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A Route to Chiral, Non-Racemic Macroheterocycles†

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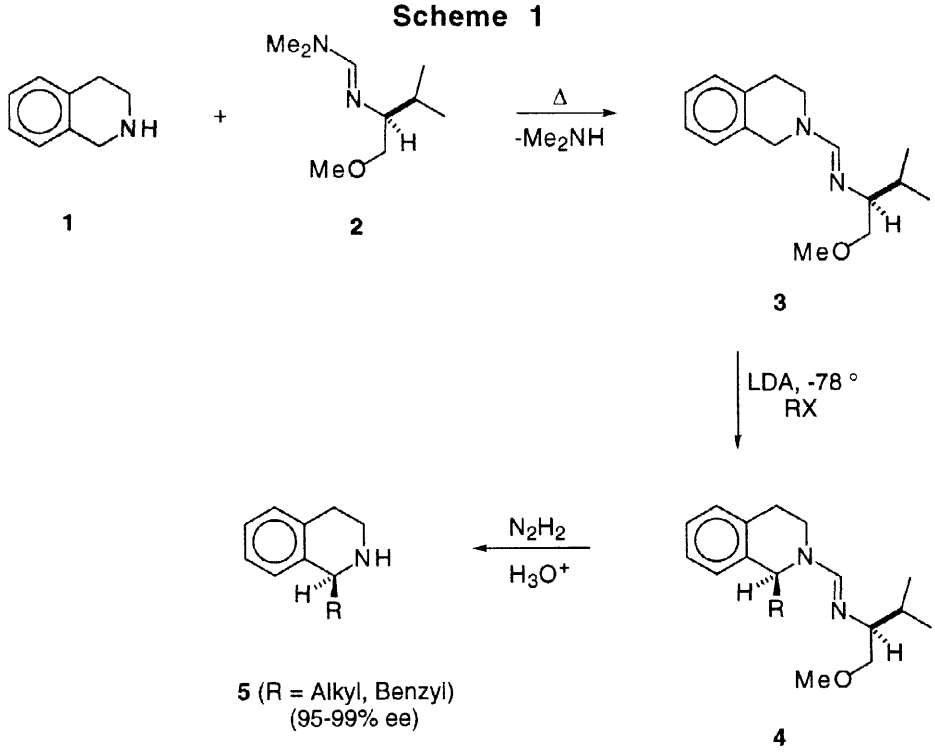
Abstract: By double alkylation of chiral isoquinoline formamidines, a 71% yield of the bis-1,3(1-tetrahydroisoquinolinyl)propane was formed in >95% ee. Macrocyclization using 2-bromoacetyl bromide gave the [9]-ring diazaheterocycle (**11**) and the [18]-ring tetra-azaheterocycle (**12**) in 24 and 57% yields, respectively. After reduction of these lactams, the title compounds **13** and **15** were obtained. X-ray structures are presented for these novel chiral ring systems.

We wish to describe a route to novel, chiral macroheterocycles which are formed using chiral formamidines and their highly efficient asymmetric alkylations (Scheme 1). We have previously shown[1] that tetrahydroisoquinolines **1**, as well as other prochiral secondary amines, can

Scheme 1



† This paper is dedicated to Professor Alan R. Katritzky in recognition of his 70th birthday and his many contributions to heterocyclic chemistry.

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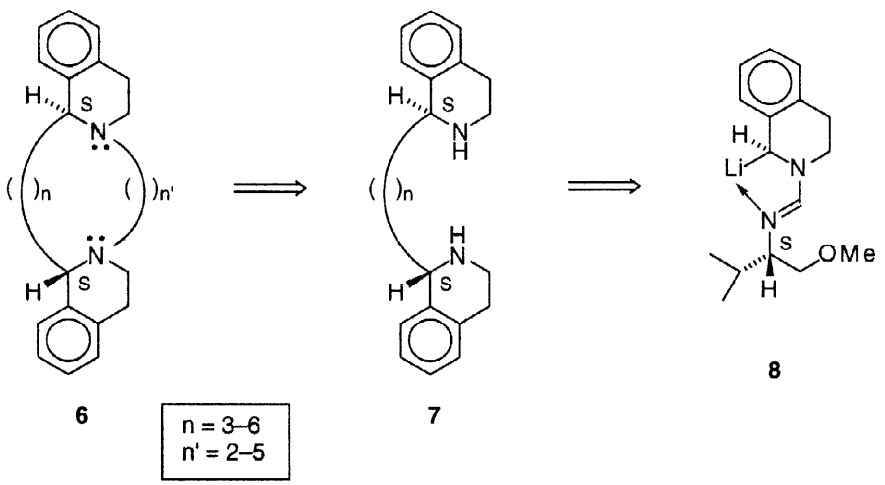
be readily transformed into their chiral formamidines **3**, by simple replacement of dimethylamine in the formamidines, **2**. Metalation, followed by alkylation with various alkyl halides resulted in the new C-1 substituent in **4** with very high diastereoselectivity (>95%). Removal of the chiral auxiliary, *via* hydrazine-assisted hydrolysis, provided the 1-substituted isoquinoline **5** in high ee's (>98%).

