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A new route to enantiomerically pure 2,5-disubstituted pyrrolidines. Total synthesis of (+)-Pyrrolidine 197B.

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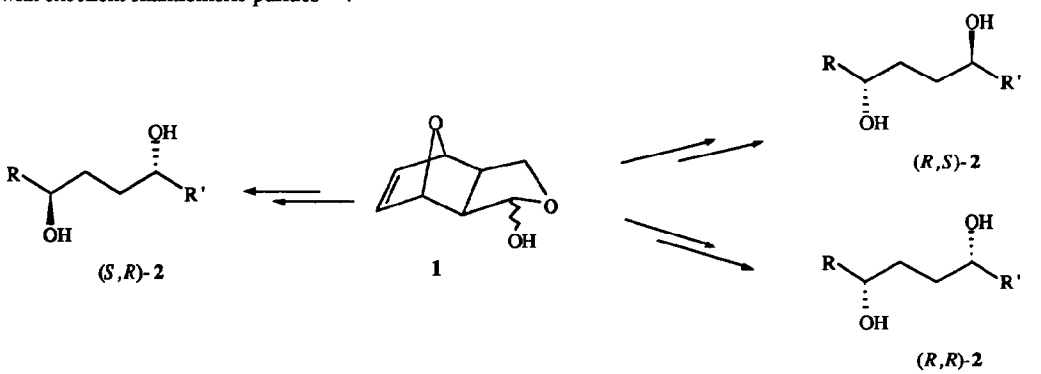
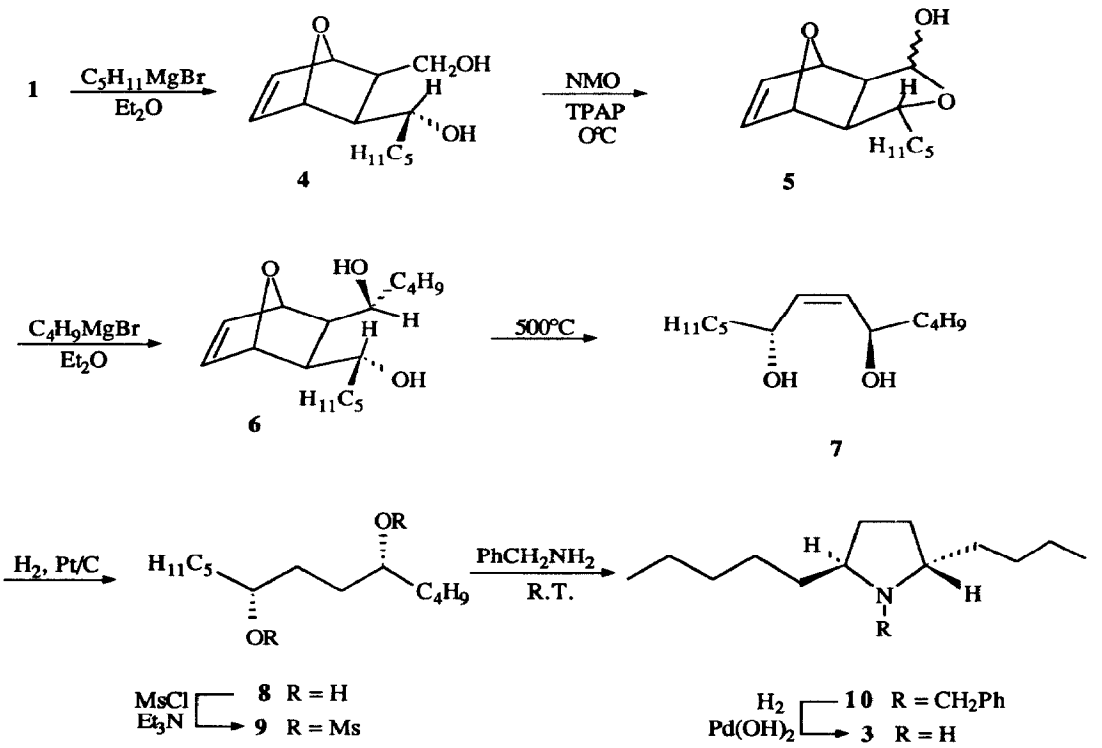
Abstract : *An enantioselective synthesis of (+)-pyrrolidine 197B, starting from the readily available lactol **1** is described. The key steps involve two chelation controlled additions of Grignard reagents to the carbonyl groups of lactols **1** and **5** and a highly stereoselective trans-pyrrolidine formation from the dimesylate **9**.*

