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The first enantioselective synthesis of chiral norbornane-type 1,4-diamine ligand

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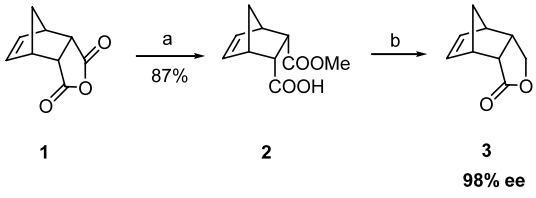
Abstract—The asymmetric synthesis of *trans*-2,3-bis(aminomethyl)norbornane was performed starting with *endo*-2,3-norbornene dicarboxylate anhydride. Desymmetrization of *meso*-anhydride **1** and following selective epimerization gave the *trans*-monoester (+)-**3** with a high enantiomeric excess (98% e.e.). $LiAlH_4$ reduction of the *trans*-monoester to the 1,4-diol, which was then treated with phthalimide under Mitsunobu conditions and, following a Gabriel type amine synthesis with hydrazine hydrate, yielded a saturated and unsaturated diamine mixture. Hydrogenation of mixture finally afforded saturated diamine (+)-**8** with a yield of 37%.

1. Introduction

Nitrogen containing ligands are becoming very useful for catalytic asymmetric synthesis. Diamine ligands are one of the most common types of nitrogen containing ligands[1] which are becoming applicable for catalytic asymmetric synthesis. Enantiomerically pure diamines are constituents of many natural compounds and commonly used in various areas of organic chemistry, particularly in pharmaceutical and medicinal chemistry.[2] Chiral diamine platinum complexes have advantages over the well known cancer drug, *cis*-platin, by reducing toxicity and blocking drug resistance.[3] Although many studies have been performed in the enantioselective synthesis of 1,2-diamines,[4] there are few examples regarding the asymmetric synthesis of 1,4-diamines.[5] Recently, chiral 1,4-diamines have served as key intermediates in the synthesis of potent HIV protease inhibitors.[6] Despite numerous studies describing the applications of 1,2-diamines in catalytic asymmetric synthesis, no examples involving 1,4-diamines have been reported in literature. In rigid backbones such as the norbornane system, 1,4-diamines have some advantages, since the existence of additional methylene units gives more flexibility and facilitates the complexation with various types of metals[7] compared to 1,2-diamine systems. This property prompted us towards the development of a new chiral 1,4-diamine ligand, which can be applicable to miscellaneous asymmetric reactions.

2. Results and discussions

In our synthetic strategy, *cis*-monoester (+)-**2** was chosen as the homochiral starting compound for the construction of norbornane backbone. For this purpose, desymmetrization of *endo*-2,3-methoxycarbonyl bicyclo-[2.2.1]hept-5-ene via enzymatic hydrolysis with PLE afforded *cis*-monoester (+)-**2** with moderate yields and enantiomeric excess,[8] although it has been reported that no hydrolysis of *endo*-2,3-methoxycarbonyl bicyclo-[2.2.1]hept-5-ene was observed with PLE.[9] On the other hand, recently, Bolm et al.[10] have reported a more efficient method for highly enantioselective desymmetrization of *meso*-anhydrides via alkaloid-mediated opening with methanol. Quinine or quinidine are used as chiral directing agents and both enantiomers of the corresponding *cis*-monoester can be obtained with very high enantiomeric excess values (up to 99% e.e.) and chemical yield.



Scheme 1. *Reagents and conditions*: (a) Quinidine, MeOH, −55°C; (b) (i) $LiBHEt_3$, THF, (ii) 1N HCl.

Quinidine-mediated opening of anhydride **1** with methanol resulted in *cis*-monoester (+)-**2** with a high enantiomeric excess (98% e.e.) (Scheme 1). Monoester

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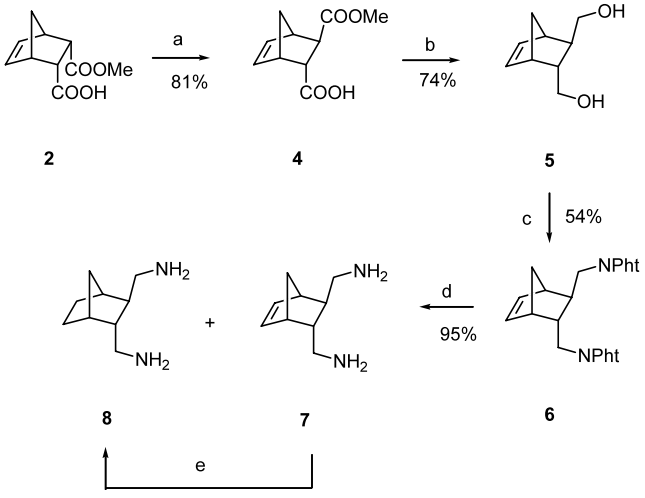
(+)-**2** was then converted to lactone (+)-**3** by selective reduction of ester group with $LiBHEt_3$, super hydride, which was then analyzed by GC for enantiomeric excess determination.[11]

