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Radical Cyclization of Chiral *N*-(1-Cycloalken-1-yl)-α-haloacetamides: Synthesis of Optically Active Bicyclic Pyrrolidinones

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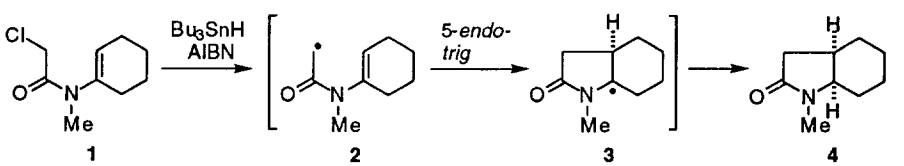
Abstract: Asymmetric induction in the 5-*endo-trig* radical cyclization of *N*-(1-cycloalken-1-yl)-α-haloacetamides has been examined. α-Iodo amide **7** bearing an (*S*)-1-(1-naphthyl)ethyl group on the nitrogen afforded a 92:8 mixture of bicyclic lactams **9a,b**, which was transformed into (3a*R*,7a*R*)-octahydroindol-2-one **10a** in 77% ee. α-Bromo amide **11** bearing an *N*-(*R*)-1-phenethyl group provided a 61:39 mixture of **13a,b**. The major product **13a** was then transformed into enantiomerically pure (1*S*,5*S*)-2-azabicyclo[3.3.0]octan-3-one **15**.

INTRODUCTION

Considerable attention has recently been directed towards the stereochemical control in radical reactions.[1,2] The primary focus of this attention has been associated with asymmetric inductions in radical cyclizations induced by chiral auxiliary control,[3] and several efforts have culminated in an efficient synthesis of optically active cyclic compounds. As part of our continuing interest in radical cyclizations leading to nitrogen-containing heterocycles,[4,5] we have studied the synthesis of optically active bicyclic pyrrolidinones by means of asymmetric radical cyclization of α-halo amides. The key feature of the method is based on our earlier finding[6]

Scheme 1



that Bu_3SnH-mediated radical cyclization of *N*-(1-cyclohexen-1-yl)-*N*-methyl-α-chloroacetamide **1** gives octahydroindol-2-one **4**. The formation of **4** from **1** may involve an attack of the carbamoylmethyl radical intermediate **2** on the internal *N*-vinylic bond to form the new radical **3**. This process is the first example of a disfavored 5-*endo-trig* radical cyclization. Our attention was then focused on the feasibility of using a chiral auxiliary on the nitrogen atom of **1** and related enamides in an asymmetric induction in radical cyclization.[7] Herein we report the results of our works in this area.

RESULTS AND DISCUSSION

Synthesis of (3a*R*,7a*R*)-Octahydroindol-2-one. We initiated our investigation by examining the cyclization of *N*-(1-cyclohexen-1-yl)-α-bromoacetamide **5** bearing an (*S*)-1-phenethyl group on the nitrogen atom as a chiral auxiliary. Compound **5** was readily prepared by condensation of cyclohexanone with (*S*)-1

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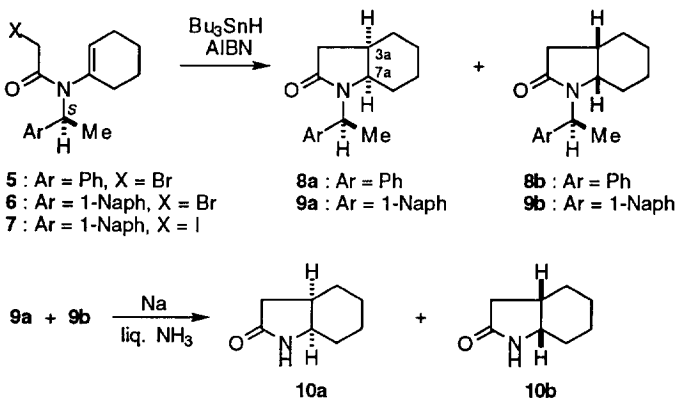
phenylethylamine followed by *N*-acylation of the resulting imine with bromoacetyl bromide. A benzene solution of Bu_3SnH (1.1 equiv) and azobis(isobutyronitrile) (AIBN) (0.1 equiv) was added slowly to a solution of **5** in benzene at reflux over 2 h, and the mixture was further heated for additional hours until no starting material was detected by TLC (General Procedure). After workup, the crude material was chromatographed on silica gel to give a mixture of two diastereoisomers **8a** and **8b** in 58% combined yield. The ^1H NMR spectrum of this mixture showed the ratio of **8a** and **8b** to be ca. 3:2, though the exact stereochemistries of **8a,b** were not determined. Thus, no remarkable diastereoselectivity was observed for the cyclization of **5**.

