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# Efficient access to enantiomerically pure rigid diamines

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**Abstract**—Asymmetric spiro cyclization of a pyrrolidine derivative was used as a key step for constructing novel rigid diamines. A selected example has proved its utility as a chiral nonmetallic catalyst in a Michael reaction.

## 1. Introduction

Chiral diamines<sup>1</sup> are largely used in asymmetric processes as chiral bases,<sup>2</sup> chiral ligands,<sup>3</sup> and chiral catalysts.<sup>4</sup> In recent years, increasing interest has been given to enantioselective reactions catalyzed by nonmetallic compounds.<sup>5</sup> Several natural products, such as the well known alkaloid sparteine, have been long recognized to be efficient reagents in asymmetric deprotonation processes and asymmetric reactions in general.<sup>6</sup> The main problem usually arising with natural products is the occurrence of only one enantiomer;<sup>7</sup> new synthetic asymmetric diamines, available in both enantiomeric forms, are thus still interesting to design, prepare, and investigate. For example, bipyrrrolidines **1**<sup>8</sup> and **2**<sup>9</sup> (Fig. 1) can be used for the enantioselective Michael addition of carbonyl compounds to nitroalkenes. Starting from these interesting results, we envisioned preparing similar compounds containing a highly constrained structure as **3**, easily accessible from the already described spiro compound **4**.

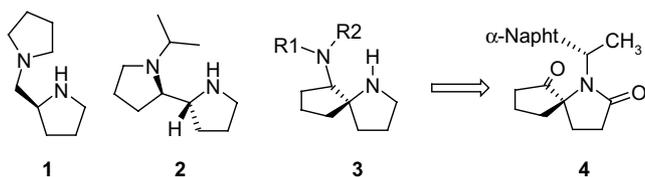


Figure 1.

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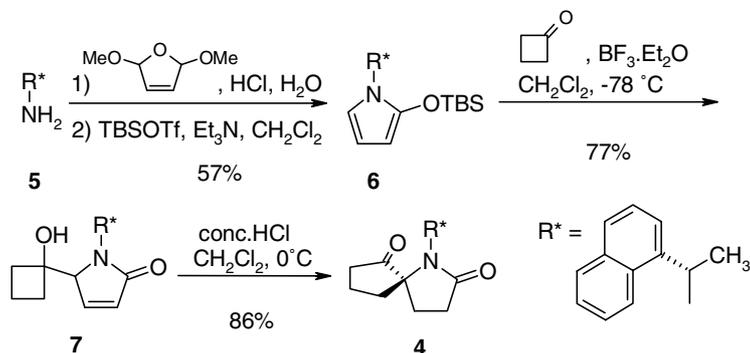
## 2. Results and discussion

We recently reported an original asymmetric access to the 1-azaspiro[4.4]nonane skeleton<sup>10</sup> using the chemistry of chiral nonracemic  $\alpha,\beta$ -unsaturated  $\gamma$ -lactams.<sup>11</sup> Compound **4** was obtained in 35% overall yield from (*S*)-naphthylethylamine through the four-step sequence shown in Scheme 1.<sup>10</sup>