Selective epimerization[12] of **2** with LDA at −78°C gave *trans*-monoester (+)-**4** with a yield of 81% after flash column chromatography. Key intermediate 1,4-diol (+)-**5** was obtained by $LiAlH_4$ reduction of *trans*-monoester (+)-**4** in THF with a yield of 74%. For the conversion of the diol to the diamine several methods have been tried and the Mitsunobu reaction was chosen as the best in terms of the yields and simplicity. Substitution of diol **5** with phthalimide under Mitsunobu condition[13] in the presence of PPh_3 and DEAD in THF gave diimide (+)-**6**, which was then treated with hydrazine hydrate for a Gabriel type amine synthesis to give surprisingly a mixture of saturated and unsaturated diamines. Probably, diimine, NH=NH, was formed in the reaction medium from hydrazine and it reduced the C–C double bond of norbornene backbone. In order to overcome this problem, full saturation of the mixture was done via hydrogenation in the presence of Pd/C and diamine (+)-**8** was synthesized with a yield of 95% from the diimide (Scheme 2).

The absolute configuration of (+)-5,6-bis(aminomethyl)bicyclo[2.2.1]heptane **8** was determined as (5*R*,6*R*) by comparing specific rotation signs determined at equal concentration in the same solvent given in the literature for *cis*-monoester (+)-**2**,[10] *trans*-monoester (+)-**4**[12] and *trans*-diol (+)-**5**.[16] Since transformation of *trans*-1,4-diol (+)-**5** to *trans*-1,4-diamine (+)-**8** has no effect on the stereocenters of the norbornene backbone, the absolute configuration was not changed during Mitsunobu and following Gabriel type amine synthesis.



Scheme 2. *Reagents and conditions*: (a) LDA, THF, −78°C; (b) $LiAlH_4$, THF; (c) phthalimide, PPh_3, DEAD, THF; (d) $NH_2NH_2{\cdot}H_2O$; (e) H_2, Pd/C.

3. Conclusion

In conclusion, 1,4-diamine **7** had been synthesized as a racemic mixture in 1960[14] for the first time. Our study is the first asymmetric synthesis of diamine **7** and **8**. The application of ligand (+)-**8** in catalytic asymmetric synthesis is currently in our focus area.

4. Experimental

Nuclear magnetic resonance spectra were acquired on Bruker Spectrospin Avance DPX 400 spectrometer at 400 MHz for ^1H and 100 MHz for ^{13}C, in $CDCl_3$. Chemical shifts are given in ppm from tetramethylsilane. IR spectra were obtained using a Perkin–Elmer model 1600 series FT-IR spectrometer and are reported in cm^{-1}. Mass spectra were recorded with a Varian MAT 212. Flash chromatography: Merck silica gel 60 (230–400 mesh). Optical rotations were measured in $CHCl_3$ solution in a 1 dm cell using a Bellingham & Stanley P20 polarimeter at 20°C.

4.1. Synthesis of (2*R*,3*R*)-3-methoxycarbonylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid 2 via alkaloid-mediated anhydride opening