During these last few years various unsymmetrical trans-1,5-dialkylpyrrolidines have been identified as the major constituents of the venom of ants belonging to different species of the genera *Solenopsis* and *Monomorium* [1] and their stereoselective syntheses have been the subject of numerous reports [2,3]. We have recently shown that addition of organometallic reagents to the carbonyl groups of Diels-Alder adducts of furan can be sterically controlled by chelation of the reagent with the oxygen bridge [4] and that, starting from the same enantiomerically pure lactol **1**, it could be possible to obtain three among the four stereoisomers of 1,4-diols **2** with excellent enantiomeric purities [5].



These diols **2** appeared to be attractive intermediates for the stereoselective preparation of optically active 2,5-disubstituted pyrrolidines. We wish to report in this paper the synthesis of trans-2-butyl-5-pentylpyrrolidine **3**, named pyrrolidine 197B, to illustrate the potential of our method. Pyrrolidine 197B, found in ant venom of various species [1] and also detected in the skin of the poison frog *Dendrobates Histrionicus* [6], has been so far synthesized by two different groups from synthons coming from the chiral pool [7].

The synthesis, depicted in Scheme 1, started with the lactol **1**, available by DIBAL-H reduction of the corresponding lactone, easily obtained from the Diels-Alder adduct of furan and maleic anhydride, either via an enzymatic hydrolysis [8] or by an asymmetric reduction [9]. Addition of pentylmagnesium bromide to a solution of **1** in diethyl ether led with good diastereoselectivity to the "unlike" diol **4** (u/l = 10/1) in 87% yield. Without separation, the diol **4** and its isomer were oxidized by the system 4-methylmorpholin N-oxide (NMO) - tetrapropylammonium perruthenate (TPAP) [10]. We have found that controlled oxidation of **4** at 0°C afforded in a single step the lactol **5** in 46% yield after separation by colum chromatography.



Scheme 1

Addition of butylmagnesium bromide to the lactol **5** gave rise with 96% yield to a unique diastereoisomer **6** corresponding to an approach of the reagent on the less hindered side of a tridentate chelate [5]. Retro Diels-Alder reaction in flash thermolysis conditions (500°C, 10^{-3} torr, 10 to 50 ms contact time) provided the unsaturated diol **7** in 90% yield. The enantiomeric purity of this diol has been estimated higher than 95% by ^1H NMR spectroscopy in the presence of the chiral shift reagent Eu(hfc)$_3$. Hydrogenation by molecular hydrogen catalyzed by platinum (palladium catalysts led to products arising from hydrogenolysis of one or two hydroxy groups) gave (5*R*,8*R*)-5,8-tridecanediol **8** {$[\alpha]_D^{20}$ -5.3 (c 1, $CHCl_3$), m.p. 81°C ; lit. [7a] for ent-**8** : $[\alpha]_D^{26}$ +4 (c 0.99, $CHCl_3$), m.p. 78°C }. Treatment of the diol **8** with methanesulfonylchloride under standard conditions led to the dimesylate **9** in 76% yield from **7**. Compound **9** was cyclised, with inversion of the two asymmetric

centers, into (2*S*,5*S*)-N-benzyl-2-butyl-5-pentylpyrrolidine **10** in 77% yield by stirring with benzylamine at room temperature [13]. The trans configuration of the two substituents in **10** was confirmed by the method of Hill and Chan [14] based on the analysis of the ^1H NMR benzylmethylene signal appearing here as an AB quartet centered at δ = 3.72 ppm. Finally hydrogenolysis of the benzyl group [(H_2/Pd(OH_2)] gave rise to (+)-pyrrolidine 197B **3** {$[\alpha]_D^{20}$ +5.6 (c 0.61, $CHCl_3$) ; lit. [7a] : $[\alpha]_D^{27}$ +5.8 (c 0.79, $CHCl_3$)} in 81% yield. The spectral data of **3** were identical to those already reported [7].