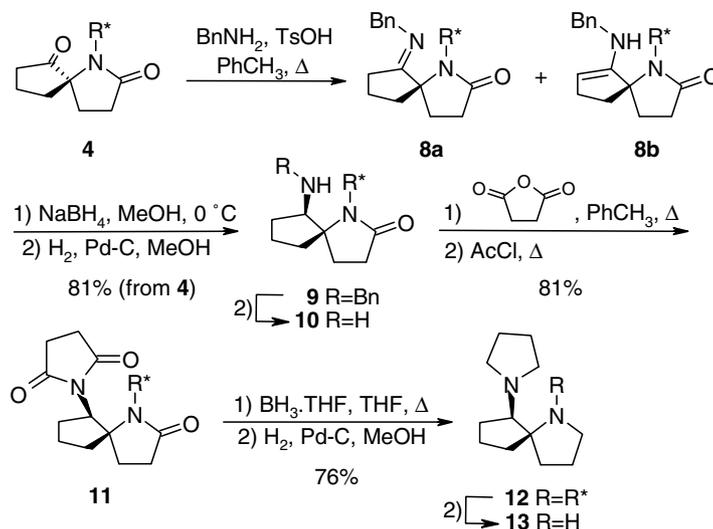
With 1-azaspiro[4.4]nonane **4** in hand, we planned to synthesize chiral diamines **3** by the use of simple reactions allowing rapid access to the target compounds. In order to develop an efficient preparation of several diamines, we first focused on the primary amine **10** (see Scheme 2), which could be further transformed to variously substituted compounds. 1-Azaspiro[4.4]nonane-2,6-dione **4**, was treated with benzylamine in refluxing toluene and in the presence of TsOH and the crude reaction mixture, which consisted of a 1:1 mixture of imine **8a** and enamine **8b**, was reduced by NaBH<sub>4</sub> in methanol to furnish, in a quantitative yield over the two steps, amine **9** as a unique stereoisomer (Scheme 2). The *N*-benzyl group was easily cleaved by simple hydrogenolysis to furnish primary amine **10** in 81% yield.

From this building block, numerous diamines can be prepared. Focusing on the access to a new rigid bipyrrrolidine, we converted this primary amine to the corresponding succinimide **11** through treatment with succinic anhydride and acetyl chloride. The exhaustive reduction of **11** using borane in THF furnished *N*-protected diamine **12**, which was hydrogenolyzed to give target diamine **13** in 76% yield after purification.

Following a method developed by Riguera et al.,<sup>12</sup> the absolute configuration of the newly formed stereogenic

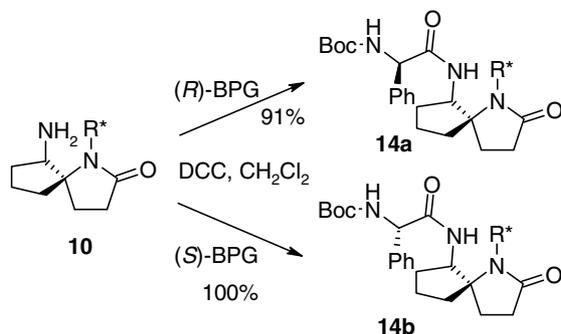


Scheme 1.



Scheme 2.

center in **10**, was deduced from the  $^1\text{H}$  NMR investigation of both diastereoisomers **14a** and **14b** formed through the coupling of primary amine **10**, respectively, with (*R*)- and (*S*)-*N*-Boc-phenylglycine (Scheme 3).



Scheme 3.

Observation of the variation in the chemical shifts of both diastereoisomers **14a** and **14b** showed either positive  $\Delta\delta^{(R,S)}$  on one side, or negative on the other side of the plane, which contains the asymmetric carbon to be examined, the nitrogen and the hydrogen linked at this

carbon (Fig. 2). This allowed the assignment of the newly formed asymmetric carbon in **10** as *R*. This absolute configuration corresponds to the reduction of the imine function of **8a** on the more accessible prochiral face (as opposed to the chiral auxiliary).

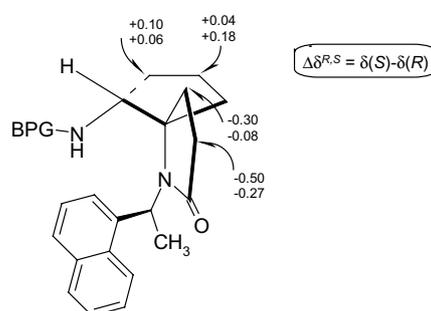
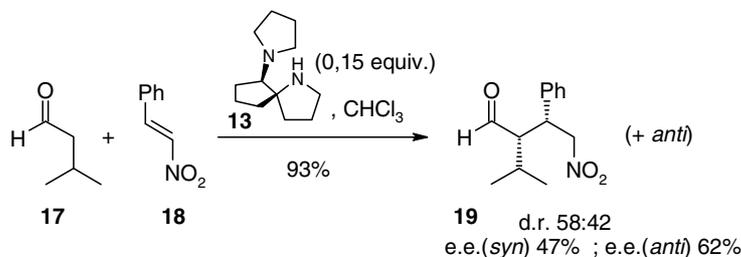


Figure 2.