Scheme 2



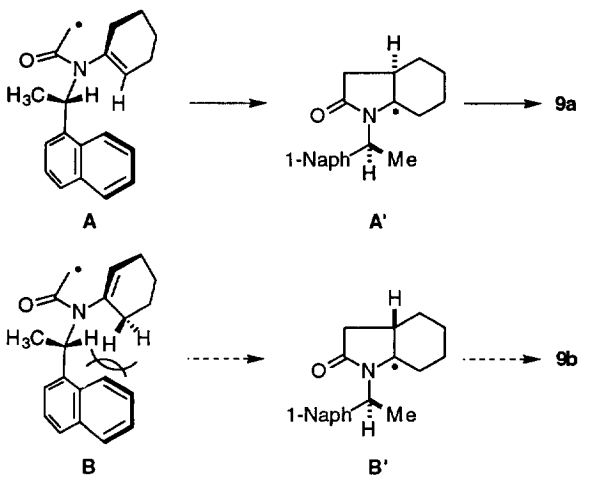
We then examined the cyclization of the enamide **6** bearing a sterically more demanding (*S*)-1-(1-naphthyl)ethyl group on the nitrogen atom. Heating **6** with Bu_3SnH in the presence of AIBN in benzene at reflux afforded a mixture of (3a*R*,7a*R*)-octahydroindol-2-one **9a** and its (3a*S*,7a*S*)-isomer **9b** in 19% yield. Although the yield was low, the diastereoisomeric ratio of **9a** and **9b** was much higher (76:24) (by ^1H NMR) than that of **8a,b** (ca. 3:2). When a similar reaction was carried out in toluene at reflux, the ratio of **9a,b** was further improved to 84:16 (by ^1H NMR). In an attempt to improve the yield, the cyclization of α-iodo amide **7** in toluene at reflux was also examined, but this gave **9a** and **9b** in 19% combined yield in a ratio of 86:14 (by ^1H NMR) or 92:8 (by GLC). This seems to be within experimental error.

The stereochemistries of **9a,b** were confirmed by transforming them to the known compounds. Thus, treatment of the mixture of **9a,b** (obtained from **7**) with sodium in liquid ammonia gave a new mixture of the *N*-deprotected octahydroindol-2-ones **10a** and **10b** in 69% combined yield. The literature indicates that (3a*R*,7a*R*)-octahydroindol-2-one (**10a**) shows a specific rotation of $[\alpha]^{20}_D$ -12.3 (*c* 1.6, EtOH).[8] The mixture of **10a,b** herein obtained showed a specific rotation of $[\alpha]^{24}_D$ -9.4 (c 0.35, EtOH), which indicated that the major isomer of the mixture of **10a,b** was **10a**, thereby confirming the stereochemistries of the original cyclization products **9a** and **9b**. The enantiomeric excess (ee) of **10a** thus obtained was estimated to be 77% based on the specific rotation.