It occurred to us that this could potentially be a route to macrocyclic chiral heterocycles, if bifunctional electrophiles were employed. Thus, rings of various sizes could conceivably be constructed with their attending chirality and provide novel materials for a host of synthetic studies (e.g. ligands, hosts, co-solvates, etc.).[2] Scheme 2 illustrates the path to be taken. Thus, alkylation

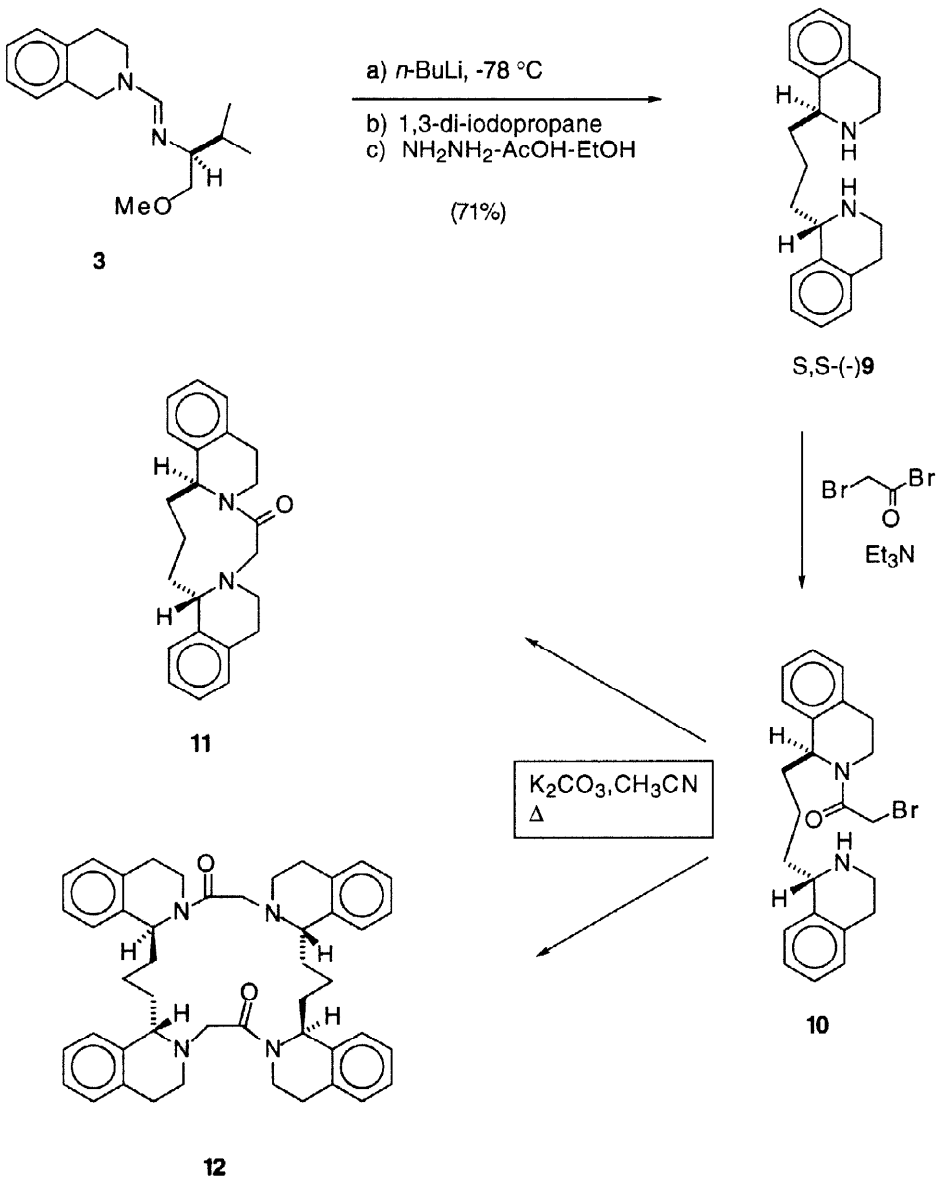
Scheme 2



of the lithio-isoquinoline **8** with an α,ω-dihaloalkane would presumably lead to the *bis*-isoquinoline **7** with S-configuration at C-1 in both isoquinoline systems. A second reaction using bifunctional alkanes would then lead to the macrocycle, **6**. We now wish to describe our early attempts to secure chiral macrocycles of the type, **6**.

The study began (Scheme 3) by treating the readily prepared isoquinoline formamidine **3** containing the chirality brought along with the valinol auxiliary.[1e] When **3** was treated with *n*-butyllithium followed by addition of 1,3-diiodopropane and the initial adduct was directly hydrolyzed, to remove the formamidine moiety the *bis*-isoquinoline **9** was produced in 71% overall yield. The latter was completely characterized as a crystalline material and analytical and chiral HPLC data showed that it was >95% enantiomerically pure. The crude *t*-Boc derivative **9a** was subjected to chiral HPLC analyses (Chiracel OD) and showed it contained >95% of the S,S-enantiomer (*vide supra*). There was also present about 2-4% of the R,R-enantiomer and 2-3% of the meso (R,S) isomer. In order to assess these ratios, the racemic *bis*-isoquinoline was also prepared, *via* the achiral formamidines[1a] and on HPLC analyses (Chiracel OD) of its *t*-Boc

Scheme 3



derivatives, showed two peaks in the ratio of 3:1 (Fig. 1a). This indicates that the meso (50%) and one of the enantiomers (25%) appear as overlapping peaks. The other enantiomer is clearly separated and visible. When the chiral derivative **9a** was similarly examined (Fig. 1b), it showed no detectable presence of the other enantiomer, and the meso product must also be present in less than 2%, under the major enantiomer peak. After further reactions to form the macrocycles **13** and **15**, no impurities were detected. A number of attempts were made to link the two nitrogen atoms in **9** to the 9-membered ring (oxalyl chloride, 1,2-dihaloethanes, etc.) but all gave very poor yields of

