Diastereoselective Tandem 6-*exo* Carbolithiation Intramolecular Ring Opening in (−)-8-Aminomenthol-Derived Perhydrobenzoxazines. A New Synthesis of Enantiopure 4-Substituted Tetrahydro Isoquinolines and 2-Azabenzonorbornanes

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Abstract: Aryllithiums prepared by bromine−lithium interchange in chiral 2-(*o*-bromophenyl)-substituted perhydro-1,3-benzoxazines participate in the intramolecular 6-*exo* carbolithiation reaction with unactivated double bonds attached to the nitrogen substituent of the heterocycle. When the reaction time is extended or no TMEDA is used, the cyclized lithium intermediates react intramolecularly with the N,O-acetal system leading to 2-azabenzonorbornane derivatives. The reactions are highly stereoselective and constitute a high-yielding synthesis of enantiopure 4-substituted tetrahydroisoquinolines or 7-substituted 2-azabenzonorbornanes.

Introduction

Anionic cyclization of hexenyllithiums has been widely used in the last years as a powerful tool for building five-membered rings. Diversely substituted cyclopentanes,[1] pyrrolidines,[2] tetrahydrofuranes,[3] and both fused[1a,4] and bridged[5] bicyclic compounds have been synthesized by anionic cyclization of 1-hexenyllithium derivatives. Alkenyl vinyllithiums and alkenyl aryllithiums have also been employed in the preparation of alkylidenecyclopentanes,[6] indanes,[7] and indolines.[8] However, this method has been restricted to the formation of four- or five-membered rings, and there are few precedents on the preparation of six-membered rings[1a,6] by carbocyclization of unactivated double bonds, although the formation of lithiated piperidine derivatives as a transient species by 6-*endo* intramolecular addition has been recently reported.[9] In addition, the asymmetric version of this reaction has not been developed with the exception of a few reports on intra-[10,11] and intermolecular[12] processes.

We have recently reported the utility of chiral perhydrobenzoxazines derived from (−)-8-aminomenthol[13] in the synthesis of a wide variety of enantiopure compounds by nucleophilic ring opening of the N,O-acetal system[14] or intramolecular reactions such as Diels−Alder[15] or radical cyclizations.[16] The high chemical yields and stereodifferentiation of that reaction prompted us to investigate the unprecedented diastereoselective cyclizations of 6-heptenylaryllithiums, and now we describe the first stereoselective, high-yielding, 6-*exo* carbolithiation of unactivated double bonds affording enantiopure 4-substituted tetrahydro isoquinolines and 2-azabenzonorbornanes.

Results and Discussion

The development of our idea required an allylbenzylamine system capable of generating an aryllithium species placed in a chiral environment, and then 2-(*o*-bromophenyl)-substituted perhydrobenzoxazines **2a**−**i**, which differ in the nature of the allylic substituent at the nitrogen atom, were prepared as summarized in Scheme 1.

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Scheme 1

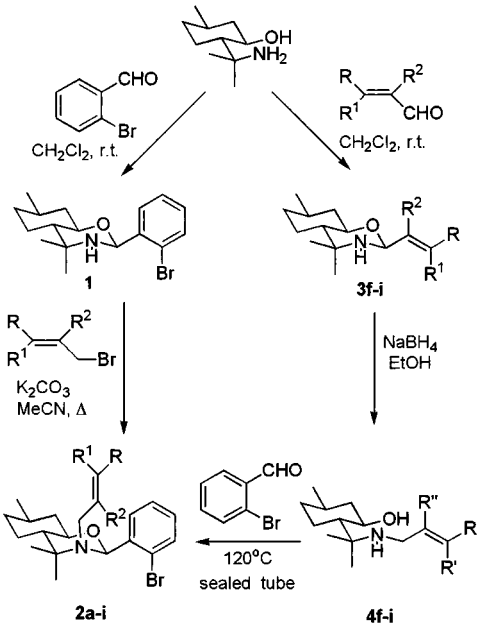


Table 1. Synthesis of Starting Compounds **2a**−**i**

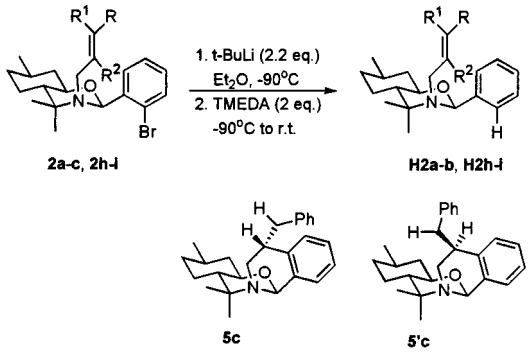
compd	R	R^1	R^2	yield (%)[a]
2a	H	H	H	88
2b	Me	Me	H	83
2c	Ph	H	H	91
2d	Me	H	H	89
2e	H	H	Me	63
2f	CH_2OBn	H	H	65
2g	Ph	Ph	H	72
2h	2-(OMe)Ph	H	H	74
2i	Ph	H	Me	72

[a] Yields refer to pure and isolated compounds.

