Journal of the Korean Chemical Society
1996, *Vol. 40, No. 4*
Printed in the Republic of Korea

단 신

(1S,2R)-노르에페드린으로부터 새로운 C_2 대칭성 키랄 디아미도- 및 디아자피리디노-18-크라운-6의 합성

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(1996. 1. 4 접수)

Synthesis of New C_2 Symmetrical Chiral Diamido- and Diazapyridino-18-crown-6 from (1S,2R)-Norephedrine

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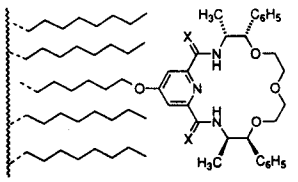
(Received January 4, 1996)

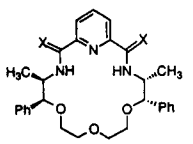
Chiral liquid chromatography has been successfully utilized in solving the stereochemical problems such as the determination of enantiomeric purity, the determination of absolute configuration of optically active compounds and the obtainment of enantiomerically pure compounds.[1] For the successful use of chiral liquid chromatography, appropriate chiral stationary phases (CSPs) are needed and various types of CSPs have been introduced for this purpose.[1]

We have been interested in the use of (1S,2R)-norephedrine as a chiral selector for chiral liquid chromatography and have developed various CSPs based on (1S,2R)-norephedrine. For example, (1S,2R)-*N*-(3,5-dinitrobenzoyl)norephedrine bonded to silica gel has been successfully utilized as a Pirkle-type π-π donor acceptor CSP in resolving various racemates[2] and (1S,2R)-*N,N*-carboxymethyl dodecylnorephedrine monosodium salt adsorbed onto a commercial octadecyl-silica gel column has also been successfully employed in resolving various racemic α-amino acids.[3]

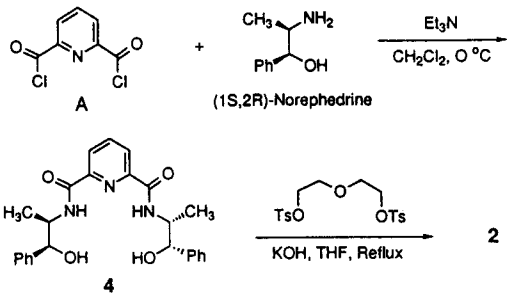
In a continuation of our effort to extend the use of (1S,2R)-norephedrine as a chiral selector for chiral liquid chromatography, we have planned to prepare CSP **1** based on chiral pyridino-crowns derived from (1S,2R)-norephedrine. Previously, several chiral crown ether type CSPs have been prepared and applied in resolving racemic organic ammonium salts since Cram's pioneering works on the use of chiral crown ethers in chiral liquid chromatography.[4] However, crown ether type CSPs based on chiral diazacrowns have not been reported. In addition, chiral crown ethers containing pyridine units have been known to form strong complexes with organic ammonium salts and show appreciable enantiomeric recognition in certain cases.[5] Therefore CSP **1** is expected to show high enantioselectivity for the two enantiomers of racemic organic ammonium salts. As a preliminary study of preparing CSP **1**, herein we report the simple and convenient method of preparing dia-



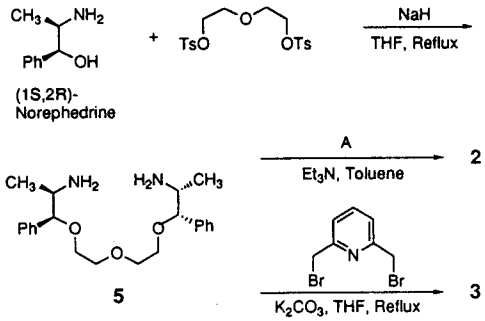
CSP 1 X = O or H_2



2, X = O
3, X = H_2



Scheme 1.



Scheme 2.

mido- and diazapyridino-18-crown-6 (**2** and **3**) from (1S,2R)-norephedrine.

New C_2 symmetrical chiral diamidopyridino-18-crown-6, **2**, was prepared as shown in *Scheme* 1. Treatment of 2,6-pyridinedicarbonyl dichloride with (1S,2R)-norephedrine in the presence of triethylamine at 0 ℃ afforded diamidopyridino compound 4 in 91% yield. Diamidopyridino compound **4** was treated with KOH in THF at 0 ℃ and then heated to reflux with diethylene glycol ditosylate for 2 days to give diamidopyridino-18-crown-6, **2**, in 27% yield. Alternatively, chiral diamidopyridino-18-crown-6, **2**, was also prepared via the procedure shown in *Scheme* 2. In this alternative procedure the non-pyridino part (diamine, **5**) of diamidopyridino-18-crown-6, **2**, was prepared (23 % yield) by treating the sodium alkoxide derived from (1S,2R)-norephedrine and NaH with diethylene glycol ditosylate. Dimine, **5**, was then cyclized with 2,6-pyridinedicarbonyl dichloride to give diamidopyridino-18-crown-6, **2**. However, the yield of the last cyclization step was only 13%.