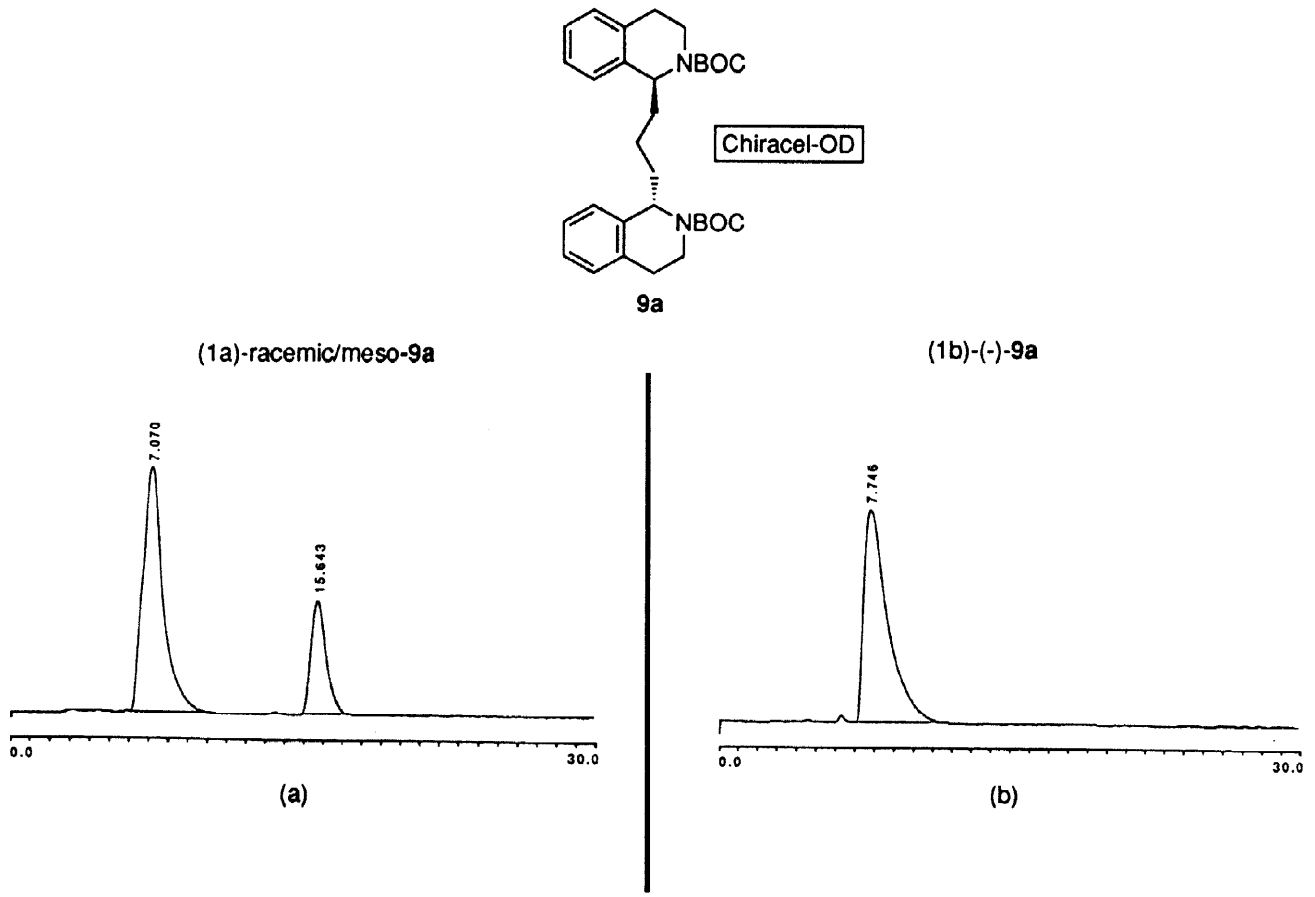


Figure 1. (1a) Chiral HPLC trace of racemic-meso mixture of Boc-**9a**. (1b) Chiral HPLC trace of product **9** from **3**, as its Boc-derivative.

many products. Nevertheless, a small amount of what was thought to be the [9]-ring diamide macrocycle was isolated from the oxalyl chloride runs, and characterized, after lithium aluminum hydride reduction as the [18]-ring macroheterocycle **15**. After extensive study, it was found that α-bromoacetyl bromide could generate the amide **10** which could then be cyclized to the [9]-ring lactam, **11** in 15-27% yield. Also accompanying this product was the [18]-ring tetra-aza lactam, **12**. These products could be separated by chromatography on silica gel. Efforts were carried out to optimize the macrocyclization and the results, to date, are given in Table 1. Currently, from entry 5

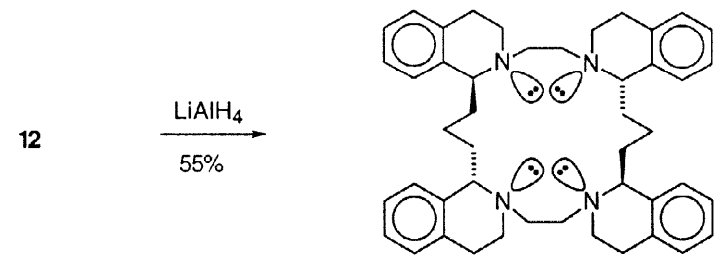
Table 1. Cyclization of **10**, at various concentrations, to **11** and **12**.

Entry	**10** (conc, mM)[a]	Yield of **11** (%)[b]	yield of **12** (%)[b]
1	26.0	19	24
2	9.5	27	41
3	8.8	27	42
4	7.3	24	34
5	7.0	24	51
6	6.7	15	49

a) Performed in acetonitrile. b) Isolated yields of material.

we can obtain the [9]-ring system and the [18]-ring system in 24 and 51% yields, respectively. Interestingly, the systematic dilution of the bromoamide **10** had little effect on the yield of the [9]-ring system, **11** and in fact seemed to slightly lower the yield with lower concentrations. On the other hand the [18]-ring yields appear to generally increase with more dilution in acetonitrile. The 24 and 51% yields achieved for **11** and **12**, respectively, at this stage of our study and the ability to cleanly separate the two products was deemed acceptable to continue. Lithium aluminum hydride reduction of **11** and **12** gave the reduced macroheterocyclic amines **13** and **15** in 94 and 55% yields, respectively, as crystalline solids.

