A Novel Case of Diastereoselection in 5-*exo* Radical Cyclization Promoted by Hydrogen Bonding

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Dedicated to Professor José Barluenga on the occasion of his 60th birthday

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Moderate stereocontrol in 5-*exo* radical cyclizations of *N*,*N*-disubstituted (–)-8-amino menthol derivatives, promoted by tributyltin hydride and AIBN, was achieved. The stereoselection was explained in terms of hydrogen bond formation in the 1,3-amino alcohol derivative. The presence of one additional stereocenter at the allylic chain enhanced the stereoselection giving a single cyclization stereoisomer. The cyclization products were easily converted into enantiopure 3-alkyl- or 2,3-dialkyl-substituted pyrrolidines.

Introduction

The design of new chiral auxiliaries for enantiocontrolled radical cyclization, leading to nitrogen-containing molecules, is a current topic of increasing interest. In recent years, chiral auxiliaries have been incorporated at the nitrogen atom of some α-haloamides, which can then undergo diastereoselective radical cyclizations. Homolysis of the carbon−halogen bond promoted by tributyltin hydride generates α-carbamoyl radicals, which add intramolecularly to a suitably placed carbon-carbon multiple bond. The formation of optically active β-lactams by 4-*exo* ring closure[1] and chiral pyrrolidinones[2] through 5-*exo* or even 5-*endo* cyclizations has been described following this protocol. The incorporation of the chiral appendage on the nitrogen atom in aminobromodienes has also been used in the stereocontrolled synthesis of pyrrolidines. [3]

One of the favorite auxiliaries involved in this type of stereoselective transformation is (*S*)-1-phenethylamine, although the observed stereoinduction in the radical cyclizations is low, especially in the case of 5-*exo* ring closures.[4] However, a family of more bulky auxiliaries has been claimed to improve the stereoselectivity of such cyclizations.[5]

Recently we have reported the diastereoselective intramolecular radical cyclizations of bromoaryl-[6] and phenylselenyl-substituted chiral perhydro-1,3-benzoxazines[7] derived from (−)-8-amino menthol, and now our interest in the preparation of enantiopure pyrrolidines has prompted us to study the stereoselectivity of the cyclization in the *N*,*N*-disubstituted 8-amino menthol **2**.

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Results and Discussion

The starting compound was prepared by reductive ring opening of perhydro-1,3-benzoxazine **(1)**, obtained from the condensation of 8-amino-*N*-(phenylselenoethyl) menthol with 3,3-dimethylacroleine, with DIBALH at 0 °C.

Treatment of 8-amino-*N*-phenylselenoethyl-*N*-prenyl menthol **(2)** with tributyltin hydride and AIBN in refluxing benzene (slow addn. 8 h) provided a mixture of two 5-*exo* diastereomers **3** and **4** in a 38:62 ratio (^{1}H NMR) and 95% combined yield. The same yield and selectivity was obtained using tris(trimethylsilyl)silane[8] instead of tributyltin hydride under the same experimental conditions.

This modest stereodifferentiation is somewhat striking because it has been reported[9] that there is no extraanular diastereoselective 1,4-induction when 1-phenylethylamine is used as an auxiliary. Instead, the stereoselectivity in the cyclization of our compounds could be attributed to the presence of the hydroxyl group. It has been demonstrated that the formation of intramolecular H-bonds can direct the stereochemical outcome of the reaction[10] and it plays an important role in the asymmetric induction of a wide range of radical reactions.[11] The same effect was observed when the reactions were carried out in the presence of Lewis acids.[12]

Unfortunately, changing the reaction solvent from benzene to ethyl acetate or 2-propanol did not change the ratio of diastereomeric **3** and **4**, although the chemical yields decreased to 90% in both cases. The absence of the hydrogen atom bonded to the oxygen, and consequently the disappearance of the possible H-bond, modified the stereodifferentiation. To confirm this fact, compound **2** was converted into the *O*-TBDMS derivative **5** by reaction with TBDMS-Cl. Compound **5** was then reacted with Bu_3SnH to give **6** and **7**. After desilylation with tetrabutylammonium fluoride, an equimolar mixture of pyrrolidinyl menthols **3** and **4** was isolated, showing a total loss of stereoselectivity (Scheme 1).