One possible rationalization of the observed diastereoselectivity in radical cyclization of **6** or **7** is based on the consideration of the Felkin-Anh model for the radical intermediates. The two conformers **A** and **B**, where the N-C bond of the amide is regarded as a double bond, can be considered for the radical intermediate generated from **6** or **7** (Fig. 1). In conformer **B** severe steric repulsion between the C-8 hydrogen of the naphthalene ring and one of the allylic hydrogens of the cyclohexene ring becomes evident, so that the cyclization might proceed

via the sterically favored radical intermediate **A** to give the new radical (3a*R*)-**A'**.[9] A subsequent attack of Bu_3SnH on the convex face of **A'** gives **9a** as the major product. Since the stereochemistry of the cyclization is determined in the step of the formation of **A'**, the reaction can be classified as a 1,4-asymmetric induction induced by the 1-arylethyl group on the nitrogen atom.

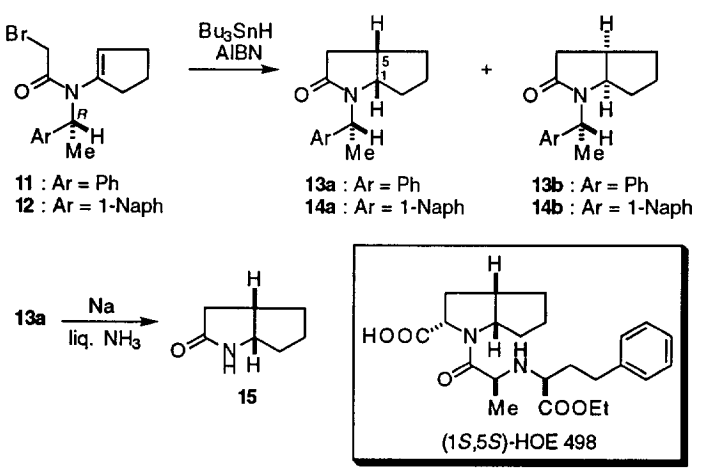
Fig. 1



Synthesis of (1*S*,5*S*)-2-Azabicyclo[3.3.0]octan-3-one. The (1*S*,5*S*)-2-azabicyclo[3.3.0]octane system is a basic structural element of an angiotensin converting enzyme (ACE) inhibitor HOE 498.[10] Our attention was next turned to the synthesis of this ring system.

Taking into account that enamide **6** bearing an (*S*)-1-(1-naphthyl)ethyl group on the nitrogen atom provided the (3a*R*,7a*R*)-isomer **9a** as the major product, the (*R*)-1-arylethyl groups were employed as chiral auxiliaries on the nitrogen atom of **11** and **12** to obtain the desired (1*S*,5*S*)-isomers of 2-azabicyclo[3.3.0]octane system.

Scheme 3



Bromo amide **11** bearing an (*R*)-1-phenethyl group on the nitrogen atom, upon treatment with Bu_3SnH and AIBN in toluene at reflux, gave a mixture of the expected (1*S*,5*S*)-2-azabicyclo[3.3.0]octan-3-one **13a** and its (1*R*,5*R*)-isomer **13b** in 33% combined yield. This result clearly indicated that the 5-*endo-trig* radical cyclization of *N*-vinylic α-haloamide was also effective for the formation of the relatively strained 2-azabicyclo[3.3.0]-octane system. The ^1H NMR spectrum showed the ratio of **13a** and **13b** to be 61:39. This value was essentially the same as that (ca. 3:2) of **8a,b** obtained from **5**.

The mixture of **13a,b** could be separated by careful chromatography on silica gel, and the stereochemistries of **13a,b** were determined as follows. Treatment of the pure isomer **13a** with sodium in liquid ammonia gave (1*S*,5*S*)-2-azabicyclo[3.3.0]octan-3-one **15** in 69% yield. The specific rotation of **15** {$[\alpha]^{24}_D$ +15.3 (*c* 1.0, EtOH)} herein obtained was close to the literature[8] value {$[\alpha]^{20}_D$ +15.8 (*c* 1.6, EtOH)}, thereby confirming the stereochemistries of the original compound **13a** together with **13b**. Thus we succeeded in the synthesis of **15** in high enantiometic purity by using radical cyclization.

