Synthesis of enantiopure 7-aminobicyclo[3.2.0]hept-2-en-6-ol; a potential N-O chelating ligand for enantioselective catalysis

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Abstract

A three step synthesis leading to the title compound in good overall yield is described. The bicyclo[3.2.0]heptane framework was formed with good stereocontrol by [$_\pi$2s + $_\pi$2a] thermal cycloaddition of the readily available phthalimidoketene with cyclopentadiene. The racemic bicyclic β-amino alcohol 4 was conveniently obtained by mild cleavage of the phthalimide protecting group, in 60 % yield. Resolution with L-aspartic acid allowed access to the (–)-enantiomer of the required β-amino alcohol ligand 4 in 34 % yield and 98 % enantiomeric excess.

Keywords: N-O chelating ligand, enantioselective catalysis

Introduction

Since Kagan's novel idea for using C_2-symmetric chiral ligands for asymmetric catalysis,[1] a wide variety of such ligands have been prepared. Despite the proven efficiency of such systems, several groups, including ourselves have retained an interest in, and prepared, C_1-symmetric chiral ligands and shown them to be excellent inducers of asymmetry.[2]

For example we reported that bisphosphinite derivatives of bicyclo[3.2.0]heptane systems were excellent chiral inducers for some asymmetric hydrogenations.[3] Following this work, we decided to prepare a chiral "bowl-shaped" *cis*-β-amino alcohol based on the bicyclo[3.2.0]heptane skeleton **4**, which can then be used as a new chiral ligand or auxiliary;[4-6] the results of our initial studies are presented herein.

Results and Discussion

A well-documented and convenient synthetic route to bicyclo[3.2.0]heptanes involves the [$_\pi$2s + $_\pi$2a] thermal cycloaddition of the appropriate ketene with cyclopentadiene.7, 8

Cycloaddition of succinimidoketene and cyclopentadiene was previously reported by Page's group providing a route to racemic *cis*-7-aminobicyclo[3.2.0]hept-2-en-6-ol **4** in 7 % overall yield.9 However, we have developed a more convenient and high yielding procedure according to the same strategy but using phthalimidoketene chemistry (Scheme 1). Commercially available *N*-phthaloyl glycine **1** was converted quantitatively into the corresponding acyl chloride **2** using oxalyl chloride. Treatment of **2** with triethylamine gave phthalimidoketene10 which reacted with cyclopentadiene, affording the adduct **3** in 75 % yield: NMR spectroscopy revealed that the *exo* isomer was present as a very minor impurity (< 5 %).
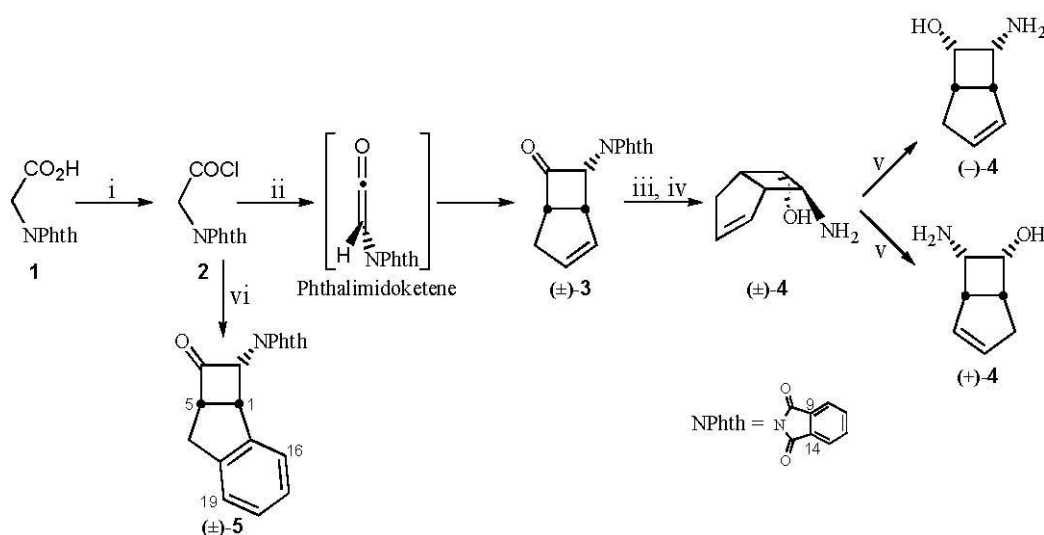
Scheme 1