Compounds **2a**−**e** were prepared, in two steps, from (−)-8-aminomenthol by condensation with *o*-bromobenzaldehyde leading quantitatively to **1** which was converted into **2a**−**e** by alkylation with commercially available allyl, prenyl, crotyl, methallyl, and cinnamyl bromide, respectively, in 63−91% yield. Perhydrobenzoxazines **2f**−**i** were obtained in three steps by condensation of the amino alcohol with the corresponding aldehyde to **3f**−**i**, which were reduced to (−)-8-amino menthol derivatives **4f**−**i** by treatment with sodium borohydride. These compounds were converted into the final perhydrobenzoxazines in 65−74% total yield (Table 1) by heating at 120 °C with *o*-bromobenzaldehyde in a sealed tube.

To test the cyclization process, a solution of compounds **2a** or **2b** in diethyl ether was treated with 2.2 equiv of *t*-BuLi at −90 °C for 5 min, 2 equiv of TMEDA was added, and the mixture was allowed to reach room temperature slowly over 30 min. Under these conditions no cyclization occurred, and debrominated *N*-allyl- (**H-2a** from **2a**) or 2-phenyl-*N*-prenyl perhydro-1,3-benzoxazine (**H-2b** from **2b**) were obtained as the only compounds. The same compounds were obtained when the reaction mixtures were stirred for 5 h at −90° C and hydrolyzed. This fact indicated that the bromine−lithium exchange had quickly occurred, but the aryllithium was unable to react in these conditions. Fortunately, a very different behavior was observed from *N*-cinnamyl derivative **2c**. In the above experimental conditions **2c** was totally transformed into 6-*exo* cyclization products, as a mixture (77/23) of diastereoisomers **5c** and **5′c** isolated in 98% yield, and no reduction product was observed.

Scheme 2



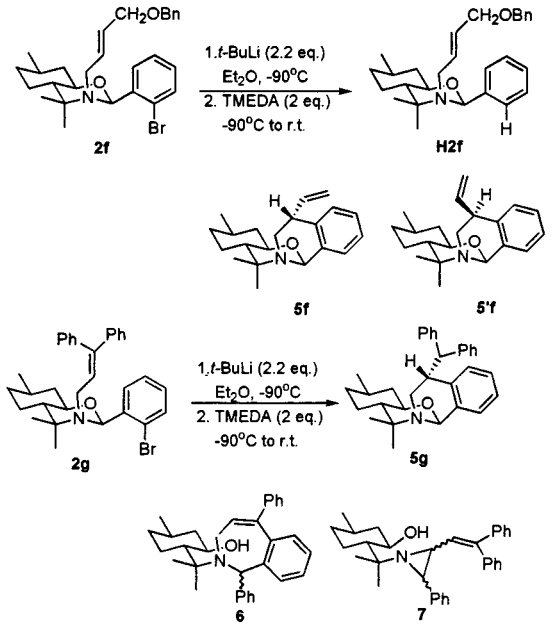
This difference in reactivity could be attributed to the benzylic character of the final lithium intermediate, or to the formation of an ion pair and extra stabilization of the anion by the phenyl group. On the basis of this hypothesis, we tested the cyclization of compounds **2h**−**i**, bearing an aromatic ring attached to the acceptor double bond capable of stabilizing the cyclized lithium intermediate. Reactions of these compounds with *t*-BuLi in the described conditions lead to debrominated **H-2h** and **H-2i** as the only reaction products. It is specially noteworthy that the presence of a donor group at the aromatic ring in **2h** inhibited the cyclization process, and that an additional methyl substituent at the inner position of the acceptor double bond in **2i** had the same effect.[3]It has been described[17] that a leaving group attached α to the accepting double bond favors the formation of five-membered rings, and we tested this fact in the reaction of benzyloxy derivative **2f** with *t*-BuLi in the described conditions. After hydrolysis, the debrominated compound **H-2f** (33%) and a mixture (3/1) of cyclic epimeric compounds **5f** and **5′f** (66%) were isolated from the reaction mixture. These isomers result from the 6-*exo* cyclization−elimination of the starting compound, and the configuration at the newly created stereocenter for the major isomer (**5f**) was assigned as *R* on the basis of ^{1}H NMR NOESY experiments. Finally, the reaction of **2g** with an additional phenyl group at the external position of the double bond led to a mixture of a single stereoisomer (**5g**) formed by 6-*exo* cyclization, in 45% yield, and aminomenthol derivatives **6** (20%) and **7** (20%). The formation of **6** could be explained as a result of the metalation of one of the phenyl groups, followed by intramolecular nucleophilic opening of the N,O-acetal, whereas **7** will be formed in the same way from a lithium derivative at the allylic position on the nitrogen substituent (Scheme 3).