Finally, in the hope of obtaining much higher diastereoselectivity, the cyclization of bromide **12** bearing a 1-(1-naphthyl)ethyl group on the nitrogen atom was examined. As expected, the diastereoisomeric ratio of **14a,b** thus obtained was improved to 81:19. However, the combined yield was only a 13%, and hence a further chemical transformation of this mixture was not carried out.

In conclusion, this paper describes our study on the 1,4-asymmetric induction in 5-*endo-trig* radical cyclization of *N*-(1-cycloalken-1-yl)-α-haloacetamides, which showed the feasibility of using a chiral 1-arylethyl group on the nitrogen. Although the combined yields were relatively low, the present results are of interest in view of the previous results that no diastereoselectivity was observed for the 1,4-asymmetric induction in 5-*exo-trig* radical cyclizations of *N*-allylic α-haloacetamides which possessed a chiral 1-phenylethyl group on the nitrogen atom.[7a]

EXPERIMENTAL[11]

2-Bromo-*N*-(1-cyclohexen-1-yl)-*N*-[(*S*)-1-phenylethyl]acetamide 5. A mixture of cyclohexanone (0.98 g, 10 mmol), (*S*)-1-phenylethylamine (1.21 g, 10 mmol), *p*-toluenesulfonic acid (catalytic amount) in benzene (30 mL) was heated under reflux with azeotropic removal of water for 2 h. After the solvent had been evaporated off, the residue containing imine was dissolved in dichloromethane (80 mL), and triethylamine (1.52 g, 15 mmol) and 4-dimethylaminopyridine (0.12 g, 1 mmol) were added. To this solution was added bromoacetyl bromide (4.04 g, 20 mmol) at 0 °C and the mixture was stirred at room temparature for 1 h. The reaction mixture was washed with brine, and the organic layer was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 7:1) to give **5** (698 mg, 22%) as an oil: IR (CCl_4) ν 1645 cm^{-1}; ^1H NMR (60 MHz) δ 1.3-2.8 (m, 8 H), 1.51 (d, *J* = 7 Hz, 3 H), 3.86 (s, 2 H), 5.3-6.0 (m, 1 H), 5.88 (q, *J* = 7 Hz, 1 H), 7.27 (s, 5 H); HRMS (FAB) calcd for $C_{16}H_{21}BrNO$ ($M+H^+$) 322.0807, found 322.0797.

2-Bromo-*N*-(1-cyclohexen-1-yl)-*N*-[(*S*)-1-(1-naphthyl)ethyl]acetamide 6. Using a procedure similar to that described above for **5**, the imine prepared from cyclohexanone (1.96 g, 20 mmol) and (*S*)-1-(1-naphthyl)ethylamine (3.42 g, 20 mmol) was treated with bromoacetyl bromide (4.04 g, 20 mmol), and the crude material was chromatographed on silica gel (hexane/AcOEt, 12;1) to give **6** (1.69 g, 23%) as an oil: IR (CCl_4) ν 1640 cm^{-1}; ^1H NMR (60 MHz) δ 0.8-2.5 (m, 8 H), 1.72 (d, *J* = 7 Hz, 3 H), 3.84 (s, 2 H), 5.6-6.0 (m, 1 H),

6.67 (q, J = 7 Hz, 1 H), 7.3-8.3 (m, 7 H); HRMS (FAB) calcd for $C_{20}H_{23}BrNO$ ($M+H^+$) 372.0963, found 372.0956.

***N*-(1-Cyclohexen-1-yl)-2-iodo-*N*-[(*S*)-1-(1-naphthyl)ethyl]acetamide 7.** To a solution of bromide **6** (447 mg, 1.2 mmol) in acetonitrile (15 mL) was added sodium iodide (198 mg, 1.3 mmol), and the mixture was stirred at room temperature for 24 h. The precipitated inorganic materials were removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was dissolved in dichloromethane, and the whole was washed with water and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 12:1) to give **7** (411 mg, 82%) as an oil: IR (CCl_4) ν 1640 cm^{-1}; ^1H NMR (60 MHz) δ 0.7-2.7 (m, 8 H), 1.65 (d, J = 7 Hz, 3 H), 3.73 and 3.77 (both s, total 2 H), 5.6-6.1 (br, 1 H), 6.64 (q, J = 7 Hz, 1 H), 7.3-8.3 (m, 7 H); HRMS (FAB) calcd for $C_{20}H_{23}INO$ ($M+H^+$) 420.0825, found 420.0815.