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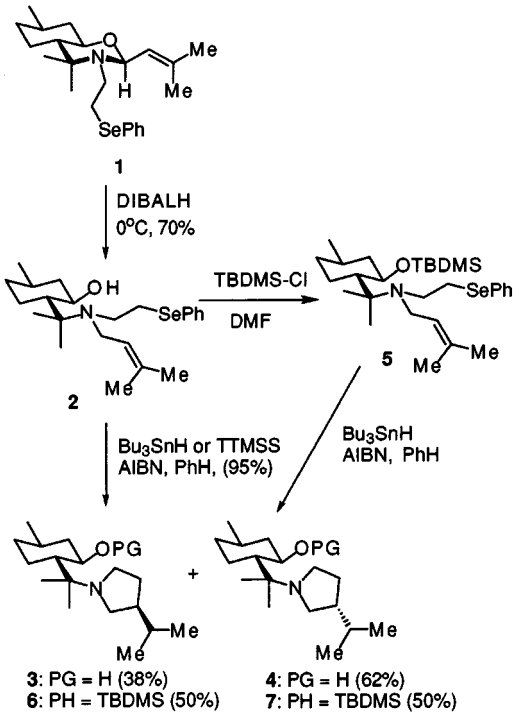
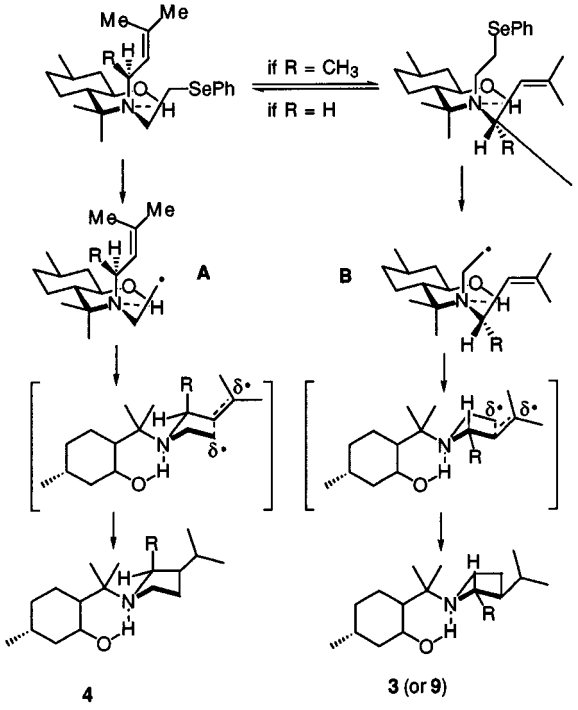


Scheme 1. Preparation and radical cyclizations of compounds **2** and **5**

This fact demonstrates the role that intramolecular H-bonding may play in controlling conformational mobility favoring a pseudo six-membered ring, and interestingly, the stereochemistry of the major isomer **4** is the same as that obtained in the cyclization of 2-vinyl-substituted perhydro-*N*-(phenylselenyl)-ethyl-1,3-benzoxazines.[7b]



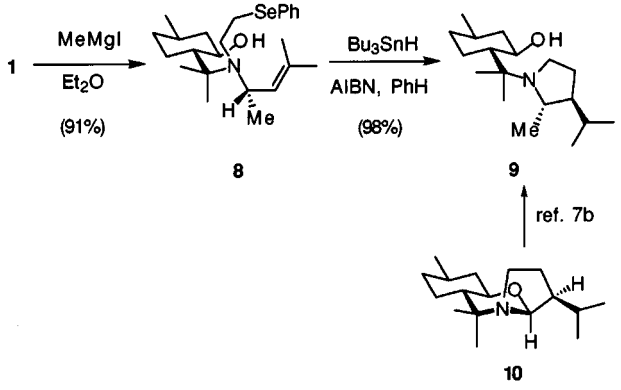
Scheme 2. Proposed stereochemical outcome for cyclizations of **2** and **8**

Assuming that the formation of the H-bond leads to two different conformations **A** and **B** (Scheme 2) in both the ground and transition states for compound **2**, the stereochemistry of the major diastereomer can be interpreted, following the Beckwith rules, from the most stable[13] conformation **A** through a chair-like transition state. The minor component **3** will be formed from the less stable structure **B**, also in a chair-like transition state.

It has been well established that the stereoinduction of cyclization of substituted 5-hexenyl radicals is dictated by both the relative position of the substituent and the stereochemistry of the stereocenter. In this way, 4-alkyl-5-hexenyl radicals provide a high level of 4,5-*trans* stereoselection[14] as a consequence of relative asymmetric induction.

In our case, and with the objective of preparing enantiopure 2,3-dialkyl-substituted pyrrolidines, the cyclization of the 8-amino menthol derivative **8** with a stereocenter of known configuration at the allylic position was examined. The starting compound was prepared, as a single stereoisomer, by reaction of **1** with methylmagnesium iodide.[15]

When radical cyclization of **8** was promoted under standard conditions (Bu_3SnH, AIBN, slow addition, 6 h) a single diastereomeric pyrrolidinylmenthol **9** was obtained in excellent yield. (Scheme 3).



