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A SHORT, STEREOSPECIFIC ROUTE TO CHIRAL *TRANS*-2,6-DISUBSTITUTED QUINUCLIDINES

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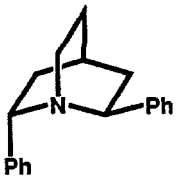
Summary: An efficient six-step stereospecific synthesis of *trans*-2,6-diphenylquinuclidine (**1**) is described together with an effective resolution of **1** into pure enantiomers. A key step in the synthesis is a highly efficient, catalyzed Diels-Alder reaction.

Although the quinuclidine ring is an important structural subunit in numerous biologically active synthetic compounds and several important alkaloids (e.g. ajmaline, cinchonine, quinine, quinidine, and sarpagine), almost all known syntheses of this system follow long-known, classical routes.[1] This paper describes a short and stereospecific route to 2,6-disubstituted quinuclidines which is based on a novel Diels-Alder construction, specifically leading to *trans*-2,6-diphenylquinuclidine (**1**). An efficient resolution of **1** is also described. The chiral amine contains three contiguous stereocenters (C-2, N-1 and C-6) embedded in a rigid bicyclic nucleus with a highly dissymmetric environment about nitrogen.

The trimethylsilyl (TMS) enol ether **2**, prepared from the corresponding methyl ketone as previously described,[2] was alkylated[3] using 1.2 equiv of chloromethyl benzyl ether and 0.014 equiv of zinc bromide in CH_2Cl_2 at 23°C for 1 h (vigorous stirring) to afford, after quenching with aqueous sodium carbonate, extractive isolation and silica gel (sg) chromatography, enone **3** (75%) as a pale yellow oil.[4] Methylenation of **3** with 1.05 equiv of methylenetriphenylphosphorane in THF (at -78°C for 30 min initially, then at 0°C for



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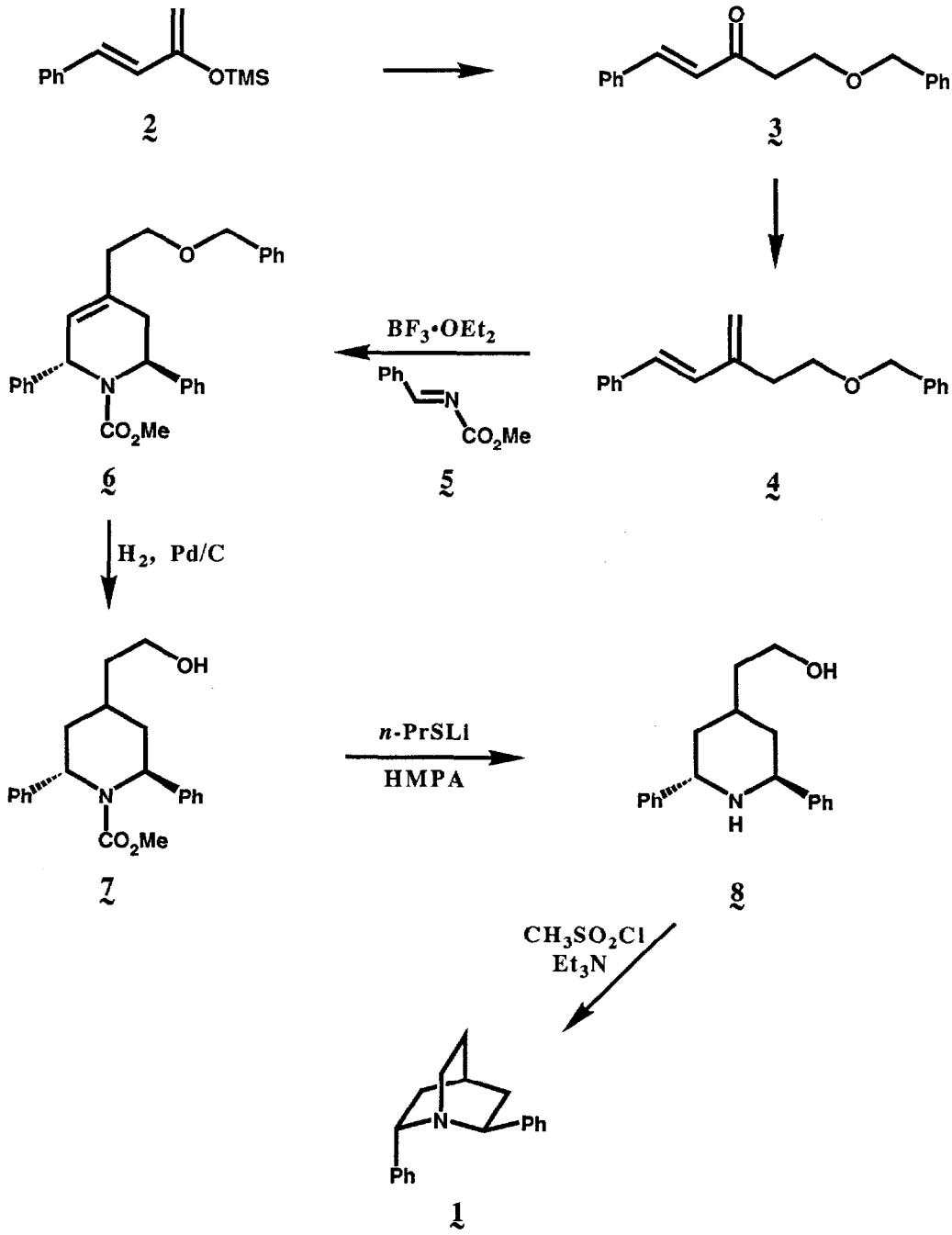
30 min) produced diene **4** (77% after purification by sg chromatography using 2 - 5% EtOAc in hexane). Treatment of a mixture of diene **4** and 1.13 equiv of *N*-benzylidene methyl carbamate (**5**)[5] in toluene at -30°C with boron trifluoride etherate (0.085 equiv) as catalyst afforded after further reaction from -30°C to 23°C over 30 min the Diels-Alder adduct **6** stereospecifically in 95% yield.[6] The *trans* arrangement of the phenyl substituents in **6**, expected on the basis of an *endo* transition state in the Lewis-acid catalyzed Diels-Alder reaction, was fully confirmed by ^{1}H NMR data for the products of the subsequent steps in the synthesis of **1** and for **1** itself, and by the resolution of **1** which is inconsistent with a *cis* (or *meso*) structure. Hydrogenation of **6** in ethyl acetate with Pd/C and 1 atm H_2 at 23°C for 18 h effected reduction of the olefinic linkage. Addition of methanol and 0.1 equiv of 0.1 *N* hydrochloric acid and further hydrogenation (monitored by the tlc analysis) resulted in complete debenzylation to give hydroxy amide **7** as a colorless oil in 85% yield after sg chromatography (30% EtOAc in hexane). The *N*-methoxycarbonyl protecting group was removed by treatment of **7** with lithium *n*-propylmercaptide in hexamethylphosphoric triamide at 23°C for 18 h to provide amino alcohol **8** as a colorless oil in 85% yield.