In summary the synthesis of (+)-pyrrolidine 197B has been accomplished in 8 steps (19% overall yield) from the readily available lactol **1** and compares favourably with the reported syntheses.

Experimental Section

IR spectra were recorded on a Perkin Elmer 682 spectrophotometer. NMR spectra were recorded on a Brucker AM250 or AC200 spectrometer with tetramethylsilane as an internal standard. Mass spectra were obtained with a GC/MS R.10-10 spectrometer. Optical rotations were measured on a Perkin Elmer 241 polarimeter. All reactions were carried out under an inert atmosphere of argon and were monitored by thin-layer chromatography (TLC). TLC was performed on Merck silicagel 60F-254 precoated on glass.

(1*R*,2*R*,3*S*,4*S*,1"*R*)-2-hydroxymethyl-3-(1"hydroxyhexyl)-7-oxabicyclo[2.2.1]hept-5-ene (4).

To a stirred solution of pentylmagnesium bromide (90 mmol) in ether (90 mL) was added at 0°C 2.8 g (18 mmol) of lactol **1**. The reaction mixture was allowed to reach room temperature and stirred for 4 h. After addition of a saturated ammonium chloride solution (80 mL), the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried ($MgSO_4$), concentrated and the residue purified by flash chromatography (ethyl acetate) to afford 3.45 g (87%) of a mixture of **4** (91%) and its isomer (9%). The spectral data for **4** follow. IR (neat) : 3340, 2960, 2930, 2870, 1035, 900 cm^{-1}. ^1H NMR (C_6D_6, 200 MHz) δ (ppm) : 0.94 (3H, t, J = 6.7 Hz) ; 1.16 - 1.54 (9H, m) ; 1.79 (1H, m) ; 3.55 (2H, m) ; 3.6 - 3.85 (2H, m) ; 3.92 (1H, m) ; 4.30 (1H, s) ; 4.58 (1H, s) ; 5.94 (2H, m). CIMS (NH_3) m/e (relative intensity) : 244 (MNH_4^+, 48) ; 227 (MH^+, 100). Anal. calcd for $C_{13}H_{22}O_3$: C, 68.98 ; H, 9.80. Found : C, 68.95 ; H, 9.96.

5-Pentyl-4,10-dioxatricyclo[5.2.1.$O^{2,6}$]dec-8-en-3-ol (5).

To a solution of diol **4** (1.5 g, 6.64 mmol) in CH_2Cl_2 (30 mL) were added molecular sieves, 4Å, activated powder (3 g) and tetrapropylammonium perruthenate (116 mg, 0.33 mmol). The stirred mixture was cooled to 0°C (ice-water bath) and a solution of 4-methylmorpholin N-oxide (932 mg, 7.96 mmol, 1.2 eq.) in CH_2Cl_2 (30 mL) was very slowly added in 4 hours. The mixture was stirred at 0°C for an additional 4 hours and was then filtered through a bed of silica gel. The solid was washed with CH_2Cl_2 (20 mL). The solvent was removed under reduced pressure and the residue was chromatographed twice on silica gel (AcOEt/hexane : 80/20) to give : 195 mg of unreacted diol **4**, 162 mg of the corresponding lactone, 44 mg of lactols arising from isomeric **4** and 684 mg (46% or 53% based on recovered **4**) of lactol **5**, a mixture of two stereoisomers (60/40), as a white solid. IR ($CDCl_3$) : 3595, 2930, 1110, 1025 cm^{-1}. ^1H NMR (C_6D_6, 250 MHz) δ (ppm), major product : 0.90 (3H, t, J = 6.3 Hz) ; 1.14 - 1.62 (8H, m) ; 1.74 (1H, dd, J = 7.1, 8.7 Hz) ; 2.06 (1H,