Reagents and conditions: (i) pyridine, (COCl)$_2$, THF, 1 h then 10 min. at 40 °C (99 %); (ii) NEt$_3$, DCM, cyclopentadiene, 0 °C, 2 h (75 %); (iii) NaBH$_4$, *i*-PrOH/H$_2$O, 24 h; (iv) AcOH, 90 °C, 4 h (81 %); (v) L-Asp. or D-Asp., *i*-PrOH/MeOH (34 %); (vi) NEt$_3$, DCM, indene, 18 h (6 %).

In contrast cycloaddition of phthalimidoketene with indene gave adduct **5** but only in very low yield (6 %). In the reactions of phthalimidoketene with cyclopentadiene and indene, ^{1}H NMR NOE experiments and X-ray crystallography confirmed the *endo* isomer as the major product. The preference for the formation of the less stable *endo* isomer is diagnostic evidence of the [$_\pi$2s + $_\pi$2a] mode of addition, resulting from the preferred position of the large phthalimide

substituent in the corresponding transition state.8

Selective hydride reduction of the ketone **3** and deprotection of the amine group were achieved using a "one-pot" sequence of reactions. TLC and NMR monitoring of the sodium borohydride reaction showed a stepwise reduction of the ketone from the less hindered *exo* face, followed by reduction of one of phthalimide carbonyl groups to furnish the corresponding alcohol. The intermediate was subsequently treated with acetic acid (as recommended previously for mild phthalimide cleavage11) furnishing the racemic β-amino alcohol **4** in 76 % yield.

Systematic screening of commercially available chiral acids for achieving the optical resolution of *rac*-**4**,12 led to the use of L-aspartic acid as an inexpensive and highly efficient resolving acid. Examples of tested acids that were unsuccessful in giving crystalline salts included L-tartaric, camphorsulfonic, malic and 3-chloromandelic acids. After optimisation, both enantiomers of the potential chiral ligand **4** have been obtained in 34 % yield with 98 % enantiomeric excess. Asymmetric catalysis using β-amino alcohol **4** is currently being investigated and will be reported in due course.

Experimental Section

General Pocedures. Manipulations of air and moisture sensitive materials were conducted under a nitrogen atmosphere using standard Schlenk techniques. Tetrahydrofuran (THF), diethyl ether, *i*-propanol and dichloromethane (DCM) were distilled prior to use. Thin layer chromatography (TLC) was carried out using aluminium sheets coated with Merck 60 F_{254} silica gel, R_f values are quoted and visualisation was achieved using ethanolic *p*-anisaldehyde followed by heating or by using a UV lamp (254 nm). Melting points are uncorrected. NMR spectra (^{1}H, ^{13}C) were recorded using Bruker AMX 400 spectrometer. The absolute value of the coupling constants (*J*) in Hz and assignments of ^{1}H and ^{13}C peaks were determined using COSY, HETCOR, 1D-nOe and DEPT135 experiments for all reported compounds. Mass spectra were recorded on Kratos profile HV3, CIPOS, Fisons TRIO1000 solid probe and VG7070E spectrometers and relative intensity is quoted. Optical rotations were measured using an Optical Activity LTD AA-1000 polarimeter operating at 589 nm. Elemental analyses were recorded on a Carlo Erba Strumentazione mod. 1106 CHN analyser. Enantiomeric excess (ee) was determined by chiral gas chromatography (GC) and retention times (t_R) are quoted in minutes. Chiral GC separations were accomplished using a Chiraldex® G-TA (30 m × 0.25 mm) column from Astec. The carrier gas was helium.

2-Phthalimido acetyl chloride (2). *N*-Phthaloyl glycine **1** (45.07 g, 219.7 mmol, 1 eq.) was dissolved in anhydrous THF (500 mL) under a N_2 atmosphere and pyridine was added (3 mL).