Conversion of the amino alcohol **8** to quinuclidine **1** was accomplished in one step simply by reaction with 1.2 equiv of methanesulfonyl chloride and 10 equiv of triethylamine in CH_2Cl_2 at 0°C for 15 min and then at reflux for 30 h; yield 85%.[7,8] Treatment of racemic **1** with (+)-camphor-10-sulfonic acid in ethyl acetate and removal of solvent in vacuo afforded a salt which was recrystallized (3x) to constant rotation using amyl acetate as solvent. The free base **1**, obtained from this salt using ethyl acetate-aqueous sodium carbonate and removal of ethyl acetate in vacuo, had $[\alpha]_D^{23}$ -16.8° (c=1.26, $CHCl_3$). The levorotatory enantiomer of **1**, $[\alpha]_D^{23}$ +16.4° (c=1.14, $CHCl_3$) was obtained from enriched (+)-**1**, isolated from the mother liquors, by conversion to the salt with (-)-camphor-10-sulfonic acid and recrystallization from amyl acetate.

The quinuclidine **1** was found to be a weak base with pK_a = 6.97 in 9 : 1 ethanol-water at 23°C as compared to pK_a = 10.30 for quinuclidine itself under the same conditions. The lowered basicity of **1** can be ascribed in part to steric shielding by the phenyl groups which lowers solvation of the conjugate acid of **1**.

The enantiomers of **1** are of interest in connection with the development of new enantioselective reagents. The following procedure gives experimental detail for the crucial Diels-Alder step in the synthesis of **1**.