(3a*R*,7a*R*)- and (3a*S*,7a*S*)-Octahydro-1-[(*S*)-(1-phenylethyl)]indol-2-ones 8a,b. General Procedure for Radical Cyclization. To a boiling solution of **5** (221 mg, 0.69 mmol) in benzene (100 mL) was added a solution of Bu_3SnH (221 mg, 0.76 mmol) and AIBN (10 mg, 0.07 mmol) in benzene (50 mL) *via* a syringe over 2 h, and the mixture was heated under reflux for 2 h. After evaporating off the solvent, diethyl ether (30 mL) and 8% aqueous KF (30 mL) were added to the residue, and the mixture was stirred vigorously at room temperature for 1 h. The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 5:1) to give an oily mixture of **8a** and **8b** (97 mg, 58%) in a ratio of ca. 3:2 (determined by ^1H NMR spectroscopy): IR (CCl_4) ν 1680 cm^{-1}; ^1H NMR (270 MHz) δ 0.8-1.9 (m, 8 H), 1.57 (d, J = 7.3 Hz, 3 H x 1/5, Me for **8b**), 1.59 (d, J = 7.3 Hz, 3 H x 3/5, Me for **8a**), 2.13-2.48 (m, 3 H), 3.03-3.15 (m, 2/5 H, H-7a for **8b**), 3.50-3.61 (m, 3/5 H, H-7a for **8a**), 5.37-5.51 (m, 1 H, C*H*Me for **8a,b**), 7.15-7.45 (m, 5 H); HRMS calcd for $C_{16}H_{21}NO$ 243.1623, found 243.1617.

(3a*R*,7a*R*)- and (3a*S*,7a*S*)-Octahydro-1-[(*S*)-1-(1-naphthyl)ethyl]indol-2-ones 9a,b. Following the general procedure, bromide **6** (257 mg, 0.69 mmol) was treated with Bu_3SnH (221 mg, 0.76 mmol) and AIBN (10 mg, 0.07 mmol) in boiling toluene, and the crude material was chromatographed on silica gel (hexane/AcOEt, 3:1) to give an oily mixture of **9a** and **9b** (38 mg, 19%) in a ratio of 84:16 (determined by ^1H NMR spectroscopy): IR (CCl_4) ν 1680 cm^{-1}; ^1H NMR (270 MHz) δ 0.21-0.33 (m, 1 H), 0.43-0.75 (m, 2 H), 0.75-0.90 (m, 1 H), 0.94-1.12 (m, 1 H), 1.18-1.30 (m, 1 H), 1.37-1.66 (m, 2 H), 1.68 (d, J = 7.3 Hz, Me for **9a**), 1.72 (d, J = 7.3 Hz, Me for **9b**), 2.17-2.42 (m, 3 H), 2.59 (dt, J = 9.6, 5.9 Hz, H-7a for **9b**), 3.45 (dt, J = 8.9, 5.9 Hz, H-7a for **9a**), 6.04 (q, J = 7.3 Hz, C*H*Me for **9b**), 6.22 (q, J = 7.3 Hz, C*H*Me for **9a**), 7.40-7.60 (m, 4 H), 7.82 (br t, J = ca. 8.6 Hz, 2 H), 8.22 (d, J = 8.6 Hz, 1 H); HRMS calcd for $C_{20}H_{23}NO$ 293.1779, found 293.1785.

A similar reaction of **7** (309 mg, 0.74 mmol) was carried out in the presence of Bu_3SnH (345 mg, 1.18 mmol) and AIBN (36 mg, 0.21 mmol) in boiling toluene, and the crude material was chromatographed on silica gel (hexane/AcOEt, 3:1) to give a mixture of **9a,b** (41 mg, 19%) in a ratio of 86:14 (determined by ^1H NMR spectroscopy) and 92:8 (determined by GLC).