As a matter of fact, diamine **13** can be considered as a rigid equivalent of diamine **1**, described as a good enantioselective catalyst for the reaction of condensation of isovaleraldehyde **17** with  $\beta$ -nitrostyrene **18**.<sup>2</sup> In order to test the efficiency of chiral diamine **13** as an



Scheme 4.

enantioselective organic catalyst, we just verified its use in one type of reaction (Scheme 4) under only one set of reaction conditions. Thus, using 0.15 equiv of **13**, following an easy-to-use protocol described by Alexakis and co-workers for diamine **2**,<sup>9</sup> the reaction proceeded smoothly to give **19** in 93% yield. The diastereoselectivity of the condensation was poor (*syn/anti* 58:42) when compared to pyrrolidine, which gave an 80:20 ratio of *syn/anti* diastereoisomers. On the other hand, the enantioselectivity was encouraging [ee = 47% (*syn*) and 62% (*anti*)], which can be compared with that obtained with diamine **2** (ee = 61% for the *syn* diastereoisomer).<sup>9</sup>

### 3. Conclusion

The first of a new series of chiral rigid diamines, 6-pyrrolidine-1-yl-1-aza-spiro[4.4]nonane **13** was easily prepared from 1-azaspiro[4.4]nonane-2,6-dione **4**. This compound proved to be an interesting catalyst in an enantioselective reaction. Further studies are currently in progress in order to extend the scope of utilization of this amine. Moreover, starting from the primary amine **10**, a large number of new rigid diamines can be synthesized and tested in organic catalyzed reaction.

## 4. Experimental section

### 4.1. General

Moisture sensitive reactions were carried out under an argon atmosphere, using solvents distilled and dried before use by standard methods. Flash chromatographies were carried out on silica gel SDS 60 A C.C 35–70  $\mu\text{m}$ . <sup>1</sup>H and <sup>13</sup>C NMR spectra were performed either with a Bruker-AC300 or a Bruker Avance 400 apparatus. Chemical shifts ( $\delta$ ) are given in ppm and coupling constant in Hz. IR spectra were performed with a Perkin-Elmer FTIR 1600 apparatus and data are reported in  $\text{cm}^{-1}$ .

### 4.2. Preparation of the chiral diamine 13

**4.2.1. (5*R*,6*R*,1'*S*)-6-Benzylamino-1-(1-naphthalen-1-yl-ethyl)-1-aza-spiro[4.4]nonan-2-one, 9.** To a solution of **4** (1.36 g, 4.42 mmol) in toluene (22 mL, 0.2 M) were added benzylamine (4.8 mL, 44.2 mmol), and PTSA (0.21 g, 1.1 mmol). The reaction mixture was refluxed in