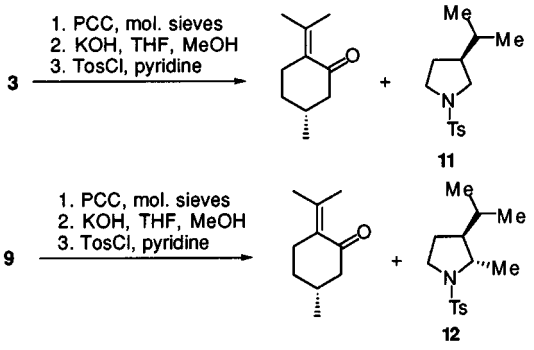
Scheme 3. Synthesis and radical cyclization of compound **8**

The complete stereoinduction can be interpreted as a consequence of the allylic 1,3-strain. This interaction favors the chair-like transition state generated from radical **B** (Scheme 2), where the methyl group is equatorial, and the interaction with the double bond is therefore minimized, and is consequently lower in energy than the transition state generated from **A**.

The absolute stereochemistry of compounds **3** and **4** was established by comparison of their spectroscopic properties with those previously described.[7a] Compound **9** was identical to that obtained from the cyclized product **10**[7b] with methylmagnesium iodide in diethyl ether.

Finally, compounds **3** and **9** were transformed into enantiopure (3*S*)-3-isopropyl pyrrolidine and (2*S*,3*S*)-2-methyl-3-isopropyl pyrrolidine, which were isolated as the tosylates **11** and **12** (Scheme 4). PCC oxidation of **3** and **9**, followed by treatment of the corresponding pyrrolidinyl

menthones with a solution of KOH in THF/MeOH, led to (+)-pulegone and the free pyrrolidine derivatives, which were isolated as the tosylates following treatment with TsCl in pyridine. Further NOESY experiments on **12** demonstrated the *trans* relationship of the substituent at the pyrrolidine nucleus, confirming the *S* configuration at C-2 and C-3.



Scheme 4. Elimination of the chiral appendage

Experimental Section

General: ^{1}H NMR and ^{13}C NMR were recorded at 300 MHz and 75 MHz, respectively, with $CDCl_3$ as the solvent and chemical shifts are given in ppm relative to TMS as the internal standard. Optical rotations were measured on a digital polarimeter in a 1-dm. cell, and concentrations are given in g/100 mL. Chromatographic separations were carried out by flash chromatography using Merck silica gel (240−400 mesh), and TLC analysis was performed on Merck 0.25 mm silica gel plates (60F-254) using mixtures of hexane and EtOAc or CH_2Cl_2 as eluents. Melting points were determined in open capillary tubes and are uncorrected. All the reactions were carried out in oven-dried glassware under an atmosphere of argon. Solvents were dried and distilled prior to use.

8-Amino-*N*-Phenylselenoethyl-*N*-prenylmenthol (2): A cooled solution (0 °C) of perhydrobenzoxazine **1**[7b] (1.0 g, 2.4 mmol) in toluene (80 mL), was treated with a 1 M solution of DIBALH (7.2 mL, 3 equiv.) in toluene under an atmosphere of argon. After 15 minutes at this temperature, the mixture was quenched by the addition of saturated ammonium chloride and then extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated yielding the amino menthol derivative **2** (704 mg, 1.7 mmol, 70%) which was purified by recrystallization. − Colorless solid, m.p. 64−65 °C (from pentane). − $[\alpha]_D^{25} = -23.7$ (c = 1.0, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.83−1.00 (m, 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.91 (s, 3 H), 1.13 (s, 3 H), 1.38−1.70 (m, 4 H), 1.54 (s, 3 H), 1.65 (s, 3 H), 1.94 (m, 1 H), 2.31−2.75 (broad, 1 H), 2.75−3.50 (m, 5 H), 3.58 (dt, J = 4.2 Hz, J = 10.5 Hz, 1 H), 5.20 (t, J = 6.2 Hz, 1 H), 7.23 (m, 3 H), 7.49 (m, 2 H), 7.95 (br. s., 1 H). − ^{13}C NMR ($CDCl_3$): δ = 17.8, 20.3, 21.1, 22.1, 25.8 (2 C), 30.9, 35.0, 44.6, 46.7, 47.7, 61.6, 72.4, 126.8, 129.0, 129.4, 132.7. − IR (nujol): $\tilde{\nu}$ = 3200, 730, 690 cm^{-1}. − $C_{23}H_{37}NOSe$ (422.51): calcd. C 65.38, H 8.83, N 3.32; found C 65.54, H 8.48, N 3.41.

