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A NEW AND CONVENIENT ACCESS TO ENANTIOPURE C_2-SYMMETRIC 2,5-DIETHYNYLPYRROLIDINE

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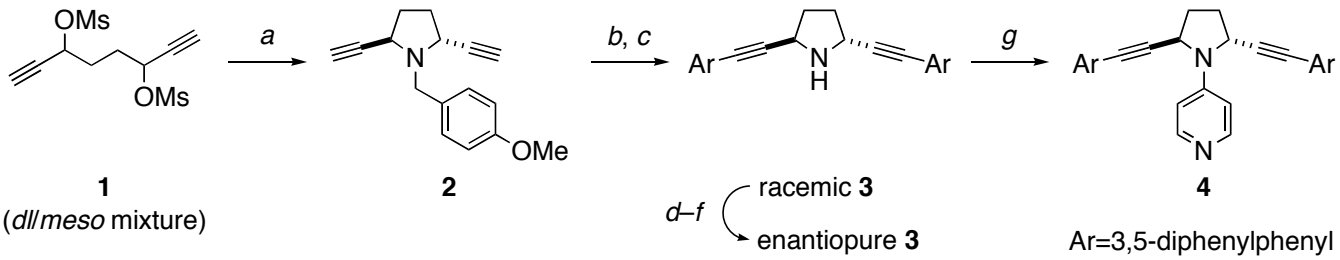
Abstract – Both (2*R*,5*R*)- and (2*S*,5*S*)-diethynylpyrrolidines were conveniently synthesized from 3,6-bis(mesyloxy)-1,7-octadiyne in optically pure forms *via* (*R*)-1-(4-methoxyphenyl)ethylamine-induced pyrrolidine ring formation, chromatographic separation of the corresponding diastereomers, and cleavage of the benzylic C–N bond.

Because of its excellent acyl transfer activity, 4-pyrrolidinopyridine (PPY) has been widely used as an efficient catalyst for the formation of esters and the development of its chiral derivatives is one of the current topics.[1] Previously, we reported the synthesis of a novel C_2-symmetric 2,5-disubstituted pyrrolidinopyridine (**4**) and also an efficient kinetic resolution of secondary alcohols using this catalyst.[2,3] However, the synthetic route is rather long and tedious manipulation is required as shown in Scheme 1.

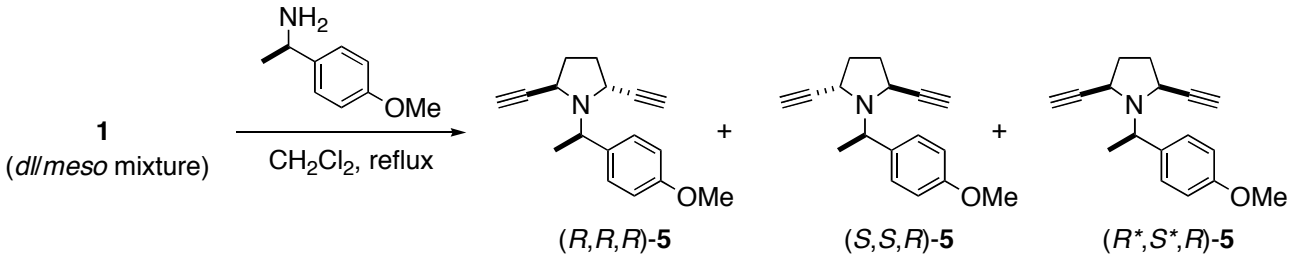


Reagents: (a) 4-methoxybenzylamine; (b) ArBr, cat. $PdCl_2(PPh_3)_2$, cat. CuI, Et_3N; (c) α-chloroethyl chloroformate, then MeOH; (d) (*R*)-PhCH(OCOCl)(COO-*i*-Pr), proton sponge®; (e) SmI_2 (1.4 molar equiv.); (f) SmI_2 (2.0 molar equiv.); (g) 4-bromopyridine, cat. [$Pd_2(dba)_3$+BINAP], *t*-BuONa; dba=(*E*,*E*)-dibezylideneacetone, BINAP=2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

Scheme 1. Previous synthetic route

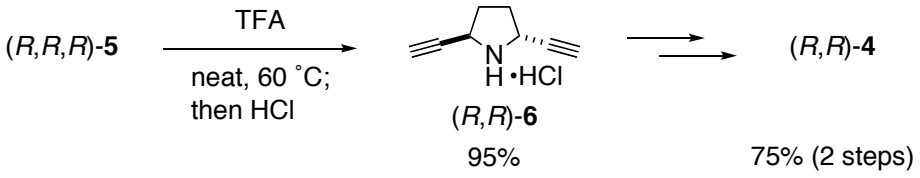
In this paper, we propose an efficient and convenient synthetic route to obtain enantiopure (2*R*,5*R*)- and (2*S*,5*S*)-diethynylpyrrolidine [(*R,R*)-**6** and (*S,S*)-**6**].