a Dean–Stark apparatus for 16 h, cooled to rt, poured into a saturated aqueous solution of  $\text{NaHCO}_3$ , and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic phase was dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum, providing a mixture of **8a** and **8b** (2.5 g, quant.). A solution of crude product in MeOH (22 mL, 0.2 M) was cooled to 0 °C and  $\text{NaBH}_4$  (334 mg, 8.83 mmol) was added portionwise. The solution was stirred for 4 h reaching rt. Additional  $\text{NaBH}_4$  (165 mg, 4.4 mmol) was added and the solution stirred overnight. The mixture was concentrated under vacuum, retaken with water, and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic phase was dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum, providing **9** (2.45 g, quant.) as a slightly colored amorphous solid. An analytical sample was obtained by flash chromatography ( $\text{CH}_2\text{Cl}_2$ –MeOH 95:5). Mp 150 °C; IR (KBr):  $\nu$  2973, 2952, 2864, 1680, 1459, 1358, 1304  $\text{cm}^{-1}$ ; MS(Cl,  $\text{NH}_3$ ):  $m/z$  = 399 ( $\text{MH}^+$ ); <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.95 (m, 2H), 1.60 (m, 1H), 1.78 (m, 1H), 1.87–1.96 (m, 2H), 1.98 (d,  $J$  = 7.2 Hz, 3H), 2.10 (m, 2H), 2.30 (m, 1H), 2.45 (ddd,  $J$  = 6.3, 8.3, 16.2 Hz, 1H), 2.73 (dd,  $J$  = 7.0, 10.1 Hz, 1H), 2.85 (m, 1H), 3.38 (AB,  $J$  = 13.4 Hz,  $\Delta\delta$  = 0.12 ppm, 2H), 5.29 (q,  $J$  = 7.2 Hz, 1H), 6.78 (m, 2H), 7.05–7.15 (m, 3H), 7.36 (t,  $J$  = 7.7 Hz, 1H), 7.51 (t,  $J$  = 7.3 Hz, 1H), 7.57 (dt,  $J$  = 1.2, 8.0 Hz, 1H), 7.73 (d,  $J$  = 7.8 Hz, 1H), 7.92 (m, 2H), 8.03 (d,  $J$  = 7.2 Hz, 1H); <sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.8, 21.0, 31.0, 32.0, 34.8, 35.7, 52.0, 52.6, 68.2, 75.1, 122.4, 125.6, 126.2, 126.6, 126.8, 127.8, 127.9, 128.3, 129.6, 130.4, 134.2, 139.4, 140.7, 178.5; HRMS (ESI<sup>+</sup>,  $[\text{MH}]^+$ ):  $m/z$  calcd 399.2436, found 399.2433.

**4.2.2. (5*R*,6*R*,1'*S*)-6-Amino-1-(1-naphthalen-2-yl-ethyl)-1-aza-spiro[4.4]nonan-2-one, 10.** To a solution of crude **9** (2.45 g, ~4.42 mmol) in MeOH (44 mL, 0.1 M) was added Pd/C 10% (850 mg, ~50% w/w) under an  $\text{N}_2$  atmosphere.  $\text{N}_2$  was replaced by  $\text{H}_2$  (1 atm) and the mixture stirred for three days, filtered through a Celite pad, concentrated under vacuum, retaken with a saturated aqueous solution of  $\text{NaHCO}_3$ , and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic phase was dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum. This crude product was recrystallized (*i*-Pr<sub>2</sub>O/EtOH 95° 60:40), providing **10** (250 mg) as a white solid. Mother liquor was purified by flash chromatography ( $\text{CH}_2\text{Cl}_2$ –MeOH– $\text{NH}_4\text{OH}$  95:5:0.5) providing additional **10** (840 mg, 81%, three steps). Mp 173 °C;  $[\alpha]_{\text{D}}^{25}$  = +282 ( $c$  1.00,  $\text{CHCl}_3$ ); IR (KBr):  $\nu$  3381, 2966, 1664, 1361  $\text{cm}^{-1}$ ; MS(Cl,  $\text{NH}_3$ ):  $m/z$  = 309 ( $\text{MH}^+$ ); <sup>1</sup>H NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.67

(br s, 2H), 1.02 (m, 1H), 1.55–1.75 (m, 2H), 1.80–1.95 (m, 2H), 1.96 (d,  $J = 7.2$  Hz, 3H), 1.95–2.10 (m, 2H), 2.33 (m, 1H), 2.47 (ddd,  $J = 6.2, 9.2, 14.8$  Hz, 1H), 2.66 (m, 1H), 2.91 (t,  $J = 7.3$  Hz, 1H), 5.39 (q,  $J = 7.1$  Hz, 1H), 7.48 (t,  $J = 7.6$  Hz, 2H), 7.54 (t,  $J = 7.0$  Hz, 1H), 7.75 (d,  $J = 8.1$  Hz, 1H), 7.87 (d,  $J = 8.0$  Hz, 1H), 7.91 (d,  $J = 8.4$  Hz, 1H), 7.99 (d,  $J = 7.2$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.1, 20.8, 31.6, 33.8, 33.9, 34.4, 51.9, 62.4, 75.1, 122.4, 125.5, 125.6, 126.2, 126.7, 128.0, 129.6, 130.2, 134.2, 139.2, 178.2. Anal. Calcd for  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}$ : C, 77.89; H, 7.84; N, 9.08. Found: C, 77.81; H, 7.81; N, 9.28.