Methanol (3.66 mL, 0.090 mol) was added to a stirred suspension of the anhydride **1** (4.92 g, 0.030 mol) and quinidine/quinine (10.71 g, 0.033 mol) in a 1:1 mixture of toluene and CCl_4 (150 mL in the case of quinidine, 600 mL in the case of quinine) at −55°C under an argon atmosphere. The reaction mixture was stirred at this temperature for 60 h during which the material gradually dissolved. Subsequently, the resulting clear solution was concentrated in vacuo to dryness, and the resulting residue was than dissolved in ethyl acetate. The solution was washed with 2N HCl, and after phase separation, followed by extraction of the aqueous phases with ethyl acetate, the organic layer was dried over $MgSO_4$, filtered and concentrated providing the corresponding *cis*-monoester **2** as white solid (5.10 g, 87%); $[\alpha]_D = +7.8$ (*c* 4.23, CCl_4), lit.[15] $[\alpha]_D^{20} = +7.9$ (*c* 4.8, CCl_4); mp 75–78°C, lit.[1] 74°C (racemic); ^1H NMR: δ 6.26 (dd, $J=$ 3.02, 5.77 Hz, 1H), 6.15 (dd, $J=3.02$, 5.49 Hz, 1H), 3.53 (s, 3H), 3.27 (dd, $J=3.30$, 10.17 Hz, 1H), 3.22 (dd, $J=3.03$, 10.17 Hz, 1H), 3.10 (m, 1H), 3.13 (m, 1H), 1.42 (dt, $J=1.92$, 8.51 Hz, 1H), 1.25–1.29 (m, 1H); ^{13}C NMR: δ 177.8, 173.1, 135.6, 134.4, 51.6, 48.8, 48.2, 47.9, 46.6, 46.1. e.e. = 98% [GC-analysis of the lactone: Lipodex E, $t_1=80.7$, $t_2=81.1$. Lipodex E: 2,6-*O*-Dipentyl-3-*O*-butyryl-γ-CD. Column head pressure: 1.0 bar N_2; 100°C (50 min), heating rate 3.0°C/min up to 180°C (60 min). Injector temperature 200°C, detector temperature 250°C.

4.2. Synthesis of (2*R*,3*R*)-3-methoxycarbonylbicyclo-[2.2.1]hept-5-ene-2-carboxylic acid 4

LDA preparation: *i*-Pr_2NH (14.3 mL, 0.102 mol) was dissolved in 75 mL of THF under an argon atmosphere. It was cooled to 0°C in an ice-bath. *n*-BuLi (0.096 mol, 1.6 M in hexane) was added carefully by the

portions of 10 mL. After addition, it was stirred for 30 min. Then it stands to come to room temperature.

(2*R*,3*S*)-3-Methoxycarbonylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid **2** (6.1 g, 0.031 mol) was dissolved in 50 mL of THF. It was cooled to −78°C with acetone and dry ice mixture. Under an argon atmosphere, the prepared LDA was added drop wisely with the help of a dropping funnel for 1.5 h. After the addition completed, it was stirred for 4 h. Then, 1N of HCl was added until it became acidic and a clear solution. It was extracted with 3×50 mL of CH_2Cl_2. It was evaporated and purified by column chromatography (1:1 Et_2O/pentane+1% HOAc mixture) to give (2*R*,3*R*)-3-methoxycarbonylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid **4** as a white solid (4.94 g, 81%); $[\alpha]_D = -152.44$ (*c* 1.54, $CHCl_3$); mp = 73°C, 95.5°C (racemic); ^{1}H NMR: δ 6.29 (dd, $J = 3.02$, 5.50 Hz, 1H), 6.14 (dd, $J = 3.02$, 5.62 Hz, 1H), 3.70 (s, 3H), 3.43 (dd, $J = 3.85$, 4.40 Hz, 1 H), 3.30 (m, 1H), 3.08 (m, 1H), 2.66 (dd, $J = 1.65$, 4.53 Hz, 1 H), 1.63 (dt, $J = 1.65$, 8.79 Hz, 1H), 1.48 (dq, $J = 1.65$, 8.79 Hz, 1H); ^{13}C NMR: δ 179.2, 174.5, 137.5, 135.0, 52.1, 47.9, 46.9, 45.6. MS (EI, 70 eV): $m/z = 196.0$ (3), 131.0 (32), 119.1 (10), 91.1 (12), 67.1 (10), 66.1 (100). IR (KBr): $\tilde{\nu} = 3002$, 1731, 1685, 1434, 1315, 1277, 1182 cm^{-1}.