In order to examine the nature of these macrocycles, X-ray structures were taken to both verify the global structures, and to assess the configuration. Both are given in Figures 2 and 3. In Figure 2, the X-ray of **15** is given and since the sample was crystallized from acetone, there is



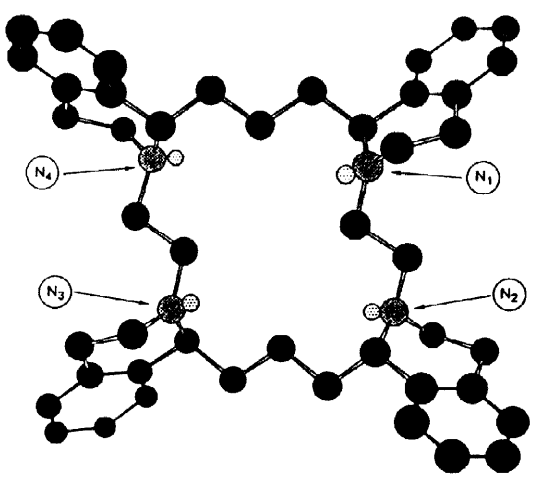


Figure 2a. Calculated minimum energy of **15**. N-lone pairs are shown. MacSparton Plus (MAC generated structure).

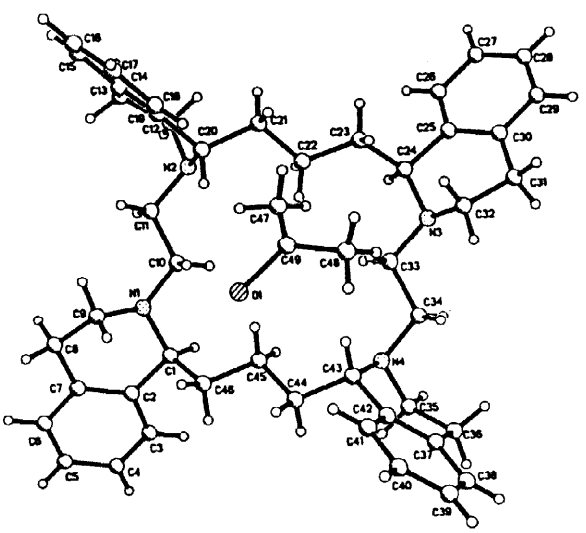
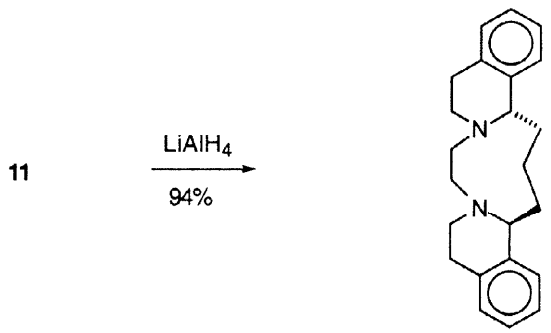


Figure 2. X-ray of **15** containing an acetone molecule below the ring plane.

present in the crystal structure, below the plane of the ring, an acetone molecule. We also calculated the minimal energy of **15** and this is given in Figure 2a. The large cavity size in **15** (~ 5-6Å) will allow a fair number of "guests" to be incorporated while the possibility of two metals to be incorporated in each of two 5-ring chelates is also reasonable. Addition of a metal or molecular "guest" will almost surely change the conformation of **15**, but this has not yet been done.

For the [9]-ring heterocycle **13** which, to date, we have only been able to prepare as a single enantiomer in 24-25% yield, the X-ray structure is shown in Figure 3. As seen from both the calculated structure and the X-ray structure, the 9-ring is not unusual as medium rings go, but the lone pairs on the two nitrogen atoms are pointing in different planes. Due to the constraints in the ring system, it appears that bringing the lone pairs to ligate to a metal may be difficult. Future studies will determine what, if any, interesting chelating properties may be found in **13**.

Studies are in progress to assess the behavior of the [18]-ring **15** and the [9]-ring **13** in a variety of processes requiring chiral recognition.