#### 4.2.3. (5'R,6'R,1''S)-1-[1-(1-Naphthalen-1-yl-ethyl)-2-oxo-1-aza-spiro[4.4]non-6-yl]-pyrrolidine-2,5-dione, **11**.

To a solution of **10** (840 mg, 2.75 mmol) in toluene (14 mL, 0.2 M) was added succinic anhydride (289 mg, 2.89 mmol). The reaction mixture was refluxed for 1.5 h, cooled to rt, concentrated under vacuum, and dissolved in acetyl chloride (14 mL, 0.2 M). The reaction mixture was refluxed for 2 h and concentrated again. Water was added and the mixture extracted with  $\text{CH}_2\text{Cl}_2$ . The organic phase was washed with a saturated aqueous solution of  $\text{NaHCO}_3$ , dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under vacuum. The crude product was purified by flash chromatography ( $\text{CH}_2\text{Cl}_2$ –MeOH 95:5) providing **11** (867 mg, 81%) as a white solid. Mp 219 °C (*i*-Pr<sub>2</sub>O);  $[\alpha]_{\text{D}}^{25} = +71$  (*c* 1.00,  $\text{CHCl}_3$ ); IR (KBr):  $\nu$  2966, 1699, 1686, 1363, 1169  $\text{cm}^{-1}$ ; MS(Cl,  $\text{NH}_3$ ):  $m/z = 391$  (MH<sup>+</sup>);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.10 (m, 4H), 1.65–1.80 (m, 2H), 1.82 (d,  $J = 7.2$  Hz, 3H), 1.96 (m, 1H), 2.00–2.20 (m, 3H), 2.22 (m, 1H), 2.41 (ddd,  $J = 1.8, 9.0, 16.3$  Hz, 1H), 2.82 (ddd,  $J = 8.9, 11.5, 16.3$  Hz, 1H), 3.01 (m, 1H), 4.40 (m, 1H), 5.29 (q,  $J = 7.1$  Hz, 1H), 7.47 (m, 2H), 7.57 (td,  $J = 7.0, 1.1$  Hz, 1H), 7.62 (d,  $J = 8.2$  Hz, 1H), 7.73 (d,  $J = 8.1$  Hz, 1H), 7.85 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.5, 21.1, 26.0, 27.4, 30.3, 36.9, 37.1, 50.8, 56.0, 76.0, 123.5, 125.8, 126.3, 126.6, 127.7, 129.2, 130.1, 133.7, 138.1, 178.3, 178.3; HRMS (ESI<sup>+</sup>, [MH]<sup>+</sup>):  $m/z$  calcd 391.2022, found 391.2019.

#### 4.2.4. (5R,6R,1'S)-1-(1-Naphthalen-1-yl-ethyl)-6-pyrrolidin-1-yl-1-aza-spiro[4.4]nonan-2-one, **12**.

To a 1 M solution of  $\text{BH}_3\cdot\text{THF}$  in THF was added **11** (220 mg, 0.56 mmol). The reaction mixture was refluxed for 16 h and cooled to rt after which MeOH (1 mL) was slowly added. The reaction mixture was stirred for 15 min, poured into a large quantity of brine, and extracted with  $\text{CH}_2\text{Cl}_2$ . Organic phase was dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum providing **12** (867 mg, quant.) as a white amorphous solid.  $[\alpha]_{\text{D}}^{25} = +107$  (*c* 1.1,  $\text{CHCl}_3$ ); IR (KBr):  $\nu$  3048, 2968, 2885, 2442, 2391, 2121, 1458  $\text{cm}^{-1}$ ; MS(Cl,  $\text{NH}_3$ ):  $m/z = 349$  (MH<sup>+</sup>);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.45–1.80 (m, 3H), 1.75 (d,  $J = 7.2$  Hz, 3H), 1.80–2.00 (m, 2H), 2.00–2.15 (m, 2H), 2.15–2.50 (m, 6H), 2.62 (m, 1H), 2.96 (m, 1H), 3.05–3.25 (m, 3H), 3.59 (m, 1H), 3.78 (m, 1H), 4.45 (m, 1H), 5.52 (q,  $J = 7.2$  Hz, 1H), 7.35–7.55 (m, 2H), 7.63 (t,  $J = 8.2$  Hz, 1H), 7.76 (d,  $J = 7.3$  Hz, 1H), 7.80–7.90 (m, 2H), 8.10 (d,  $J = 8.6$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,

