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AN IMPROVED PROCEDURE FOR THE SYNTHESIS OF CHIRAL 2-AZA-BICYCLO[2.2.1]HEPTANE

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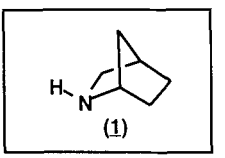
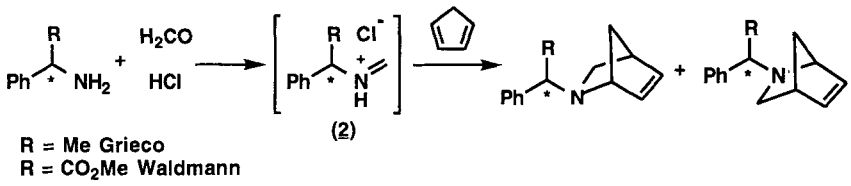
Abstract: Grieco's protocol for the synthesis of 2-aza-bicyclo[2.2.1]heptane is modified and adapted for large scale preparation. The optical purity of the material is readily upgraded by purification through a chiral salt.

One of our research programs requires the chiral 2-aza-bicyclo[2.2.1]heptane (**1**) in large quantity. The synthesis of chiral cyclic amines *via* asymmetric hetero-Diels-Alder reaction is well documented in the literature.[1] Grieco[2] and Waldmann[3] have separately reported the synthesis of (**1**) *via* an asymmetric cycloaddition of cyclopentadiene and the chiral iminium salt (**2**), which is formed *in situ* from a chiral amine and formaldehyde. The reaction (Scheme 1) is quite diastereomerically selective (80:20).



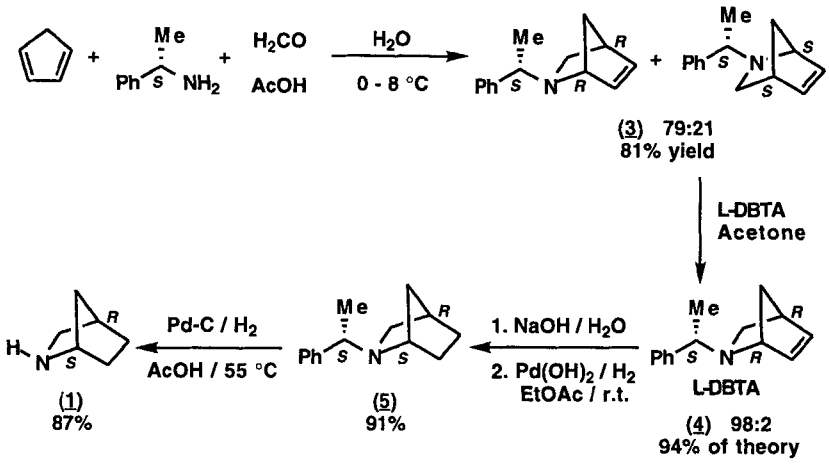
(1)



Scheme 1

We are particularly interested in adopting Grieco's protocol[2] for the preparation of (1), which entails reaction of cyclopentadiene, chiral α-methylbenzylamine and formaldehyde in an aqueous medium. This reaction is promoted by HCl, but the combination of HCl with formaldehyde precludes its scale-up due to the possible formation of chloromethyl ether, a carcinogen. In the search for an alternative, acetic acid is found to be equally effective in promoting the Diels-Alder reaction (Scheme 2). The adducts (3) are isolated in good yield (81%) and with comparable diastereomeric selectivity (79:21).

The mixture of diastereomeric adducts (3) is typically separated by tedious column chromatography, which is impractical on large scale operation. We reasoned that a successful chemical separation of the diastereomeric amine (3) *via* a chiral salt would provide a process which is more amenable to scale. After screening various acids, L-dibenzoyl tartaric acid (L-DBTA) was identified as the resolving agent that most effectively separates the desired diastereomer. The desired salt (4) is isolated with good diastereomeric purity (>95:5, within the detection limit of ^{1}H-NMR) and in high yield (94-97% of theory from the 79:21 diastereomeric mixture). It is worth noting that the amine (3) in our hands, as the free base or salt, is prone to undergo retro-Diels-Alder reaction. The purified salt



Scheme 2

(**4**) is, therefore, neutralized (10% NaOH) to give the free base, which is immediately hydrogenated to remove the olefinic double bond and, hence, defuse the retro-Diels-Alder process. It is also possible to remove the chiral α-methyl-benzyl auxiliary under this hydrogenolysis condition, to provide the amine (**1**) directly from the purified amine (**3**), but the reaction is rather sluggish. Nevertheless, the α-methyl-benzyl auxiliary is readily removed by hydrogenation of the amine (**5**) in glacial acetic acid (Pd-C/H_2/55 °C). The resulting amine (**1**) is fairly volatile and is more conveniently handled as the *p*-toluenesulfonic acid salt, which is an easy-to-handle crystalline solid (mp = 135-137 °C).