dd, J = 5.7, 8.7 Hz) ; 3.61 (1H, m) ; 4.18 (1H, s) ; 4.27 (1H, d, J = 10.5 Hz) ; 4.62 (1H, s) ; 5.35 (1H, dd, J = 7.1, 10.5 Hz) ; 5.78 (2H, m). Minor product : 0.93 (3H, t, J = 6.2 Hz) ; 1.14 - 1.62 (8H, m) ; 1.87 (1H, dd, J = 3.9, 7.5 Hz) ; 2.19 (1H, dd, J = 2.3, 7.5 Hz) ; 2.60 (1H, m) ; 3.85 (1H, m) ; 4.35 (1H, s) ; 4.55 (1H, s) ; 5.22 (1H, m) ; 5.83 (2H, bs). Anal. calcd for $C_{13}H_{20}O_3$: C, 69.61 ; H, 8.99. Found : C, 69.72 ; H, 8.95.

(-)-(1*R*,2*R*,3*S*,4*S*,1'*R*,1"*R*)-2-(1'-hydroxypentyl)-3-(1"-hydroxyhexyl)-7-oxabicyclo [2.2.1]hept-5-ene (6).

To a stirred solution of butylmagnesium bromide (30 mmol) in ether (30 mL) was added at 0°C 1.22 g (5.45 mmol) of lactol **5**. The solution was stirred for 5 hours at room temperature and a saturated ammonium chloride solution (20 ml) was added. The aqueous phase was extracted with CH_2Cl_2 (3x20 mL) and the organic layers were dried over magnesium sulfate. The solvents were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc) to give 1.47 g (96%) of diol **6** as a colorless oil. $[\alpha]_D^{20}$ = -8.5 (c 1, $CHCl_3$). IR (neat) : 3400, 2960, 2935, 1465 cm^{-1}. ^1H NMR (C_6D_6, 200 MHz) δ (ppm) : 0.88 (6H, m) ; 1.1 - 1.8 (16H, m) ; 3.96 (1H, m) ; 4.0 (2H, m) ; 4.40 (1H, m) ; 4.53 (1H, s) ; 4.94 (1H, s) ; 5.96 (2H, m). CIMS (NH_3) m/e (relative intensity) : 283 (MH^+, 100) ; 247 (67) ; 211 (21) ; 195 (73) ; 139 (33). Anal. calcd for $C_{17}H_{30}O_3$: C, 72.28 ; H, 10.71. Found : C, 72.30 ; H, 10.48.

(+)-(5*R*,8*R*)-6-tridecen-5,8-diol (7).

1.44 g (5.1 mmol) of bicyclic adduct **6** were evaporated through an horizontal mullite tube (500°C, 10^{-3} torr) and the product was collected in a trap cooled to liquid nitrogen temperature. After warming to room temperature, the content of the trap was dissolved in ether and the resulting solution was dried ($MgSO_4$) and after filtration, concentrated under reduced pressure. The residue was purified by chromatography (silica gel, ether/hexane : 50/50) to provide 990 mg (90%) of unsaturated diol **7** as an oil. $[\alpha]_D^{20}$ = +1.7 (c 1, $CHCl_3$). IR (neat) : 3350, 2960, 1575, 1465, 1115 cm^{-1}. ^1H NMR (C_6D_6, 250 MHz) δ (ppm) : 0.93 (6H, m) ; 1.22 - 1.67 (14H, m) ; 1.75 (2H, m) ; 4.45 (2H, m) ; 5.50 (2H, m). CIMS (NH_3) m/e (relative intensity) : 232 (MNH_4^+, 10) ; 215 (MH^+, 15) ; 214 (M^+, 61) ; 197 (100). Anal. calcd for $C_{13}H_{26}O_2$: C, 72.83 ; H, 12.23. Found : C, 72.90 ; H, 12.15.