This time, we selected the (*R)*-1-(4-methoxyphenyl)ethylamine-induced pyrrolidine ring formation of dimesylate (**1**, *dl/meso*=2:1).[4] The reaction proceeded smoothly to afford a mixture of three diastereomers (*R,R,R*)-**5**, (*S,S,R*)-**5**, and (*R*,S*,R*)-**5**, the ratio of which was almost 1:1:1, with 83% combined yield. Fortunately, these diastereomers could be easily separated by column chromatography on silica gel. (Scheme2)



Scheme 2. Synthesis of the diastereomers (**5**)

The absolute configuration of (*S,S,R*)-**5** was determined by X-Ray crystallography.[5] Treatment of (*R,R,R*)-**5** with trifluoroacetic acid at 60 ˚C under neat conditions gave rise to clean cleavage of the benzylic C–N bond to give, after ethereal HCl treatment, the desired (*R,R*)-**6** in 95% isolated yield. (Scheme 3) Although other conditions such as the use of *p*-TsOH•H_2O in 2-propanol at high concentration and the treatment with α-chloroethyl chloroformate in acetonitrile in the presence of KI also afforded the corresponding free pyrrolidine in moderate to high yield, the attempted oxidative cleavage by CAN[6] or DDQ resulted in failure. By using the Sonogashira-Hagihara coupling followed by the Buchwald coupling, (*R,R*)-**6** could be converted to (*R,R*)-**4** with 75% overall yield.



Scheme 3. Synthesis of the key intermediate (**6**)

In summary, we have developed a new and efficient route to synthesize enantiopure **6**, where clean separation of a diastereomeric mixture of **5** and efficient cleavage of the benzylic C–N bond of **5** without affecting propargylic amine moiety are the major improvements. Since various aromatic groups can be attached at the terminal ethynyl carbons of **6**, this compound may serve as an important common intermediate for a variety of optically pure pyrrolidine ring-containing chiral ligands and catalysts.

EXPERIMENTAL

Pyrrolidine ring-forming reaction. To a solution of 3,6-bis(mesyloxy)-1,7-octadiyne (**1**, *dl/meso*=2:1, 6.61 g, 22.5 mmol) in CH_2Cl_2 (40 mL) was added (*R*)-1-(4-methoxyphenyl)ethylamine (11.9 g, 78.6 mmol), and the mixture was stirred at 50 ˚C for 5 days. The reaction mixture was cooled to rt and filtered through a short column of silica gel. The eluate was concentrated and subjected to column chromatography on silica gel (hexane/AcOEt=15:1 to 4:1) to give the desired products (*R,R,R*)-**5** (1.58 g, 28%), (*S,S,R*)-**5** (1.59 g, 28%), and (*R*,S*,R*)-**5** (1.50 g, 27%), respectively.

(2*R*,5*R*,1'*R*)-1-[1'-(4"-Methoxyphenyl)ethyl]-2,5-diethynylpyrrolidine [(*R,R,R*)-**5**]. A colorless oil. R_f 0.41 (hexane/AcOEt=6:1). IR (NaCl): 3290, 2976, 1611, 1511, 1242, 1138, 1038, 833, 643 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.32 (2H, d, *J*=8.79 Hz), 6.82 (2H, d, *J*=8.79 Hz), 3.80 (3H, s), 3.78 (3H, m), 2.32 (2H, m), 2.08 (2H, d, *J*=2.20 Hz), 1.91 (2H, m), 1.48 (3H, d, *J*=6.59 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 137.5, 135.6, 134.5, 131.3, 128.3, 113.4, 111.3, 85.1, 72.1, 60.9. HRMS-FAB (*m*/*z*): calcd for $C_{17}H_{19}NO$, 254.1545. Found, 254.1519.

(2*S*,5*S*,1'*R*)-1-[1'-(4"-Methoxyphenyl)ethyl]-2,5-diethynylpyrrolidine [(*S,S,R*)-**5**]. A white solid (recrystallized from hexane/AcOEt): mp 58.6–59.1 ˚C. R_f 0.30 (hexane/AcOEt=6:1). IR (KBr): 3267, 1617, 1511, 1249, 1029, 816, 669, 419 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.34 (2H, d, *J*=8.79 Hz), 6.83 (2H, d, *J*=8.79 Hz), 3.88 (1H, dd, *J*=6.83, 6.83 Hz), 3.80 (3H, s), 3.55 (2H, d, *J*=7.57 Hz), 2.33 (2H, m), 2.31 (2H, s), 1.93 (2H, m), 1.56 (3H, d, *J*=6.83 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 158.6, 136.3, 129.2, 112.9, 83.5, 71.8, 60.6, 54.9, 51.6, 31.4, 21.8. HRMS-FAB (*m*/*z*): calcd for $C_{17}H_{19}NO$, 254.1545. Found, 254.1525.