4.3. Synthesis of (5*R*,6*R*)-5,6-bis(hydroxymethyl)bicyclo-[2.2.1]hept-2-ene 5

$LiAlH_4$ (2.09 g, 55 mmol) was dissolved in 25 mL of dry THF under an argon atmosphere. (2*R*,3*R*)-3-Methoxycarbonylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid **4** (4.6 g, 25 mmol) dissolved in 25 mL of dry THF was added at a rate maintaining vigorous reflux, and the reaction solution was refluxed an additional hour. $LiAlH_4$ was decomposed with cold water by cooling in an ice bath. It was filtered off and filtrate is stored. The solid residue part was dissolved in dilute H_2SO_4 and it was extracted repeatedly with diethyl ether and all extracts were combined, washed once with cold water and, then dried over $MgSO_4$. It was concentrated to give diol **5**. The filtrate, concentrated to a smaller volume, yielded a second crop of diol **5** (2.85 g, 74%); $[\alpha]_D = +28.1$ (*c* 0.018, $CHCl_3$), lit.[16] $[\alpha]_D = -21.0$ (in $CHCl_3$, for other enantiomer); ^{1}H NMR: δ 6.23 (dd, $J = 3.20$, 5.47 Hz, 1H), 5.98 (dd, $J = 2.76$, 5.54 Hz, 1H), 3.77 (dd, $J = 5.52$, 9.75 Hz, 1H), 3.66 (dd, $J = 5.23$, 9.72 Hz, 1H), 3.42 (t, $J = 9.95$ Hz, 1H), 2.82 (s, 1H), 3.03 (t, $J = 9.85$ Hz, 1H), 2.59 (s, 1H), 1.91–1.96 (m, 1H), 1.45 (bs, 2H), 1.28–1.33 (m, 1H); ^{13}C NMR: δ 138.3, 133.8, 66.9, 66.4, 48.3, 47.5, 47.3, 45.0 44.9.

4.4. Synthesis of (5*R*,6*R*)-5,6-bis[(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)]methylbicyclo[2.2.1]hept-2-ene 6

Diethyl azodicarboxylate (5.3 mL, 34 mmol) was added at 0°C to a solution of diol **5** (3.0 g, 14.3 mmol), phthalimide (5.0 g, 34 mmol) and triphenylphosphine (9.0 g, 34 mmol) in 100 mL anhydrous THF. The mixture was stirred for 48 h at room temperature; the precipitated product was isolated by filtration and washed with cold THF. After removing the solvent from the filtrate by evaporation, additional product was isolated which had to be recrystallized from methanol. The combined crystals were chromatographed on a silica gel column using ethyl acetate as an eluent, to afford diphthalimide **6** as a white solid (3.35 g, 57%); $[\alpha]_D = +31.2$ (*c* 0.048, $CHCl_3$); ^{1}H NMR: δ 7.65–7.70 (m, 4H), 6.18–6.23 (m, 2H), 3.91 (dd, $J = 7.71$, 13.64 Hz, 1H), 3.84 (dd, $J = 7.93$, 13.63 Hz, 1H), 3.59 (d, $J = 7.61$ Hz, 2H), 2.80 (s, 1H), 2.95 (s, 1H), 2.39–2.45 (m, 1H), 1.55 (d, $J = 9.05$ Hz, 1H), 1.49 (bs, 2H); ^{13}C NMR: δ 168.8, 168.6, 138.1, 135.1, 134.2, 134.1, 132.4, 123.5, 46.7, 46.0, 45.4, 44.4, 43.6, 42.9, 42.0. Exact mass calcd for ($C_{25}H_{20}N_2O_4$) 412.1423, found 412.1430.

4.5. Synthesis of (5*R*,6*R*)-5,6-bis(aminomethylbicyclo)-[2.2.1]heptane 8

Hydrazine hydrate (3.94 mL, 126 mmol) was added to a stirred solution of diphthalimide **6** (3.39 g, 7.9 mmol), and the solution was heated to reflux for eight hours. It was then cooled to room temperature, and the solvent was removed under reduced pressure. The residue was dissolved in NaOH (30 mL, 20%), and the resulting two layers were then extracted with CH_2Cl_2 (3×50 mL). The combined organic solution was then dried over $MgSO_4$. The filtrate was evaporated to leave the diamine mixture as pale yellow oil. The characterization of diamine mixture was done by GC–MS and ^{1}H NMR spectroscopy.

The mixture was then dissolved in 25 mL THF and Pd/C was added under an argon atmosphere. With a balloon filled with H_2, it was stirred overnight. It was filtered through Celite and concentrated to give diamine **8** as pale yellow oil (1.15 g, 95%); $[\alpha]_D = +3.2$ (*c* 0.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62–2.67 (m, 2H), 2.51 (dd, $J = 7.8$, 12.0 Hz, 1H), 2.41 (dd, $J = 6.1$, 11.6 Hz, 1H), 2.25 (bs, 4H), 2.18 (bs, 1H), 1.97 (bs, 1H), 1.48–1.54 (m, 1H), 1.27–1.34 (m, 4H), 1.00 (m, 2H), 0.84 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 52.0, 49.7, 47.4, 44.2, 40.0, 38.6, 37.1, 30.3, 22.3. Exact mass calcd for ($C_9H_{18}N_2 - NH_3 \rightarrow C_9H_{15}N$) 137.1205, found 137.1207.

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