Under vigorous stirring, a 2.05 M solution of oxalyl chloride (39.04 g, 307.6 mmol, 1.4 eq.) in anhydrous DCM (150 mL) was added dropwise at room temperature over 1 hour. The solution was heated at 40 °C for 10 more minutes and concentrated to 200 mL; anhydrous Et_2O (200 mL) was added and the mixture was filtered through a pad of charcoal and Celite®. The filter cake was washed with dry Et_2O (1000 mL) and the solvent was removed under reduced pressure yielding **2** as an off-white powder (49.00 g, 99 %) which was kept under N_2. ^{1}H NMR (400 MHz, $CDCl_3$) 4.85 (2 H, s, 2 H^2), 7.81 (2 H, m, H^{aro}) 7.92 (2 H, m, H^{aro}); ^{13}C NMR (100 MHz, $CDCl_3$) 47.64 (CH_2, C^2), 124.01 (2 CH, C^{aro}), 131.59 (2 C^{IV}, C$^{4 \text{ and } 9}$), 134.77 (2 CH, C^{aro}), 166.60 (2 C^{IV}, C$^{3 \text{ and } 10}$), 169.19 (C^{IV}, C^1). MS (EI) m/z 225 (0.12 %, [M^{37}Cl]$^+$), 223 (0.4, [M^{35}Cl]$^+$), 187 (0.73, [M – HCl]$^+$), 160 (100, [M – COCl]$^+$); HRMS (EI) calcd for $C_{10}H_6ClNO_3$, [M^{35}Cl]$^+$ 223.00362, found 223.00314.

(1RS,5SR,7RS)-(±)-7-Phthalimidobicyclo[3.2.0]hept-2-en-6-one (3). To a solution of **2** (49.12 g, 219.7 mmol, 1 eq.) in anhydrous DCM (1000 mL) under N_2 was added freshly distilled cyclopentadiene (145 g, 2.19 mol, 10 eq.). The solution was stirred vigorously in an ice bath for 10 minutes and a solution of triethylamine (28.9 g, 285.6 mmol, 1.3 eq.) in anhydrous Et_2O (200 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 2 hours and filtered over Celite®; the filter cake was washed with DCM (3 × 100 mL) and the dark filtrate was evaporated under reduced pressure. The brown residue was dissolved in DCM (1000 mL) and extracted with water (3 × 100 mL). The organic layer was dried ($MgSO_4$), filtered through a large pad of silica, charcoal and Celite®. Evaporation of the solvent gave the desired compound as a white powder (41.64 g, 75 %). $R_{f(EtOAc)}$ = 0.62; mp 186-187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 2.65 (1 H, ddddd as "ddq", ^2J = 17.4, ^3J = 10.1, ^3J = ^4J = ^4J = 2.1, H^{4exo}), 2.98 (1 H, ddddd as "dp", ^2J = 17.4, ^3J = ^3J = ^4J = ^4J = 2.1, H^{4endo}), 3.82 (1 H, m, H^5), 3.96 (1 H, m, H^1), 5.44 (1 H, ddd, ^3J = 8.7, ^4J = 2.8, ^4J = 0.7, H^7), 5.64 (1 H, m, H^3), 5.95 (1 H, m, H^2), 7.71 (2 H, m, H^{aro}), 7.80 (2 H, m, H^{aro}); ^{13}C NMR (100 MHz, $CDCl_3$) 36.10 (CH_2, C^4), 46.59 (CH, C^1), 58.10 (CH, C^5), 64.59 (CH, C^7), 123.67 (2 CH, C^{aro}), 128.04 (CH, C^3), 131.73 (2 C^{IV}, C$^{9 \text{ and } 14}$), 134.41 (2 CH, C^{aro}), 136.37 (CH, C^2), 169.93 (2 C^{IV}, C$^{8 \text{ and } 15}$), 206.57 (C^{IV}, C^6); MS (EI) m/z 253 (2 %, [M]$^+$), 225 (12, [M – CO]$^+$), 187 (56), 160 (33), 148 (28), 132 (65), 105 (68), 104 (100); HRMS (EI) calcd for $C_{15}H_{11}NO_3$, [M]$^+$ 253.07388, found 253.07415; Anal. found (C) 70.64, (H) 4.49, (N) 5.42; Calcd for $C_{15}H_{11}NO_3$ (C) 71.14, (H) 4.38, (N) 5.53; IR (KBr) 3067.8 (sh), 2950.0 (sh), 2907.7 (sh), 1786.3 (sh), 1706.9 (br), 1386.9 (sh).