(3a*R*,7a*R*)- and (3a*S*,7a*S*)-Octahydroindol-2-ones 10a,b. To liquid ammonia (ca. 3 mL) were added successively sodium (51 mg, 2.2 mmol) and a solution of a mixture of **9a,b** (108 mg, 0.37 mmol) (obtained from **7**) in dry THF (4 mL) at -78 °C, and the mixture was stirred at the same temperature for 30 min. To quench the reaction an appropriate amount of ammonium chloride was added to the reaction mixture, and the whole was allowed to warm to room temperature to remove any excess ammonia. The inorganic material was removed by filtration and washed with diethyl ether. The organic layer was concentrated and the residue was

chromatographed on silica gel (hexane/AcOEt, 1:1) to give a mixture of **10a** and **10b** (35mg, 69%) as an oil, whose IR and ^{1}H NMR spectra were identical to those of (±)-**10** prepared according to the procedure reported by Stork:[12] IR (CCl_4) ν 3220, 1690 cm^{-1}; ^{1}H NMR (60 MHz) δ 1.1-2.0 (m, 8 H), 2.0-2.6 (m, 3 H), 3.5-3.9 (m, 1 H), 6.2-7.0 (br, 1 H); $[\alpha]^{24}_D$ -9.4 (*c* 0.35, EtOH); HRMS calcd for $C_8H_{13}NO$ 139.0997, found 139.0997.

2-Bromo-*N*-(1-cyclopenten-1-yl)-*N*-[(*R*)-1-phenylethyl]acetamide 11. Using a procedure similar to that described above for **5**, the imine prepared from cyclopentanone (1.00 g, 12 mmol) and (*R*)-1-phenylethylamine (1.21 g, 10 mmol) was treated with bromoacetyl bromide (4.04 g, 20 mmol), and the crude material was chromatographed on silica gel (hexane/AcOEt; 7:1) to give **11** (1.01 g, 44%) as an oil: IR (CCl_4) ν 1660 cm^{-1}; ^{1}H NMR (60 MHz) δ 1.3-2.7 (m, 6 H), 1.49 (d, *J* = 7 Hz, 3 H), 3.86 (s, 2 H), 5.4-5.7 (br s, 1 H), 5.92 (q, *J* = 7 Hz, 1 H), 7.31 (s, 5 H); HRMS calcd for $C_{15}H_{18}BrNO$ 307.0572, found 307.0602.

2-Bromo-*N*-(1-cyclopenten-1-yl)-*N*-[(*R*)-1-(1-naphthyl)ethyl]acetamide 12. Using a procedure similar to that described above for **5**, the imine prepared from cyclopentanone (313 mg, 3.7 mmol) and (*R*)-1-(1-naphthyl)ethylamine (532 mg, 3.1 mmol) was treated with bromoacetyl bromide (1.25 g, 6.2 mmol), and the crude material was chromatographed on silica gel (hexane/AcOEt; 7:1) to give **12** (399 mg, 36%) as an oil: IR (CCl_4) ν 1650 cm^{-1}; ^{1}H NMR (60 MHz) δ 0.8-2.8 (m, 6 H), 1.65 (d, *J* = 7 Hz, 3 H), 3.84 (s, 2 H), 5.2-5.4 (br s, 1 H), 6.62 (q, *J* = 7 Hz, 1 H), 7.3-8.2 (s, 7 H); HRMS calcd for $C_{19}H_{20}BrNO$ 357.0728, found 357.0710.