In order to verify the absolute configuration of the bicyclic amine, a crystalline salt of the saturated amine (**5**) with L-DBTA was prepared and subjected to X-ray analysis. The absolute configuration of the amine (**5**) so prepared is established as (1*S*, 4*R*) (Figure 1). This configuration is in agreement with the assignment determined by the Sandoz group.[4,5]

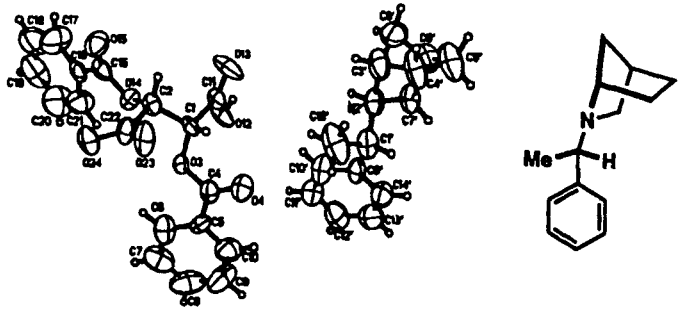


Figure 1: X-ray structure of the amine (4) as the L-DBTA salt.

In summary, we have demonstrated a practical modification of Grieco's synthesis[2] of 2-aza-bicyclo[2.2.1]heptane (1).

Experimental

General Topics: All reagents and solvents were obtained from commercial sources and used as received. Melting points were determined with a Thomas Hoover capillary melting point apparatus. Melting points (mp) and boiling points (bp) are uncorrected. ^{1}H and ^{13}C NMR were performed on a Bruker AM-250 spectrometer (250 MHz), and samples were run in deuteriochloroform using residual chloroform (7.27 and 77.0 ppm respectively) as an internal standard. ^{1}H-NMR data were presented in the following order: chemical shift (δ in ppm downfield from tetramethylsilane); multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublets of doublet, dt = doublets of triplet, m = multiplet, bs = broad signal, e = envelope); integration as the number of protons; coupling constant (J in hertz); and assignment (if appropriate). GC/MS was performed on a Hewlett-Packard 5890 GC (HP-1 column 12m x 0.2mm,

0.33μm; injection temperature 280 °C, initial temperature 133 °C, ramp 19 °C/min. to 330 °C) in tandem with a Hewlett-Packard 5971A Mass Selective Detector. X-ray data were collected on a Nicolet R3m/μ diffractometer. Elemental analysis was conducted by Schwarzkopf Microanalytical Laboratory, Woodside, NY.

Diastereomeric 2-[(1'(*S*)-phenyl)-ethyl]-2-aza-bicyclo[2.2.1]hept-5-ene (3)

(-)-α-Methyl-benzylamine (35.3g, 0.29mol) in water (100mL) was treated with a solution of acetic acid (16.7mL, 0.29mol) in water (50mL) at 0 °C, followed by freshly distilled cyclopentadiene (38.5g, 0.58mol) and aqueous formaldehyde (35.5mL, 0.44mol). The resulting mixture was stirred mechanically for 20 hours with temperature maintained between 0 and 8 °C. The reaction mixture was poured into water (75mL) and washed twice with hexanes (2 x 50mL). The aqueous layer was laced with crushed ice and 10% EtOAc/hexanes (50mL), chilled in an icewater bath, and basified with NaOH pellets (~9.5g) to pH ~10. The mixture was extracted trice with 10% EtOAc/hexanes (3 x 150mL), and the combined extract was dried over Na_2SO_4. Evaporation of solvent by Rotavap (bath temp 18-20 °C) provided the bicycloadduct (3) as an oil (47.4g, 81%). ^{1}H-NMR of the product showed that it was a 79:21 diastereomeric mixture.

Major diastereomer (1*R*,4*R*,1'*S*): ^{1}H-NMR ($CDCl_3$) δ 7.36-7.17 (m, 5H), 6.33 (m, 1H), 6.12 (dd, 1H, J = 1.9 & 5.7 Hz), 4.14 (bs, 1H), 3.05 (q, 1H, J = 6.5 Hz), 2.89 (dd, 1H, J = 3.0 & 8.8 Hz), 2.83 (bs, 1H), 1.62 (m, 1H), 1.47 (m, 1H), 1.41-1.31 (m, 1H), 1.35 (d, 3H, J = 6.5 Hz). GC/MS (retention time 2.45 min.) 199 (M^+), 184, 134, 105.

Minor diastereomer (1*S*,4*S*,1'*S*): ^{1}H-NMR ($CDCl_3$) δ 7.35-7.19 (m, 5H), 6.32 (m, 1H), 5.83 (dd, 1H, J = 1.9 & 5.7 Hz), 3.49 (bs, 1H), 3.30 (dd, 1H, J = 3.1

& 8.8 Hz), 2.95 (m, 2H), 1.66 (m, 1H), 1.55 (m, 1H), 1.38-1.25 (m, 1H), 1.29 (d, 3H, 6.5 Hz). GC/MS (retention time 2.27 min.) 199 (M^+), 184, 134, 105.