$\text{CDCl}_3$ ):  $\delta$  20.6, 21.7, 22.2, 22.3, 23.8, 25.8, 34.4, 38.0, 57.9, 58.7, 64.4, 60.7, 77.7, 89.4, 122.7, 125.5, 125.9, 126.2, 127.5, 129.7, 130.0, 131.5, 134.2, 135.3; HRMS (ESI<sup>+</sup>, [MH]<sup>+</sup>):  $m/z$  calcd 349.2644, found 349.2648.

#### 4.2.5. (5R,6R)-6-Pyrrolidin-1-yl-1-aza-spiro[4.4]nonane, **13**.

To a solution of crude **12** (102 mg, ~0.26 mmol) in MeOH (3 mL, 0.1 M) was added Pd/C 10% (50 mg, ~50% w/w) under an N<sub>2</sub> atmosphere. N<sub>2</sub> was replaced by H<sub>2</sub> (1 atm) and the mixture stirred for 16 h, filtered through a Celite pad, concentrated under vacuum, and retaken with a 1 M aqueous solution of HCl. This aqueous phase was washed with  $\text{CH}_2\text{Cl}_2$ , basified by 15% aqueous solution of NaOH, and extracted with Et<sub>2</sub>O. Organic phase was dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum, providing **13** (38 mg, 76%, two steps) as a colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.45–1.63 (m, 4H), 1.65–1.95 (m, 10H), 2.45–2.60 (m, 6H), 2.71 (m, 1H), 3.05 (m, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.7, 23.7, 27.5, 30.8, 36.6, 41.1, 46.8, 53.4, 71.5, 77.4. IR (KBr):  $\nu$  3278, 2956, 2870, 2785, 1458, 1415, 1343  $\text{cm}^{-1}$ ; HRMS (ESI<sup>+</sup>, [MH]<sup>+</sup>):  $m/z$  calcd 195.1861, found 195.1867.

**13**-Picric acid (3/2): mp 185 °C (EtOH);  $[\alpha]_{\text{D}}^{25} = -48$  (*c* 0.4,  $\text{CHCl}_3$ ).

#### 4.2.6. (1R,6'R,1''R)-{[1-(1-Naphthalen-2-yl-ethyl)-2-oxo-1-aza-spiro[4.4]non-6-ylcarbamoyl]-phenyl-methyl}-carbamamic acid *tert*-butyl ester, **14a**.