(1*S*,5*S*)- and (1*R*,5*R*)-2-[(*R*)-1-Phenylethyl]-2-azabicyclo[3.3.0]octan-3-ones 13a,b. Following the general procedure, bromide **11** (514 mg, 1.7 mmol) was treated with Bu_3SnH (544 mg, 1.9 mmol) and AIBN (28 mg, 0.17 mmol) in boiling toluene, and the crude material was chromatographed on silica gel (hexane/AcOEt, 3:1) to give an oily mixture of **13a** and **13b** (128 mg, 33%) in a ratio of 61:39 (determined by ^{1}H NMR spectroscopy). IR (CCl_4) ν 1675 cm^{-1}; ^{1}H NMR (270 MHz) for **13a** δ 1.16-1.80 (m, 6 H), 1.62 (t, *J* = 7.6 Hz, 3 H), 2.12-2.24 (m, 2 H), 2.47-2.75 (m, 1 H), 4.05-4.23 (m, 1 H), 5.40 (q, *J* = 7.6 Hz, 1 H), 7.22-7.41 (m, 5 H); ^{1}H NMR (270 MHz) for **13b** δ 1.16-1.80 (m, 6 H), 1.60 (t, *J* = 7.6 Hz, 3 H), 2.47-2.75 (m, 3 H), 3.59 (dt, *J* = 8.2, 5.0 Hz, 1 H), 5.44 (q, *J* = 7.6 Hz, 1 H), 7.22-7.41 (m, 5 H); HRMS calcd for $C_{15}H_{19}NO$ 229.1467, found 229.1482.

This mixture was carefully chromatographed on silica gel (hexane/AcOEt, 3:1). The first eluent gave **13b** (47 mg), and the second eluent gave **13a** (53 mg).

(1*S*,5*S*)- and (1*R*,5*R*)-2-[(*R*)-1-(1-Naphthyl)ethyl]-2-azabicyclo[3.3.0]octan-3-ones 14a, b. Following the general procedure, bromide **12** (347 mg, 0.97 mmol) was treated with Bu_3SnH (310 mg, 1.07 mmol) and AIBN (16 mg, 0.1 mmol) in boiling toluene, and the crude material was chromatographed on silica gel (hexane/AcOEt, 5:1) to give an oily mixture of **14a** and **14b** (35 mg, 13%) in a ratio of 81:19 (determined by ^{1}H NMR spectroscopy). IR (CCl_4) ν 1685 cm^{-1}; ^{1}H NMR (270 MHz) for **14a** δ 1.2-1.4 (m, 1 H), 1.6-2.0 (m, 5 H), 1.69 (t, *J* = 7.3 Hz, 3 H), 2.23-2.47 (m, 1 H), 2.33 (dd, *J* = 17.8, 5.1 Hz, 1 H), 2.76 (dd, *J* = 17.8, 10.9 Hz, 1 H), 3.01-3.12 (m, 1 H), 5.78 (q, *J* = 7.3 Hz, 1 H), 7.29-7.40 (m, 3 H), 7.40-7.55 (m, 2 H), 7.70-7.80 (m, 2 H): Small peaks due to the methyl and methine protons of the naphthylethyl group of **14b** appeared at δ 1.63 (q, *J* = 7.3 Hz) and 6.23 (q, *J* = 7.3 Hz), respectively; HRMS calcd for $C_{19}H_{21}NO$ 279.1623, found 279.1638.

(1*S*,5*S*)-2-Azabicyclo[3.3.0]octan-3-one 15. Using a procedure similar to that described above for the preparation of **10a,b**, compound **13a** (101 mg, 0.44 mmol) was treated with sodium (61 mg, 2.64 mmol) in liquid ammonia (ca. 3 mL), and the crude material was chromatographed on silica gel (hexane/AcOEt; 1:3) to

give **15** (38 mg, 69%) as an oil: IR (CCl_4) ν 3220, 1690 cm^{-1}; ^1H NMR (300 MHz) δ 1.6-2.4 (m, 6 H), 2.19 (dd, J = 17.6, 3.4 Hz, 1 H), 2.76 (dd, J =17.6, 10.3 Hz, 1 H), 2.87-3.05 (m, 1 H), 4.19-4.27 (m, 1 H), 5.9-6.4 (br, 1 H); $[\alpha]^{24}_D$ +15.3 (*c* 1.0, EtOH) [lit.[8] $[\alpha]^{20}_D$ +15.8 (*c* 1.6, EtOH)].

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