8-Amino-*O*-TBDMS-*N*-Phenylselenoethyl-*N*-prenylmenthol (5): A mixture of **2** (150 mg, 0.36 mmol), imidazole (68 mg, 1.0 mmol) and *tert*-butyldimethylsilyl chloride (78 mg, 0.50 mmol) in DMF (1 mL) was stirred for 12 h at room temperature under an atmosphere of argon. Then, the crude mixture was poured into saturated ammonium chloride and extracted with diethyl ether. The organic extracts were dried over anhydrous $MgSO_4$, and the solvent was removed under vacuum yielding **5** (150 mg, 0.28 mmol, 77%) as a colorless oil. − $[\alpha]_D^{25} = -20.7$ (c = 1.0, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.07 (s, 3 H), 0.09 (s, 3 H), 0.74−1.04 (m, 3 H), 0.89 (s, 12 H), 0.91 (d, J = 6.6 Hz, 3 H), 0.97 (s, 3 H), 1.16 (s, 3 H), 1.27 (m, 1 H), 1.36−1.45 (m, 2 H), 1.56 (s, 3 H), 1.56−1.69 (m, 1 H), 1.68 (s, 3 H), 1.87 (m, 1 H), 2.08 (m, 1 H), 2.58−2.67 (m, 1 H), 2.80−2.96 (m, 2 H), 3.03 (m, 2 H), 3.54 (dt, J = 3.9 Hz, J = 10.2 Hz, 1 H), 5.18 (t, J = 6.5 Hz, 1 H), 7.22 (m, 3 H), 7.50 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = −2.9, −2.3, 18.8, 19.1, 22.3, 23.2, 24.8, 26.8, 26.9, 27.1 (3C), 30.4, 33.1, 35.9, 47.7, 48.0, 51.2, 53.0, 60.4, 75.2, 126.7, 127.3, 129.9 (2 C), 131.4, 132.4, 133.2 (2 C). − IR (neat): $\tilde{\nu}$ = 3100, 740, 690 cm^{-1}. − $C_{29}H_{51}NOSeSi$ (536.77): calcd. C 64.89, H 9.58, N 2.61; found C 65.04, H 9.76, N 2.38.

Synthesis of Aminomenthol (8): A solution of **1**[7b] (2.0 g, 4.75 mmol) in dry diethyl ether was slowly added to a 1 M solution of MeMgI (20 mL) in dry diethyl ether, and the mixture was stirred for 1 h at room temperature. After this time, the reaction mixture was quenched with a saturated ammonium chloride solution and then extracted with diethyl ether. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated affording 1.87 g (5.3 mmol, 91%) of pure amino menthol **8** as a pale yellow oil. − $[\alpha]_D^{25} = -7.2$ (c = 1.0, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.68−0.95 (m, 3 H), 0.88 (s, 3 H), 0.90 (d, J = 6.6 Hz, 3 H), 0.97−1.15 (m, 1 H), 1.00 (d, J = 7.0 Hz, 3 H), 1.13 (s, 3 H), 1.32−1.50 (m, 2 H), 1.52−1.67 (m, 1 H), 1.58 (s, 3 H), 1.65 (s, 3 H), 1.93 (m, 1 H), 2.91 (m, 3 H), 3.20−3.40 (m, 1 H), 3.53 (dt, J = 4.0 Hz, J = 10.5 Hz, 1 H), 3.95 (quintet, J = 7.2 Hz, 1 H), 5.3 (m, 1 H), 7.27 (m, 3 H), 7.62 (m, 2 H), 7.97 (br.s., 1 H). − ^{13}C NMR ($CDCl_3$): δ = 17.7, 20.7, 22.1, 22.7, 23.2, 25.7, 25.9, 30.7, 30.9, 35.0, 44.8, 44.9, 48.6, 50.5, 62.5, 73.0, 125.1, 127.3, 129.0 (2 C), 129.2, 130.2, 133.8. − IR (neat): $\tilde{\nu}$ = 3200, 750, 700 cm^{-1}. − $C_{24}H_{39}NOSe$ (436.54): calcd. C 66.03, H 9.00, N 3.21; found C 65.89, H 9.16, N 3.38.