Spirodiamine **13** (50 mg, 0.16 mmol) and (*R*)-*N*-Boc-phenylglycine (40.7 mg, 0.16 mmol) were dissolved in dry  $\text{CH}_2\text{Cl}_2$  (1 mL, *c* = 0.16 M) under an argon atmosphere. The solution was cooled to 0 °C and *N,N'*-dicyclohexylcarbodiimide (37 mg, 0.18 mmol) added in one drop. The mixture was allowed to warm to rt and stirred at this temperature for 90 min. The white precipitate, which formed, was filtered and washed with  $\text{CH}_2\text{Cl}_2$ . The solvent was evaporated to dryness and the crude reaction mixture purified by flash chromatography on silica gel (AcOEt–cyclohexane 60:40) to provide **14a** (80 mg, 91%) as a white solid. Mp 153–155 °C (EtOH);  $[\alpha]_{\text{D}}^{20} = +203$  (*c* 1.03,  $\text{CHCl}_3$ ); IR (film):  $\nu$  3387, 3058, 2973, 2934, 2884, 1714, 1682, 1510, 1367;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.96 (m, 1H), 1.46 (s, 9H), 1.73 (m, 2H), 1.93 (m with d,  $J = 7.1$  Hz, 2H), 1.95 (m, 1H), 2.00 (m, 1H), 2.04 (m, 1H), 2.16 (m, 1H), 2.28 (m, 1H), 4.06 (m, 1H), 4.68 (br s, 1H), 5.14 (q,  $J = 7.1$  Hz, 1H), 5.29 (d,  $J = 5.4$  Hz, 1H), 5.66 (d,  $J = 8.0$  Hz, 1H), 6.97 (m, 2H), 7.25 (m, 3H), 7.45–7.65 (m, 3H), 7.81 (t,  $J = 7.2$  Hz, 2H), 7.89 (dd,  $J = 1.5, 7.0$  Hz, 1H), 7.98 (d,  $J = 6.7$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.7, 21.1, 28.6, 31.0, 33.1, 36.4, 51.7, 58.8, 59.7, 74.2, 80.7, 121.7, 124.9, 126.3, 127.2, 127.4, 128.9, 129.4, 129.9, 130.2, 134.3, 138.0, 140.2, 154.9, 170.6, 178.0; HRMS (ESI<sup>+</sup>, [MH]<sup>+</sup>):  $m/z$  calcd 564.2838, found 564.2818.

#### 4.2.7. (1S,6'R,1''R)-{[1-(1-Naphthalen-2-yl-ethyl)-2-oxo-1-aza-spiro[4.4]non-6-ylcarbamoyl]-phenyl-methyl}-carbamamic acid *tert*-butyl ester, **14b**.

The same procedure

as above furnished **14b** in a quantitative yield (75 mg) starting from **13** (42 mg, 0.14 mmol) and (*S*)-*N*-Boc-phenylglycine (35.5 mg, 0.14 mmol). Mp 105–108 °C (EtOH);  $[\alpha]_{\text{D}}^{20} = +279$  (*c* 1.00, CHCl<sub>3</sub>); IR (film):  $\nu$  3386, 3058, 2974, 2936, 2885, 1714, 1683, 1510, 1369; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  0.92 (m, 1H), 1.39 (s, 9H), 1.55 (m, 1H), 1.63 (m, 1H), 1.89 (m, 1H), 1.96 (d, *J* = 7.1 Hz, 1H), 2.04 (m, 1H), 2.08 (m, 1H), 2.24 (m, 1H), 2.35 (m, 1H), 2.43 (m, 2H), 4.14 (m, 1H), 4.33 (br s, 1H), 5.08 (br s, 1H), 5.12 (q, *J* = 7.1 Hz, 1H), 5.56 (br s, 1H), 6.76 (br s, 2H), 7.00–7.10 (m, 3H), 7.55 (m, 2H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.85 (m, 2H), 7.94 (m, 1H), 8.14 (dd, *J* = 0.8, 7.2 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  20.8, 21.0, 28.6, 31.6, 31.8, 33.9, 36.5, 51.9, 58.9 (2C), 74.4, 80.2, 121.7, 125.7, 126.1, 126.7, 127.3, 128.3, 128.9, 130.1, 130.1, 134.3, 138.2, 139.2, 154.8, 170.5, 178.2; HRMS (ESI<sup>+</sup>, [MH]<sup>+</sup>): *m/z* calcd 564.2838, found 564.2838.

#### 4.3. Michael addition reaction

To a mixture of propionaldehyde (10 equiv) and either pyrrolidine or diamine **13** (0.15 equiv) in chloroform (0.1 M) was added nitrostyrene (1 equiv). The mixture was stirred at rt for three days. The reaction was quenched at 0 °C with a 1 M aqueous solution of HCl and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under vacuum, and purified by flash chromatography, providing **19** (93–95%) as a colorless oil. A sample of each pure diastereoisomer was then obtained. Analytical data are identical as those described.<sup>9a</sup> Enantiomeric excesses have been determined by chiral HPLC (Chiralpak AD, hexane–*i*-PrOH 90:10).

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