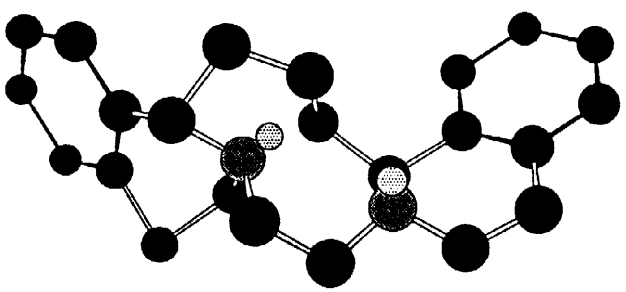


Figure 3a. Calculated minima for **13**. N-lone pairs are shown.

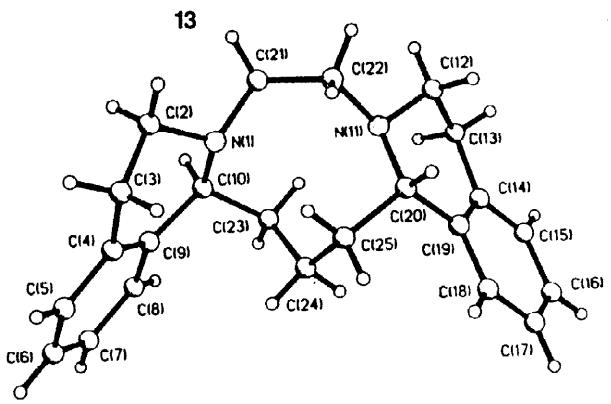


Figure 3. X-ray structure of **13**.

Experimental

Valine-derived Dimethylaminoformamidine, 2. A mixture of (*S*)-valinol (12.4 g, 0.12 mol) and DMF-dimethyl acetal (15.0 g, 0.13 mol) was heated at 40°C under Ar for 3h. After cooling to rt, the volatiles were removed *in vacuo* and the resulting clear oil was dissolved in dry THF (50 mL) and added to a suspension of NaH (4.47 g, 0.19 mol) in THF (50 mL). The mixture was stirred at rt for 3h. After cooling to 0°C, iodomethane (26.4 g, 0.19 mol) was added and the resulting mixture was stirred at ambient temperature overnight. Water was added to the reaction mixture, and THF was removed *in vacuo*. The aqueous solution was extracted with ethyl acetate and the combined organic layers were washed with brine solution and dried over anhydrous sodium sulfate. Vacuum distillation provided 12.6 g (61%) of formamidine **2** as a colorless oil: b.p. = 50°C (0.25 mm Hg); ^{1}H NMR (300 MHz, $CDCl_3$) δ; 0.64 (d, J = 4.41 Hz, 3H), 0.86 (d, J = 4.41 Hz), 1.71 (ddd, J = 13.5, 12.9, 6.9 Hz, 1H), 2.77 (ddd, J = 8.1, 6, 4.2 Hz, 1H), 2.83 (s, 6H), 3.33 (s, 3H), 3.34 (dd, J = 9.3, 7.8 Hz, 1H), 3.50 (dd, J = 9.3, 4.2 Hz, 1H), 7.21 (s, 1H).[16]

Isoquinoline-Valine Formamidine, 3. A mixture of tetrahydroisoquinoline **1** (11.7 g, 0.09 mol), formamidine **2** (16.8 g, 0.10 mol) and a catalytic amount of camphorsulfonic acid in toluene (82 mL) was heated at reflux for 3 d. The mixture was cooled to rt and the solvent was removed *in*

vacuo. Flash chromatography (silica gel, hexanes/ethyl acetate/triethyl amine, 7.5:2:0.5) resulted in 22g (96%) of formamidine **3** as a yellow oil. Kugelrohr distillation provided a colorless oil: b.p. = 190°C (0.005 mm Hg); $[\alpha]_D$ -62.7 (c, 9.73, $CHCl_3$); IR (NaCl) ν; 2870, 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ; 0.87 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 1.78 (m, 1H), 2.79-2.89 (m, 3H), 3.35 (s, 3H), 3.37 (m, 1H), 3.54 (m, 3H), 4.55 (dd, J = 30, 17.1 Hz, 2H), 7.16 (m, 4H), 7.42 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 18.6, 20.0, 29.2, 30.8, 44.3, 46.7, 58.9, 71.4, 76.2, 100.0, 126.1, 126.4, 128.7, 133.7, 134.6, 153.5.[1e]

