis* and *trans* 2,5-disubstituted pyrrolidine. However, corresponding *meso*-isomer with primary amine affords only a single *cis*-2,5-disubstituted pyrrolidine isomer. The exact reasons for these differences in the selectivity have not been determined. N-Debenzylation was accomplished by $Pd(OH)_2/C$ mediated hydrogenation to give free amine (7) which was obtained also as an inseparable mixture of *trans* and *cis* isomer. The above mixture was transformed into the N-propionate pyrrolidine derivatives with propionyl chloride and the resulting *trans* and *cis* propionate pyrrolidine derivatives (8a, 9a) could be separated by flash column chromatography. Each isomer was assigned by spectroscopic analysis (^1H, ^{13}C NMR, IR, HRMS). Also, GC analysis of N-propionate pyrrolidine derivatives showed almost the same ratio (*trans* : *cis* = 97.6 : 2.4) when comparing with the data of N-benzyl-2,5-disubstituted pyrrolidines (5, 6). The acylation of free amine (7) with 4-pentenoyl chloride gave also desired N-acyl products (8b, 9b) in good yield.

Sterically bulky silyl group protection at 2,5-position of pyrrolidine provided not only the possibility in increased stereoselectivity of chiral pyrrolidine but also facile deprotection of silyl group to give free alcohol which may be transformed to other functionalities for potential use. Desilylation of *trans* (or *cis*)-N-propionated pyrrolidine (8a, 9a) was accomplished using Amberlyst A-26 F form resin (an anion exchange resin, 3 mmole F/g)[6]. As *t*-butyldimethylsilyl fluoride is soluble in bezene, the solvent was filtrated off, whereas the dihydroxylated compound (9), which remained absorbed on the resin, was obtained in pure form by washing with methanol. This procedure is highly useful for avoiding an aqueous work-up process.

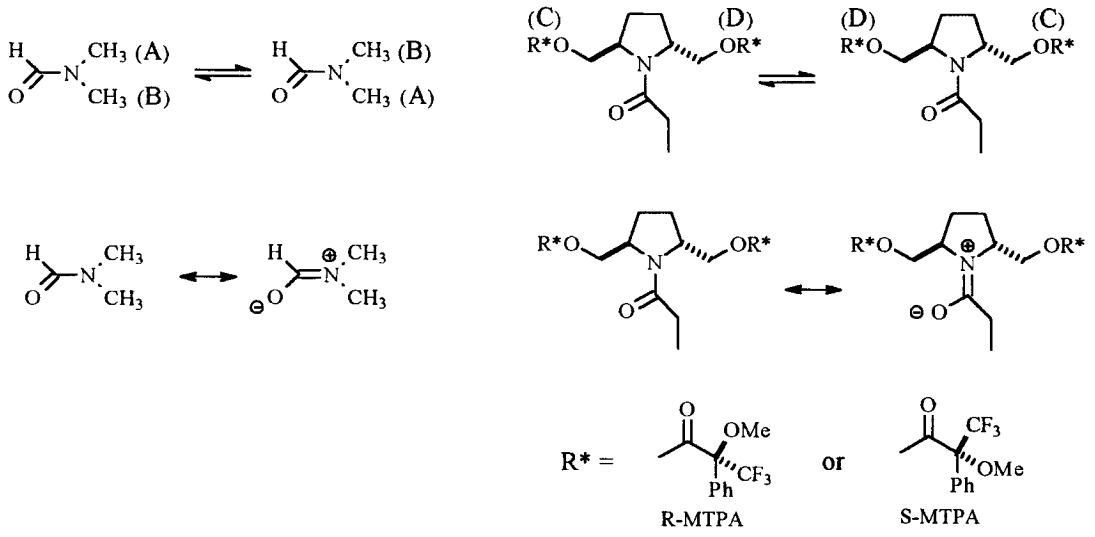
3.2. Determination of optical purity of 2,5-disubstituted-C_2-symmetric pyrrolidine amides

Because partial racemization occurred during the cyclization reaction of mesylated hexitol (4) with benzylamine, it was necessary to determine that *trans*-2,5-disubstituted-C_2-symmetric pyrrolidine such as (8a) is optically pure chiral compound or contaminated by its enantiomer even though it showed optical rotation [α] = 29.99 (26 ℃, c = 1.75 in $CHCl_3$). The Mosher derivatives were prepared to determine the optical purity by NMR spectra.

Two derivatives (13, 14) were easily prepared by coupling of the dihydroxy pyrrolidine (10) with two equivalent of (*R*)-(-)-2-methoxy-2-phenyl-2-trifluoromethylacetyl chloride [(*R*)-MTPACl, (11)] or two equivalent of (*S*)-MTPACl (12)[7]. The ^1H-NMR analysis of *R,R*-Mosher derivative (13) shows two singlets [δ 3.51 (3H) and 3.48 (3H)] for the methoxy groups as *S,S*-Mosher derivative (14) does [δ 3.50 (3H) and 3.503 (3H)]. Another attempt was made to determine the ratio of diastereomers in each derivative (13, 14) by ^{19}F NMR spectroscopy. The result of this experiment revealed the same pattern as the ^1H NMR experiment. The spectrum of *R,R*-Mosher derivative (13) shows two singlets at δ 107.27 and 107.07 ppm. On the other hand, the data for the *S,S*-Mosher derivative (14) gives two singlets at δ 107.25 and 107.18 ppm. According to dynamic NMR spectroscopy[8], ^1H



Scheme 2. Synthesis of Mosher esters (13, 14) of C_2 symmertric pyrrolidine amides (8a).



Scheme 3. Accounts for the difference in chemical shifts of methyl groups in DMF and methoxy groups in Mosher esters.

NMR of dimethylformamide shows two methyl peaks at δ 2.79 and 2.94 ppm at 22.5 ℃. The carbon-nitrogen bond in amides has a high proportion of double bond character, which results in the rotation being hindered, so that methyl groups A (or C) and B (or D) are in different magnetic environments (see Scheme 3).

If Mosher derivative (13 or 14) is a racemic mixture, the ^1H NMR and ^{19}F NMR spectra of (13 or 14) should show four peaks at room temperature based on dynamic NMR spectra. However, our results showed only two peaks confirming 2,5-disubstituted-C_2-symmetric pyrrolidine (8a) is optically pure chiral compound.

Further work on the stereoselective alkylation of 2,5-disubstituted C_2-symmetric pyrrolidine amides to give α-substituted amides, which could be hydrolyzed to give corresponding α-substituted acids, is underway.

4. Conclusions

C_2-Symmetric pyrrolidine amides (8) which have powerful potential as chiral auxiliaries were synthesized from readily available 1,2 : 5,6-di-*O*-isopropylidene-D-mannitol (1). Optical purity of the pyrrolidine amide (8a) was determined with its Mosher derivatives. ^1H NMR and ^{19}F NMR of each Mosher derivative showed two peaks of corresponding OCH_3 and CF_3 group, confirming that pyrrolidine amide (8a) is optically pure.

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