(1RS,5SR,6SR,7RS)-(±)-7-Aminobicyclo[3.2.0]hept-2-en-6-ol (±)-(4). To a stirred suspension of (1RS,5SR,7RS)-(±)-7-phthalimidobicyclo[3.2.0]hept-2-en-6-one **3** (15 g, 59.2 mmol, 1 eq.) in i-PrOH (600 mL) and water (102 mL) was added sodium borohydride (14.12 g, 373.1 mmol, 6.3 eq.). The suspension was stirred at room temperature for 24 hours, whereupon TLC indicated complete consumption of the starting material. Acetic acid (89 mL) was CAREFULLY added, and the flask stoppered and heated to 90 °C for 4 hours, then allowed to cool. Water (600 mL)

was added and *i*-PrOH was removed under reduced pressure. The reaction was acidified to pH 1 (1 M HCl) and extracted with DCM (5 × 700 mL). The combined organic phase was dried (MgSO$_4$), filtered and evaporated under reduced pressure to leave a clear solid identified and characterised as phthalide (6.06 g, R$_{f(EtOAc)}$ = 0.56, ^{1}H, ^{13}C NMR and MS confirmed the structure: C$_8$H$_6$O$_2$). The remaining acidic aqueous phase was made alkaline (pH 13) by addition of few NaOH pellets and extracted with DCM in a continuous extractor apparatus for 16 hours. The organic phase was dried (Na$_2$SO$_4$), filtered through a pad of charcoal and Celite® and evaporated under reduced pressure to give the racemic amino alcohol **4** as a white crystalline solid (6.03 g, 81 %) which could be recrystallised from *n*-hexane. $R_{f(EtOAc; MeOH/ 9:1))}$ = 0.12; mp 97-97.5 °C; ^{1}H NMR (400 MHz, CDCl$_3$) 2.26 (3 H, br s, NH$_2$ + OH, H/D exch.), 2.32 (1 H, ddddd, ^2J = 17.3, ^3J = 9.2, ^3J = ^4J = ^4J = 2.0, H^{4exo}), 2.69 (1 H, br d, ^2J = 17.3, H^{4endo}), 2.95 (1 H, br ddd as "br q", ^3J = ^3J = ^3J = 7.1, H^5), 3.51 (1 H, m, H^1), 3.72 (1 H, ddd as "dt", ^3J = ^3J = 7.1, ^4J = 1.0, H^7), 4.28 (1 H, ddd as "dt", ^3J = ^3J = 7.1, ^4J = 2.2, H^6), 5.63 (1 H, m, H^2), 6.05 (1 H, m, H^3); ^{13}C NMR (100 MHz, CDCl$_3$) 31.90 (CH$_2$, C^4), 38.91 (CH, C^5), 51.37 (CH, C^1), 51.76 (CH, C^7), 68.94 (CH, C^6), 128.84 (CH, C^2), 137.74 (CH, C^3); MS (CI/NH$_3$) m/z 126.1 (16 %, [M + H]$^+$), 124.1 (17, [M − H]$^+$), 110.1 (70), 108.1 (100, [M − NH$_3$]$^+$), 106.1 (92, [M − H$_3$O]$^+$);); HRMS (FAB) calcd for C$_7$H$_{12}$NO, [M + H]$^+$ 126.09189, found 126.09281; Anal. found (C) 66.88, (H) 8.82, (N) 11.15; Calcd for C$_7$H$_{11}$NO (C) 67.17, (H) 8.86, (N) 11.19; IR (KBr) 3339.3 (sh), 3264.6 (sh), 3100.0 (br), 3049.2 (sh), 2972.6 (sh), 2934.3 (sh), 1578.7 (sh).