S,S-(-)-Bis-Isoquinoline, 9. The tetrahydroisoquinoline formamidine **3** (5.00 g, 0.02 mol) was degassed by heating the flask under vacuum with a heat gun, followed by cooling and back filling the flask with argon. This was repeated four times. THF (64 mL) was added and the solution was cooled to -100°C. *n*-Butyllithium (2.1M solution in THF (9.6 mL, 0.02 mol) was added and the resulting solution was stirred for 30 min. 1,3-Diiodopropane (3.40 g, 0.01 mol) was added dropwise at -100°C, and the mixture was stirred for 3 d. The reaction mixture was quenched with methanol, and the solvent was removed *in vacuo*. Flash chromatography (silica gel, hexanes, ethyl acetate, triethyl amine, 4:1:0.25) provided the crude product which was dissolved in 95% ethanol (95 mL). Hydrazine monohydrate (0.04 mol), and acetic acid (0.02 mol) were added and the mixture was stirred at rt for 14h under argon, and the solvent was removed *in vacuo*. Flash chromatography (CH_2Cl_2/hexanes/ethyl acetate/methanol/triethyl amine, 4.5:3:2:0.5:0.5 provided 2.1 g (71%) of **9** as an off white solid; m.p. = 111.5-113.5°C; $[\alpha]_D$ -60 (c = 0.65, $CHCl_3$); IR (NaCl) ν; 3302, 2916, 1492; ^1H NMR (300 MHz, $CDCl_3$) δ; 1.67 (m, 2H), 1.80-1.93 (m, 4H), 2.19 (bs, 2H), 2.71-2.91 (m, 4H), 3.00 (ddd, J = 12.6, 7.5, 5.1 Hz, 2H), 3.25 (dt, J = 12.6, 5.4 Hz, 2H), 4.01 (dd, J = 8.4, 4.2, Hz, 2H), 7.07-7.16 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 22.8, 29.9, 36.4, 40.9, 55.6, 125.8, 125.8, 126.0, 129.2, 135.1, 139.4. MS(FAB) m/e (rel. inten.); 307 (M+1, 83), 305 (41), 158 (45), 132 (100); HRMS; calcd. for $C_{21}H_{26}N_2$ + 1, 307.2096, found: 307.2179. The HPLC (Fig. 1b) was taken of the *t*-Boc derivative and showed >95% ee.

Racemic and Meso Bis-Isoquinoline, 9. The tetrahydroisoquinoline *t*-butyl formamidine[1a] corresponding to **3** (1.00 g, 4.06 mmol) was degassed by heating the flask under vacuum with a heat gun, followed by cooling and back filling the flask with argon. This was repeated four times. THF (13.5 mL) was added and the solution was cooled to -78°C. *n*-Butyllithium (2.2M solution in hexanes, 2.03 mL, 4.47 mmol) was added and the resulting solution was stirred for 30 min. 1,3-Diiodopropane (0.720 g, 2.44 mmol) was added dropwise at -78°C, and the mixture was stirred for 36h. The reaction was quenched by the addition of methanol, and the solvent was removed *in vacuo*. Flash chromatography (silica gel, hexanes, ethyl acetate, triethyl amine, 4:1:0.25) provided the crude product which was dissolved in 95% ethanol (20 mL). Hydrazine monohydrate (0.44 mL, 9.12 mmol), and acetic acid (0.29 mL, 5.06 mmol) were added and the mixture was stirred at rt for 14h, and the solvent was removed *in vacuo*. Flash chromatography (CH_2Cl_2/hexanes/ethyl acetate/methanol/triethyl amine, 4.5:3:2:0.5:0.5 provided 0.46 g (74%) of (±)-**9** as a yellow oil: IR (NaCl) ν; 3302, 2916, 1492; ^1H NMR (300 MHz, $CDCl_3$) δ; 1.67 (m, 2H), 1.80-1.93 (m, 4H), 2.71-2.91 (m, 4H), 3.00 (ddd, J = 12.6, 7.5, 5.1 Hz, 2H), 3.25 (m, 2H), 4.01 (m, 2H), 4.45 (bs, 2H), 7.07-7.16 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 22.8, 29.9, 36.4, 40.9, 55.6, 125.8, 125.8, 126.0, 129.2, 135.1, 139.4.