(2*R**,5*S**,1'*R*)-1-[1'-(4"-Methoxyphenyl)ethyl]-2,5-diethynylpyrrolidine [(*R*,S*,R*)-**5**]. A colorless oil. R_f 0.34 (hexane/AcOEt=6:1). IR (NaCl): 3290, 2971, 1611, 1512, 1461, 1247, 1175, 1039, 834, 546 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.32 (2H, d, *J*=8.55 Hz), 6.83 (2H, d, *J*=8.55 Hz), 4.21 (1H, dd, *J*=6.59, 6.59 Hz), 3.97 (1H, m), 3.81 (3H, s), 3.41 (1H, t, *J*=5.86 Hz), 2.34 (1H, s), 2.26 (2H, s), 2.16 (2H, m), 2.05 (2H, m), 1.50 (3H, d, *J*=6.59 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 158.2, 135.5, 128.5, 113.2, 84.1, 83.6, 56.4, 55.0, 50.8, 48.9, 31.3, 22.4. HRMS-FAB (*m*/*z*): calcd for $C_{17}H_{19}NO$, 254.1545. Found, 254.1500.

Debenzylation procedure. A mixture of **5** (92.1 mg, 0.36 mmol) and trifluoroacetic acid (0.15 mL) was stirred at 60 ˚C for 6 h. After the mixture was cooled to rt, 1N aqueous HCl and $CHCl_3$ were added. The organic layer was extracted with water several times. To the combined aqueous layer, KOH was added until the solution became basic. The desired product was then extracted with ether several times and the extract was dried over anhydrous Na_2SO_4. After filtration of Na_2SO_4, the filtrate was treated with 4N-HCl/AcOEt. The resulting white precipitates were collected and dried to give 2,5-diethynylpyrrolidine hydrochloride (**6**, 53.7 mg, 95%).

(2*R*,5*R*)-Diethynylpyrrolidine hydrochloride [(*R*,*R*)-**6**]. A colorless crystalline solid (recrystallized from MeOH): mp 135.1–135.2 ˚C (decomp). $[\alpha]_D^{13.9}$=–105.7˚ (*c*=1.00, MeOH). IR (KBr): 3326, 3194, 2858, 2767, 2647, 2594, 2362, 2118, 1420, 1362, 1034, 757, 701 cm^{-1}. ^1H NMR (400 MHz, CD_3OD, δ): 4.02 (2H, m), 2.20 (2H, s), 2.17 (2H, m), 1.82 (2H, m). ^{13}C NMR (100 MHz, CD_3OD, δ): 79.2, 77.8, 50.3, 32,7. Anal. Calcd for $C_8H_{10}NCl$: C, 61.74; H, 6.48; N, 9.00. Found: C, 61.22; H, 6.47; N, 8.84.
(2*S*,5*S*)-Diethynylpyrrolidine hydrochloride [(*S*,*S*)-**6**]. A colorless solid (recrystallized from MeOH): mp 135.1–135.3 ˚C (decomp). $[\alpha]_D^{14.2}$=+104.9˚ (*c*=0.98, MeOH).

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REFERENCES

1. For examples, see: T. Kawabata, M. Nagato, K. Takasu, and K. Fuji, *J. Am. Chem. Soc.*, 1997, **119**, 3167; J. C. Ruble and G. C. Fu, *J. Am. Chem. Soc.*, 1998, **120**, 11532; some recent reports, see: A. C. Spivey, A. Maddaford, T. Fekner, A. J. Redgrave, and C. S. Frampton, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3640; T. Kawabata, R. Stragies, T. Fukaya, Y. Nagaoka, H. Schedel, and K. Fuji, *Tetrahedron Lett.*, 2003, **44**, 1545; G. Priem, B. Pelotier, S. J. F. Macdonald, M. S. Anson, and I. B. Campbell, *J. Org. Chem.*, 2003, **68**, 3844; A. H. Mermerian and G. C. Fu, *J. Am. Chem. Soc.*, 2005, **127**, 5604.
2. T. Hanamoto, N. Shimomoto, T. Kikukawa, and J. Inanaga, *Tetrahedron: Asymmetry*, 1999, **10**, 2951.
3. G. Naraku, N. Shimomoto, T. Hanamoto, and J. Inanaga, *Enantiomer*, 2000, **5**, 135.
4. Feringa and co-workers successfully used optically pure phenylethylamine to obtain enantiopure 2,5-dimethylpyrrolidine: M. E. Zwasgstra, A. Moctama, and B. L. Feringa, *Tetrahedron: Asymmetry*, 1993, **4**, 2163. Palladium-catalyzed hydrogenolysis was used for the cleavage of the benzylic C–N bond.
5. CCDC 279119 contains the supplementary crystallographic data for (*S,S,R*)-**5**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambrige Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).
6. A. B. Bragg, J. Clayden, and C. J. Menet, *Tetrahedron Lett.*, 2002, **43**, 1955.