(-)-(5*R*,8*R*)-tridecane-5,8-diol (8).

To a stirred suspension of 30 mg of 5% platinum on carbon in ethyl acetate (5 mL) under a hydrogen atmosphere was added 428 mg (2 mmol) of diol **7** in ethyl acetate (4 mL). When the required amount of hydrogen had been taken up (44.8 mL) the catalyst was removed by filtration. The filtrate was concentrated and the residue was purified by flash chromatography on silica gel (ether/hexane : 70/30) to yield 392 mg (91%) of diol **8** as a white solid. mp = 81°C. $[\alpha]_D^{20}$ = -5.3 (c 0.8, $CHCl_3$). IR ($CHCl_3$) : 3620, 3400, 2940, 2860 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm) : 0.91 (6H, m) ; 1.22 - 1.72 (18H, m) ; 2.05 (2H, m) ; 3.64 (2H, m). CIMS (NH_3) m/e (relative intensity) : 234 (MNH_4^+, 18) ; 217 (MH^+, 100) ; 199 (43) ; 181 (20). Anal. calcd for $C_{13}H_{28}O_2$: C, 72.17 ; H, 13.04. Found : C, 72.13 ; H, 13.07.

(+)-(5*R*,8*R*)-5,8-bis[(methylsulfonyl)oxy]tridecane (9).

To an ice-cold, stirred mixture of **8** (375 mg, 1.74 mmol) and triethylamine (0.6 mL, 4.31 mmol, 2.5 eq.) in CH_2Cl_2 (5 mL) was added dropwise methanesulfonyl chloride (438 mg, 3.83 mmol). The mixture was stirred in the ice bath for another 10 min. and a 1N HCl aqueous solution (2.5 mL) was added dropwise. After separation of the organic phase, the aqueous phase was extracted with CH_2Cl_2 (3x10 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with ether/hexane (70:30) as eluent to give **9** (565 mg, 87%) as a colorless oil. $[\alpha]_D^{20}$ = +4.3 (c 1, $CHCl_3$). IR (neat) : 2960, 1345 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) : 0.90 (6H, m) ; 1.22 - 1.5 (10H, m) ; 1.71 (4H, m) ; 1.86 (4H, m) ; 3.04 (6H, s) ; 4.78 (2H, m). CIMS (NH_3) m/e (relative intensity) : 390 (MNH_4^+, 100). Anal. calcd for $C_{15}H_{32}O_6S_2$: C, 48.36 ; H, 8.66. Found : C, 48.53 ; H, 8.72.

(+)-(2*S*,5*S*)-N-benzyl-2-butyl-5-pentylpyrrolidine (10).

A solution of the bis(methanesulfonate) **9** (273 mg, 0.73 mmol) in benzylamine (0.46 mL, 4.2 mmol, 6 eq.) was stirred at room temperature for one week. The solution was poured in water (10 mL) and extracted with CH_2Cl_2 (3x5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel (ether/hexane : 15/85) to give the pyrrolidine **10** (163 mg, 77%) as a colorless oil. $[\alpha]_D^{20}$ = +94 (c 0.83, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) : 0.87 (6H, t, J = 6.4 Hz) ; 1.01 - 1.35 (12H, m) ; 1.40 - 1.62 (4H, m) ; 1.78 - 1.95 (2H, m) ; 2.82 (2H, m) ; 3.64 and 3.81 (2H, ABq, J = 14 Hz) ; 7.2 - 7.4 (5H, m). CIMS (NH_3) m/e (relative intensity) : 288 (MH^+, 100) ; 287 (M^+, 7) ; 230 (21) ; 216 (25). Anal. calcd for $C_{20}H_{33}N$: C, 83.56 ; H, 11.57. Found : C, 83.88 ; H, 11.57.