Radical Cyclization of Aminomenthols − General Method: To a solution of the corresponding 8-amino menthol derivatives **2**, **5** or **8** (0.12 mmol) in refluxing benzene (6 mL) was slowly added (by syringe pump) a solution of tributyltin hydride (45 μL, 0.18 mmol) and AIBN (2 mg) in benzene (6 mL) over 5−7 h. The heating was continued until the reaction was finished (TLC). The mixture was then diluted with diethyl ether and extracted with 2 N hydrochloric acid. The aqueous layer was neutralized with NaOH solution, and extracted with chloroform. The organic layer was dried over anhydrous $MgSO_4$, and the solvent evaporated under vacuum. The residue was purified by flash chromatography (silica gel, EtOAc/hexane: 1:20) to give the known pyrrolidinylmenthols **3**[7b] and **4** in 95% combined yield. The same treatment of **5** yielded **6** and **7**, which, without separation, were then transformed into an equimolar mixture of **3** and **4** by desilylation with tetrabutylammonium fluoride. The cyclization reaction of **8** under identical conditions led to **9** in 98% yield.

8-[(2′*S*,3′*S*)-3′-Isopropyl-2′-methylpyrrolidinyl] Menthol (9): Colorless oil. − $[\alpha]_D^{25} = -17.8$ (c = 1.0, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$) δ = 0.80−1.01 (m, 3 H), 0.87 (d, J = 6.6 Hz, 3 H), 0.91 (d, J = 8.0 Hz, 3 H), 0.92 (s, 3 H), 0.95 (d, J = 6.0 Hz, 3 H), 1.18 (d, J = 6.0 Hz, 3 H), 1.20 (s, 3 H), 1.30−1.40 (m, 1 H), 1.40−1.60 (m, 5 H), 1.62−1.79 (m, 2 H), 1.86−1.97 (m, 1 H), 2.77−2.85 (m, 1 H), 2.86−3.01 (m, 2 H), 3.60 (dt, J = 4.0 Hz, J = 10.5 Hz, 1 H), 9.05 (s, 1 H). − ^{13}C NMR ($CDCl_3$) δ = 19.3, 19.7, 21.6, 21.8, 22.0, 25.6 (2 C), 27.1, 29.1, 30.9, 35.1, 44.3, 46.2, 49.1, 54.6, 56.0, 60.4, 72.2.

− IR (film): ṽ = 3100, 1450, 1170 cm^{-1}. − $C_{18}H_{35}NO$ (281.48): calcd. C 76.81, H 12.53, N 4.98; found C, 76.99, H 12.74, N 5.03.

Elimination of the Chiral Appendage − General Method: The pyrrolidinyl menthols **3** or **9** (1.3 mmol) were transformed into the corresponding pyrrolidinyl menthones by oxidation with PCC (1.1 g, 5.3 mmol) and 4 Å mol sieves in dichloromethane at room temperature for 2 h. The mixture was then treated with a 15% NaOH solution, extracted with chloroform and the organic phase evaporated to dryness. The residue was dissolved in a mixture containing 14% KOH (4 mL), THF (8 mL) and MeOH (4 mL) and stirred for 2 h. The mixture was extracted with diethyl ether to eliminate the (+)-pulegone and the corresponding pyrrolidine was isolated as the hydrochloride. This hydrochloride was then transformed into the *N*-tosylate by reaction with TsCl (510 mg, 2.65 mmol) and diisopropylethylamine (1.1 mL, 6.36 mmol) in dichloromethane (20 °C, 48 h), which yielded pure **11**[7b] (219 mg, 63%) or **12** (245 mg, 67%) after flash chromatography (silica gel, CH_2Cl_2/hexane, 1:1).

(2*S*,3*S*)-3-Isopropyl-2-methyl-*N*-Tosylpirrolidine (12): Colorless oil. − $[\alpha]_D^{25}$ = +72.2 (*c* = 1.0, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.64 (d, *J* = 6.7 Hz, 3 H), 0.78 (d, *J* = 6.7 Hz, 3 H), 1.00−1.20 (m, 2 H), 1.34 (d, *J* = 6.3 Hz, 3 H), 1.40−1.50 (m, 1 H), 1.60−1.80 (m, 1 H), 2.40 (s, 3 H), 3.20−3.40 (m, 2 H), 3.40 (q, *J* = 6.3 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.70 (d, *J* = 8.0 Hz, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 19.4, 21.4, 21.6, 23.2, 27.4, 29.4, 47.8, 54.1, 59.3, 127.2 (2 C), 129.5 (2C), 135.4, 143.1. − IR (film): ṽ = 1600, 1340 cm^{-1}. − $C_{15}H_{23}NO_2S$ (281.41): calcd. C 64.02, H 8.24, N 4.98; found C 64.35, H 8.27, N 4.82.

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