Synthesis of Diels-Alder Adduct 6. To a solution of the diene **4** (0.5 g, 1.89 mmol) and dieneophile **5** (0.35 g, 2.14 mmol) in 10 mL of toluene at -30°C under an argon atmosphere was added boron trifluoride etherate (20 μL, 0.16 mmol). The reaction mixture was stirred at this temperature for 15 min and then


Ph
OTMS
2
O
Ph
O
Ph
3
O
Ph
Ph
N
Ph
CO2Me
6
BF3·OEt2
Ph
N
CO2Me
5
Ph
O
Ph
4
H2, Pd/C
OH
Ph
N
Ph
CO2Me
7
n-PrSLi
HMPA
OH
Ph
N
H
Ph
8
CH3SO2Cl
Et3N
N
Ph
Ph
1

allowed to warm to room temperature over 0.5 h. Solvent was removed in vacuo and the yellow oil was chromatographed on silica gel with 20% ethyl acetate in hexanes to give 0.77 g (95% yield) of the Diels-Alder adduct **6** as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40 - 7.10 (m, 15H), 5.73 (br s, 1H), 5.50 (br m, 2H), 4.23 (AB_q, 2H, J_{AB} = 11.87 Hz, υ_{AB} = 16.76 Hz), 3.47 (s, 3H), 3.18 (br t, 2H, J = 4.91 Hz), 2.98 (br d, 1H, J = 12.91 Hz), 2.41 (d, 1H, J = 15.32 Hz), 2.15 (t, 2H, J = 6.50 Hz); IR (neat): 3029, 2951, 2856, 1705, 1495, 1443, 1379, 1342, 1302, 1264, 1195, 1120, 1103, 1077, 1030, 778, 764, 737, 698 cm^{-1}.[9]

References and Notes

1. For reviews see (a) L. N. Yakhontov, *Adv. Heterocyc. Chem.*, A. R. Katritzky, Ed. (Acad. Press, N.Y.), Vol. 11, 473-523, 1970; (b) L. N. Yakhontov, *Heterocycles*, **7**, 1033 (1977).
2. G. M. Rubottom and J. M. Gruber, *J. Org. Chem.*, **42**, 1051 (1977).
3. I. Paterson, *Tetrahedron Letters*, 1519 (1979).
4. All reactions involving air or moisture sensitive reactants or products were conducted under an atmosphere of nitrogen or argon using flame-dried glassware. Satisfactory spectroscopic data were obtained for each reaction product.
5. R. Kupfer, S. Meier and E.-U. Würthwein, *Synthesis*, 688 (1984); (b) D. J. Hart, K.-i. Kanai, D. G. Thomas, and T.-K. Yang, *J. Org. Chem.*, **48**, 289 (1983).
6. For other examples of Diels-Alder reactions of various imine derivatives see (a) G. Krow, R. Rodebaugh, R. Carmosin, W. Figures, H. Pannella, G. DeVicaris, and M. Grippi, *J. Am. Chem. Soc.*, **95**, 5273 (1973); (b) G. R. Krow, C. Johnson and M. Boyle, *Tetrahedron Letters*, 1971 (1978); (c) M. E. Jung, K. Shishido, L. Light, and L. Davis, *Tetrahedron Letters*, **22**, 4607 (1981).
7. The success of this cyclization implies a higher rate of mesylation at the hydroxyl group relative to the secondary amino function. This is probably a consequence of steric shielding about nitrogen by the two vicinal phenyl substituents.
8. Quinuclidine **1** was obtained as a colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55 (t, 4H, J = 1.11 Hz), 7.36 - 7.14 (m, 6H), 4.16 (t, 1H, J = 9.08 Hz), 3.90 (t, 1H, J = 9.15 Hz), 2.97 (m, 2H), 2.29 (m, 1H), 2.12 (m, 1H), 2.06 (m, 1H), 1.77 (ddt, 1H, J = 1.93, 8.90, 10.72 Hz), 1.61 (m, 2H), 1.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.52 (s), 144.35 (s), 128.04 (d, 2C), 126.90 (d, 2C), 126.62 (d, 2C), 126.16 (d, 2C), 126.00 (d, 2C), 58.28 (d), 51.93 (d), 43.50 (t), 33.72 (t), 33.24 (t), 26.64 (t), 23.43 (d); IR (neat): *3083, 3059, 3024, 2930, 2861, 1600, 1493, 1447, 1359, 1324, 1295, 1175, 1080, 1060, 1049, 1030,* 992, 975, 836, 798, 759, 742, 721, 700, 627, 613 cm^{-1}; MS (EI): m/e 263 (M^+), 177, 158, 149, 118, 91, 69. HRMS calcd for $C_{19}H_{21}N$ M^+ 263.167, found 263.166.
9. This research was assisted financially by grants from the National Institutes of Health and the National Science Foundation.

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