(+)-(2*S*,5*S*)-2-butyl-5-pentylpyrrolidine [(+)-Pyrrolidine 197B] (3).

A solution of **10** (149 mg, 0.52 mmol) in acetic acid (3 mL) was hydrogenated in a Parr apparatus (30 psi) over 20% $Pd(OH)_2/C$ (5 mg) for 24 hours. After filtration the solution was diluted with water (3 mL) and neutralized with aqueous NaOH. The solution was extracted with ether (3x10 mL) and the organic phase was concentrated under reduced pressure. The residue was purified by chromatography on silica gel ($CHCl_3$/MeOH/NEt_3 : 94/5/1) to give the pyrrolidine **3** (83 mg, 81%) as a pale yellow oil. Spectral data of **3** are in good agreement with those reported in the literature [7].

References and Notes

1) Jones, T.H.; Blum, M.S.; Fales, H.M. *Tetrahedron*, **1982**, *38*, 1949.

2) For recent syntheses of racemic trans-2,5-dialkylpyrrolidines see : a) Miyashita, M.; Awen, B.Z.E.; Yoshikoshi, A. *Chem. Lett.*, **1990**, 239. b) Bäckvall, J.E.; Schink, H.E.; Renko, Z.D. *J. Org. Chem.*, **1990**, *55*, 826. c) Dumas, F.; d'Angelo, J. *Tetrahedron Lett.*, **1992**, *33*, 2005.

3) For syntheses of enantiomerically enriched trans-2,5-dialkylpyrrolidines see : a) Shiosaki, K.; Rapoport, H. *J. Org. Chem.*, **1985**, *50*, 1229. b) Arseniyadis, S.; Huang, P.Q.; Piveteau, D.; Husson, H.P.; *Tetrahedron*, **1988**, *44*, 2457. c) Jegham, S.; Das, B.C. *Tetrahedron Lett.*, **1989**, *30*, 2801. d) Skrinjar, M.; Wistrand, L.G. *Tetrahedron Lett.*, **1990**, *31*, 1775. e) Rosset, S.; Celerier, J.P.; Lhommet, G. *Tetrahedron Lett.*, **1991**, *32*, 7521.

4) Bloch, R.; Gilbert, L. *Tetrahedron Lett.*, **1987**, *28*, 423.
5) Bloch, R.; Brillet, C.. *Tetrahedron : Asymmetry*, **1992**, *3*, 333. The fourth stereoisomer (*SS*) is available from ent-**1** : Brillet, C. Ph. D. Thesis, Orsay, **1992**.
6) Daly, J.W.; Spande, T.F.; Whittaker, N.; Highet, R.J.; Feigl, D.; Nishimori, N.; Tokuyama, T.; Myers, C.W. *J. Nat. Prod.*, **1986**, *49*, 265.
7) a) Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.*, **1990**, *31*, 3637 and *J. Org. Chem.*, **1991**, *56*, 1386. b) Takahata, H.; Takehara, H.; Ohkubo, N.; Momose, T. *Tetrahedron : Asymmetry*, **1990**, *1*, 561.
8) Bloch, R.; Guibé-Jampel, E.; Girard, C. *Tetrahedron Lett.*, **1985**, *26*, 4087.
9) Matsuki, K.; Inoue, H.; Takeda, M. *Tetrahedron Lett.*, **1993**, *34*, 1167.
10) This reagent developed by S.V. Ley [11] can be used for the oxydation of 1,4 diols in β-lactones [12].
11) Griffith, W.P.; Ley, S.V. *Aldrichim. Acta*, **1990**, *23*, 13 and references there in.
12) Bloch, R.; Brillet, C. *Synlett*, **1991**, 829.
13) Short, R.P.; Kennedy, R.M.; Masamune, S. *J. Org. Chem.*, **1989**, *54*, 1755.
14) Hill, R.K.; Chan, T.H. *Tetrahedron*, **1965**, *21*, 2015.

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