(±)-*t*-Boc protected Bis-Isoquinoline, 9. To a solution of the above bis-isoquinoline **9** (104 mg, 0.34 mmol) and triethylamine (205 mg, 2.03 mmol) in dichloromethane (1.7 mL) was added *t*-Boc anhydride (443 mg, 2.03 mmol) at 0°C. The mixture was warmed to rt and stirred 15h. The solvent was removed *in vacuo* and baseline material was removed by flash chromatography (silica gel, hexanes/ethyl acetate, 4:1) which provided 148 mg of **9**. HPLC analysis showed >95% ee (Chiracel OD column, Hexanes/2-propanol, 97:3, 1.00 ml/min).

Macrocyclization of S,S-(-)-9 to 11 and 12. To a refluxing mixture of diamine **9** (0.54 g, 1.76 mmol) and sodium carbonate (0.75 g, 7.04 mmol) in CH_3CN (251 mL) was added a solution of bromoacetyl bromide (0.36 g, 1.76 mmol) in CH_3CN (5 mL) via a syringe pump (0.254 mL/hr, 5 mL syringe). Once the addition was complete, the reaction mixture was heated at reflux an additional 24h. The mixture was cooled to rt and concentrated *in vacuo*. Flash column chromatography (silica gel, hexanes/ethyl acetate, 10:1) provided 147 mg (24%) of **11** as a colorless oil and 314 mg (51%) of **12** as pale yellow oil. Both compounds were used without further purification in the next step.

Reduction of 11 to 13. To a solution of lactam **11** (52 mg, 0.150 mmol) in THF (1.5 mL) was added a 1.0M solution of LAH in THF (0.30 mL). The reaction mixture was stirred for 16h at which time water (10 mL) and 10% aq NaOH (10 mL) were cautiously added and the resulting solution was stirred for 3h. The solution was extracted with CH_2Cl_2 (5 X 25 mL) and the combined organic layers were dried over anhydrous sodium sulfate. Flash chromatography (silica gel, hexanes/ethyl acetate/triethyl amine, 8.5:1.0:0.5) gave 47 mg (94%) of **13** as a clear oil which crystallized on standing: m.p. = 122-123.5°C (diethyl ether); $[\alpha]_D$ -135.7 (c = 0.21, $CHCl_3$); IR (NaCl) ν; 2930, 1488, 1446, 1108, 906 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ; 1.56 (m, 6H), 1.84 (m, 2H), 2.22-2.31 (m, 2H), 2.60-2.85 (m, 8H), 2.94-3.11 (m, 4H), 4.21 (m, 2H), 7.08-7.18 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 24.3, 27.7, 35.5, 48.3, 56.9, 63.8, 125.1, 125.7, 127.4, 128.4, 136.1, 140.4; MS (EI) m/e (rel int) 332 (M^+, 12), 158 (100), 145 (63), 117 (38). Anal. calcd. for $C_{23}H_{28}N_2$: C, 83.09, H, 8.49, N, 8.43: found: C, 83.01, H, 8.55, N, 8.40.

Reduction of 12 to 15. To a solution of lactam **12** (314 mg, 0.906 mmol) in THF (9 mL) was added a 1.0M solution of LAH in THF (2.72 mL). The reaction mixture was stirred for 16h and then was quenched by the addition of water, and 20% aq NaOH (10 mL). The resulting solution was stirred for 3h and extracted with CH_2Cl_2 (5 X 50 mL). The combined organic layers were dried over anhydrous sodium sulfate. Flash chromatography (silica gel, hexanes/ethyl acetate/triethyl amine, 8.5:1.0:0.5) gave 154 mg (51%) of **15** as a clear oil which crystallizes on standing: m.p. = 97-99°C (acetone); $[\alpha]_D$ -8.5 (c = 0.15, $CHCl_3$); IR (NaCl) ν; 29270, 1476, 1113; ^1H NMR (300 MHz, $CDCl_3$) δ; 1.64 (m, 2H), 1.76-1.91 (m, 4H), 2.58 (m, 2H), 2.75-2.94 (m, 8H), 3.20 (m, 2H), 3.78 (m, 2H), 7.05-7.14 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 25.1, 36.5, 43.7, 52.8, 62.2, 125.6, 125.6, 127.8, 128.7, 134.4, 139.7. HRMS: calcd. for $C_{46}H_{56}N_4$ + 1, 665.4505, found: 665.4589. Anal. calcd. for $C_{46}H_{56}N_4$: C, 83.09, H, 8.49, N, 8.43: found: C, 82.38, H, 8.39, N, 8.43.

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