Our initial attempt to form diazapyridino-18-crown-6, **3**, by reducing diamidopyridino-18-crown-6, **2**, with $LiAlH_4$ in THF was not successful. Alternatively, diazapyridino-18-crown-6, **3**, was prepared via the cyclization of diamine, **5**, with 2,6-pyridinedimethyl dibromide as shown in *Scheme* 2. Diamine, **5**, reacted with K_2CO_3 and then 2,6-pyridinedimethyl dibromide to give diazapyridino-18-crown-6, **3**, in 21% yield. In this cyclization step, we also tried to use 2,6-pyridinedimethyl ditosylate instead of 2,6-pyridinedimethyl dibromide. However, we found that 2,6-pyridinedimethyl dibromide was better than 2,6-pyridinedimethyl ditosylate.

In conclusion, new C_2 symmetrical diamido- and diazapyridino-18-crown-6 (**2** and **3**) were prepared from (1S,2R)-norephedrine in a simple two-step process. The chiral recognition ability of diamido- and diazapyridino-18-crown-6 (**2** and **3**) for the two enantiomers of racemic organic ammonium salts may be determined in the future from the chromatographic results for resolving racemic organic ammonium salts on CSP **1**. To this end, the preparation of CSP **1** based on the method described herein is under way in our laboratory.

EXPERIMENTAL

General. ^1H NMR spectra were recorded on Varian Gemini 200 (200 MHz) or Gemini 300 (300 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) from internal standard using $CDCl_3$ as solvent. IR spectra were recorded on a Mattson Polaris FT-IR spectrometer. Optical rotations were observed at 589 nm at room temperature using a Rudolph Autopol III polarimeter and a 1 dm polarimetric cell. High-resolution mass spectra were measured by the Korea Basic Science Center, Daejeon, Korea using Jeol JMS-HX110/110 A mass spectrometer. Melting points were taken on a Rigaku Thermal Analyzer TAS 100. All reactions were done under argon atmosphere. Solvents such as THF, CH_2Cl_2 and toluene were dried before use by the conventional method.

***N,N'*-*Bis*[(1R,2S)-1-methyl-2-phenyl-2-hydroxyethyl]-2,6-pyridinedicarboxamide (4).** To a solution of (1S,2R)-norephedrine (2.29 g, 15 mmole) and Et_3N (2.51 mL, 18 mmole) in CH_2Cl_2 (50 mL)

was added dropwise a solution of 2,6-pyridinedicarbonyl dichloride in CH_2Cl_2 (30 mL) at 0 ℃. The resulting mixture was stirred for 1 hr at room temperature. The mixture was washed sequentially with 2 N HCl, diluted aqueous K_2CO_3 and brine. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated on a rotary evaporator. The residue was recrystallized from a mixture of acetone and hexane to afford product **4** (2.97 g, 91% yield) as a white crystalline solid. mp 181~184 ℃; ^{1}H NMR ($CDCl_3$) δ 1.11(d, 6H), 2.90(broad s, 2H), 4.43~4.55(m, 2H), 5.00(d, 2H), 7.20~7.34(m, 10H), 7.95~8.11(m, 3H), 8.31(d, 2H); IR (KBr) 3381, 3085, 2984, 1669, 1537 cm^{-1}.

(2R,3S,11S,12R)-2,12-Diamino-3,11-diphenyl-4,7,10-trioxatridecane (5). To a suspension of NaH (1.06 g, 26.5 mmole; 60% in mineral oil) in THF (25 mL) was added dropwise a solution of (1S,2R)-norephedrine (2.0 g, 13.2 mmole) in THF (25 mL) at 0 ℃. The resulting mixture was stirred at room temperature for 30 min and then heated to reflux for 3 days. To the mixture cooled at 0 ℃ was added a solution of diethylene glycol ditosylate (2.74 g, 6.6 mmole) in THF (25 mL) with stirring. The whole mixture was stirred at room temperature for 2 days and then heated to reflux for 5 days. THF was removed by rotary evaporation at reduced pressure, and the resulting residue was dissolved in CH_2Cl_2 (50 mL). The organic solution was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure. The residue was eluted through a silica gel flash column (eluent : EtOH/NH_4OH 1 : 400), and then the fraction containing product was subjected to high vacuum to afford **5** (0.58 g, 23% yield) as a pale yellow viscous oil. ^{1}H NMR ($CDCl_3$) δ 1.05(d, 6H), 2.41(broad, 4H), 3.15~3.25(m, 2H), 3.41~3.70(m, 8H), 4.22(d, 2H), 7.31(s, 10H); IR (NaCl window in $CDCl_3$) 3363, 3293, 3040, 2869, 1601, 1495 cm^{-1}.