(1*R*,5*S*,6*S*,7*R*)-(−)-7-Aminobicyclo[3.2.0]hept-2-en-6-ol(−)-(4). To a vigorously stirred suspension of *rac*-**4** (0.891 g, 7.12 mmol, 1 eq.) in *i*-PrOH (9 mL) and MeOH (4.4 mL), was introduced L-aspartic acid (0.948 g, 7.12 mmol, 1 eq.). The suspension was stirred for 17 hours; the resulting slurry was filtered and filter cake washed with *i*-PrOH (25 mL) and Et$_2$O (20 mL). After drying, the filter cake was refluxed for 5 min. in MeOH (50 mL), filtered and the solvent removed under reduced pressure to leave the L-aspartate-ammonium alcohol salt (1:1 mixture by ^{1}H NMR) as a white hygroscopic solid (0.625 g, 34 %); ee = 98 % by chiral GC (Chiraldex® G-TA). Injection: 200 °C, program: 140 °C for 10 min. then 15 °C/min. to 180 °C and left for 10 min., detection: FID 200 °C, split 1/100, 1 µL injected of a prepared sample of **4** in TBME + 3 drops of trifluoroacetic anhydride. t_R: 7.31: (+)-**4**, 7.59: (−)-**4**. [α]$^{25}_D$ = − 0.92 (H$_2$O, *c* 0.5). The L-aspartate-ammonium alcohol salt was extracted from 2 M NaOH with EtOAc yielding (−)-**4**, ee = 98 %. [α]$^{27}_D$ = − 239 (CHCl$_3$, *c* 2.55); the absolute configuration was determined by X-ray crystallography, other data were the same as *rac*-**4**. The (+)-**4** enantiomer was recovered from the first filtrate in 54 % yield and 79 % ee.

(1*SR*,5*SR*,7*RS*)-(±)-2,3-Benzo-7-phthalimidobicyclo[3.2.0]heptan-6-one (5). To a solution of **2** (1.00 g, 4.47 mmol, 1 eq.) in anhydrous indene (5.2 mL, 44.7 mmol, 10 eq.) under N$_2$ was added dropwise triethylamine (0.5 g, 4.9 mmol, 1.1 eq.) in anhydrous DCM (2 mL). The reaction mixture was heated at 50 °C for 5 min., stirred 17 hours at 20 °C and indene was distilled off

(30-31 °C, 0.3 mbar). The dark residue was dissolved in EtOAc (50 mL), filtered over Celite® and the filtrate evaporated under reduced pressure to leave a brown foam, which was purified by column chromatography on silica using EtOAc:petroleum ether (3:7) as eluent to give **5** (0.078 g, 6 %) as a white solid. $R_{f(\text{EtOAc:pet ether / 1:1})}$ = 0.53; ^{1}H NMR (400 MHz, CDCl$_3$) 3.33 (1 H, dd, ^2J = 16.8, ^3J = 10.7, H$^{4\text{exo}}$), 3.61 (1 H, d, ^2J = 16.8, H$^{4\text{endo}}$), 4.06 (1 H, br dd, ^3J = ^3J = 9.1, H^5), 4.45 (1 H, dd, ^3J = ^3J = 9.1, H^1), 6.08 (1 H, dd, ^3J = 9.1, ^4J = 2.9, H^7), 6.91 (1 H, d, ^3J = 7.0, H^{16}), 6.94 (1 H, dd, ^3J = ^3J = 7.0, m, H^{17}), 7.17 (1 H, dd, ^3J = ^3J = 7.0, H^{18}), 7.28 (1 H, d, ^3J = 7.0, H^{19}), 7.67 (4 H, m, H$^{\text{Phth}}$); ^{13}C NMR (100 MHz, CDCl$_3$) 35.87 (CH$_2$, C^4), 45.29 (CH, C^1), 59.17 (CH, C^5), 64.79 (CH, C^7), 123.59 (2 CH, C$^{11\text{ and }12}$), 125.40 (CH, C^{16}), 125.52 (CH, C^{19}), 126.91 (CH, C^{17}), 128.10 (CH, C^{18}), 131.54 (2 C$^{\text{IV}}$, C$^{9\text{ and }14}$), 134.30 (2 CH, C$^{10\text{ and }13}$), 139.46 (C$^{\text{IV}}$, C^3), 145.06 (C$^{\text{IV}}$, C^2), 166.34 (2 C$^{\text{IV}}$, C$^{8\text{ and }15}$), 206.75 (C$^{\text{IV}}$, C^6); MS (EI) m/z 303 (9 %, [M]$^+$), 275 (14, [M – CO]$^+$), 187 (46, [M – HPhth]$^+$), 128 (100); HRMS (EI) calcd for C$_{19}$H$_{13}$NO$_3$, [M]$^+$ 303.08954, found 303.08913.

Acknowledgements

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