(1*R*,4*R*) 2-[(1'(*S*)-Phenyl)-ethyl]-2-aza-bicyclo[2.2.1]hept-5-ene/ L-dibenzoyl tartaric acid salt (4)

The diastereomeric amine (3) (47.2g, 0.24mol) in acetone (300mL) was added *via* addition funnel to a solution of L-dibenzoyl tartaric acid (84.8g, 0.24mol) in acetone (900mL) over 25 min. White solids gradually precipitated out at the end of the addition, and the resulting slurry was stirred at 25 °C for 14 hours. The white solids were collected by suction filtration, washed with acetone (3 x 100mL) and dried under house vacuum at room temperature overnight (98.4g, 94.4% yield of theory). A sample of the salt (4) was free-based (partitioned between 10% NaOH and EtOAc) and analyzed by ^{1}H-NMR, which showed that the diastereomeric ratio was 98:2.

(1*S*,4*R*) 2-[(1'(*S*)-Phenyl)-ethyl]-2-aza-bicyclo[2.2.1]heptane (5)

The resolved salt (4) (98.3g, 0.18mol) was added portionwise to a mixture of 10% NaOH (500mL) and EtOAc/hexanes (2:1, 300mL) at 0 °C. After 15 min. of stirring, the aqueous layer (pH ~10) was separated from the organic layer and extracted with EtOAc/hexanes (2 x 100mL). The extracts were combined with the organic layer, washed with water (2 x 100mL) and dried over Na_2SO_4. After being concentrated to ~150mL of volume, the material was transferred to a Parr bottle with the aid of more EtOAc (100mL). 20% Palladium hydroxide-on-carbon catalyst (2g, 50% wet) was added, and the mixture was shaken under hydrogen at 25 °C for 3.25 hours. The solution was filtered through a bed of celite to remove the catalyst. The catalyst was washed with EtOAc (3 x 30mL), and the combined

filtrate/washings was concentrated to yield (**5**) as a colorless oil (32.4g, 91%). A sample (8g) was purified by distillation to afford a colorless oil (6.4g, 80%) for analysis.

bp = 149-150 °C/19mm Hg. ^{1}H-NMR ($CDCl_3$) δ 7.37-7.18 (m, 5H), 3.43 (q, 1H, J = 6.5 Hz), 3.36 (bs, 1H), 2.70 (dt, 1H, J = 3.4 & 9.1 Hz), 2.28 (bs, 1H), 2.05 (dd, 1H, J = 1.2 Hz & 9.1 Hz), 1.86-1.23 (m, 6H), 1.26 (d, 3H, J = 6.5 Hz). ^{13}C-NMR ($CDCl_3$) δ 146.72, 128.25, 127.29, 126.59, 62.53, 59.16, 58.20, 37.97, 36.24, 28.92, 25.94, 23.70. GC/MS (retention time 2.27 min.) 201 (M^+), 186, 172, 158, 105, 77. $[\alpha]_D^{25}$ = -62.52° (c = 7.1, $CHCl_3$). Elemental analysis for $C_{14}H_{19}N$ calculated: C 83.53, H 9.51, N 6.96; found: C 83.41, H 9.89, N 6.98.

(1*S*,4*R*) 2-Aza-bicyclo[2.2.1]heptane (1)

The amine (**5**) (4.4g, 21.9mmol) in glacial acetic acid (20mL) was treated with 10% palladium-on-carbon catalyst (1g, 50% wet) and shaken under hydrogen at 55 °C for 25 hours. The reaction mixture was filtered through a pad of celite, neutralized with 10% NaOH and extracted with ether. Removal of solvent provided the amine free base (**1**) as a volatile oil (1.9g, 87%).

^{1}H-NMR ($CDCl_3$) δ 3.40 (bs, 1H), 2.82 (dt, 1H, J = 3.1 & 9.4 Hz), 2.56 (dd, 1H, J = 1.0 & 9.4 Hz), 2.35 (bs, 1H), 2.25 (bs, 1H), 1.62-1.29 (m, 6H). GC/MS (retention time 0.43 min.) 97 (M^+), 82, 68. $[\alpha]_D^{25}$ = -29.50° (neat).

The HCl salt of the amine (**1**) was prepared according to the literature[6] and its ^{1}H-NMR spectrum was identical to that reported in the literature.[3b]

Acknowledgment

The X-ray analysis of the amine (**5**) was conducted by D. L. DeCosta and J. Bordner of Pfizer Inc., Central Research, Groton, and is greatly appreciated.

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5 It might seem confusing at first glance because the Sandoz group's assignment is (1*R*,4*R*,1'*S*) for the desired hetero-Diels-Alder adduct (**3**). After the hydrogenation of the C_5-C_6 olefinic double bond, though, the priority rule demands a change in the assignment of the absolute configuration to (1*S*,4*R*,1'*S*) for the amines (**1**) and (**5**).

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