(4R,5S,13S,14R)-4,14-Dimethyl-5,13-diphenyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (2). (Method shown in *Scheme* 1) A solution of compound **4** (1 g, 2.3 mmole) and KOH (0.26 g, 4.6 mmole) in THF (80 mL) was stirred at room temperature for 30 min. To the solution was added slowly a solution of diethylene glycol ditosylate (0.96 g, 2.3 mmole) in THF (30 mL) at 0 ℃ with stirring. The reaction mixture was then heated to reflux for 2 days. After removing THF at the reduced pressure, the residue was dissolved in CH_2Cl_2 (100 mL) and washed with water (80 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated on a rotary evaporator. The residue was purified by silica gel flash chromatography (eluent : EtOAc/hexane/CH_2Cl_2/acetone 2 : 6 : 2 : 1) to afford product **2** (0.32 g, 27% yield) as a white crystalline solid. (Method shown in *Scheme* 2) A solution of diamine **5** (0.624 g, 1.5 mmole) and Et_3N (0.42 mL, 3.0 mmole) in toluene (50 mL) and another solution of 2,6-pyridinedicarbonyl dichloride in toluene (50 mL) were added simultaneously over a 2-hr period to toluene (100 mL) at 0 ℃ with stirring vigorously. The whole mixture was stirred at room temperature for 1 day and then filtered. The filtrate was concentrated at the reduced pressure, and then the residue was purified by silica gel flash chromatography (eluent : EtOAc/hexane 1 : 1) to afford product **2** (0.1 g, 13% yield) as a white crystalline solid. mp 188~192 ℃; ^{1}H NMR ($CDCl_3$) δ 1.13(d, 6H), 3.60~3.66(m, 2H), 3.77~3.91(m, 4H), 4.09~4.15(m, 2H), 4.46~4.52(m, 2H), 4.71(d, 2H), 7.30~7.42(m, 10H), 8.06(t, 1H), 8.33(d, 2H), 8.46(d, 2H); IR (KBr) 3372, 2939, 1674, 1518 cm^{-1}; $[\alpha]^{25}_D$ +108.2° (c 1.0, CH_3OH); High Resolution MS calcd for $C_{29}H_{33}O_5N_3$ 503.2420; found 503.2441(M^+).

(4R,5S,13S,14R)-4,14,Dimethyl-5,13-diphenyl-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene (3). To a stirred suspension of K_2CO_3 (0.4 g, 2.9 mmole) in THF (60 mL) were added a solution of compound **5** (0.54 g, 1.4 mmole) and 2,6-pyridinedimethyl dibromide (0.38 g, 1.4 mmole), which was prepared by treating 2,6-pyridinedimethanol with triphenylphospine and CBr_4 in diethylether, in THF (90 mL) at 0 ℃. The mixture was stirred for 5 hrs at room temperature and then heated to reflux for 2 days. Solvent was removed by rotary evaporation at reduced pres-

sure, and the resulting residue was dissolved in CH_2Cl_2 (150 mL). The organic solution was washed with cold water, dried over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure. The residue was purified by silica gel flash column chromatography (gradient eluent : EtOAc/Et_3N 40 : 1~20 : 1) to afford product **3** (0.15 g, 21% yield) as a pale yellow viscous oil. ^1H NMR ($CDCl_3$) δ 0.96(d, 6H), 2.72(broad, 2H), 2.92~3.03(m, 2H), 3.53~3.90(m, 8H), 4.01(s, 4H), 4.74(d, 2H), 7.14(d, 2H), 7.21~7.39(m, 10H), 7.57(t, 1H); IR (KBr in $CDCl_3$) 3309, 2868, 1576, 1450 cm^{-1}; $[\alpha]^{25}_D$+55.1° (c 2.15, CH_3OH); High Resolution MS calcd for $C_{29}H_{37}O_3N_3$, 475.2835; found, 475.2852(M^+).

Acknowledgment. This work was supported by OCRC-KOSEF and basic science research program, Ministry of Education, Korea (BSRI-95-3410).

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