The results described until now point to the fact that the formation of the aryllithium by bromine−lithium interchange was a fast reaction, but as described,[11] the 6-*exo* cyclization is a slow process. The study was continued by changing the reaction conditions to force the cyclization. To this end, **2a**−**c** and **2h**−**i** were treated with *t*-BuLi (2.2 equiv) at −90°C and then TMEDA (2 equiv) was added at the same temperature, and the reaction mixture was allowed to warm to room temperature and the stirring continued for extended periods of time. In these conditions, **2a**,**b**,**i** lead to the corresponding uncyclized debrominated perhydrobenzoxazines **H-2** even after being stirred for 48 h at room temperature.

On the contrary, we were pleased to find that compound **2h** led to the 7-aryl-substituted 2-azabenzonorbornane **8h**, as a single diasteroisomer, in 81% isolated yield, in the above experimental conditions after being stirred for 15 h at room tmeperature. It is also noteworthy that when the reaction mixture

(17) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1336.

Scheme 3



Scheme 4

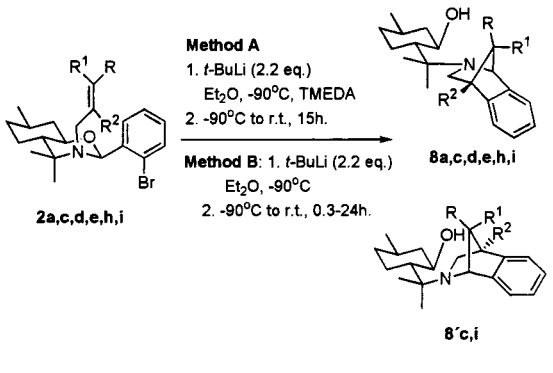


Table 2. Cyclization of Compounds **2a**,**c**,**d**,**e**,**h**,**i**

compd	R	R^1	R^2	method	time (h)	products (%)[a]
2a	H	H	H	B	8	**8a** (80)
2c	Ph	H	H	A	10	**8c** (75), **8′c** (22)
2c	Ph	H	H	B	0.3	**8c** (69), **8′c** (21)
2d	Me	H	H	B	24	**8d** (5)
2e	H	H	Me	B	24	**8e** (35)
2h	2-(OMe)Ph	H	H	A	15	**8h** (81)
2h	2-(OMe)Ph	H	H	B	1	**8h** (95)
2i	Ph	H	Me	B	2	**8i** (60), **8′i** (9)

[a] Yields refer to pure and isolated compounds.

was quenched after being stirred for 10 h, it was possible to isolate **8h** and debrominated perhydrobenzoxazine **H-2h**, but it was not possible to detect the formation of the corresponding 6-*exo* cyclization derivative. In a similar way, after the mixture was stirred for 15 h at room temperature, **2c** gives 7-phenyl-2-azabenzonorbornanes, as a mixture of diastereoisomers **8c** (77%) and **8′c** (23%) ,which differ in the stereochemistry at the stereocenters of the bicyclic system (Scheme 4). The formation of bicyclic compounds is a consequence of a tandem 6-*exo* carbolithiation of starting perhydrobenzoxazines, followed by stereospecific intramolecular nucleophilic *N*,*O*-acetal opening by the lithiated intermediate.With this information in mind, a novel set of experiences was planned *in the absence of TMEDA*, although it is well-known that the cosolvent enhances the reactivity of organolithiums by diminishing the aggregation of

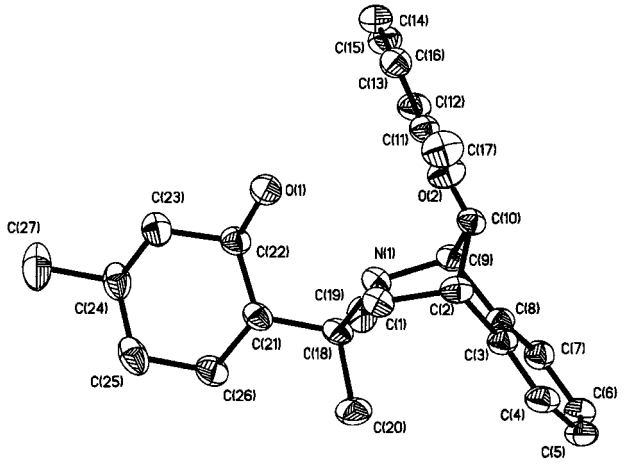


Figure 1. X-ray structure for compound **8h**.

the intermediates.[18] In this way, a solution in diethyl ether of perhydrobenzoxazines **2a**−**e** and **2h**−**i** was treated with *t*-BuLi (2.2 equiv) at −90 °C, and after 10 min at this temperature, the mixture was allowed to reach room temperature and stirred until the reaction was finished (TLC). In these experimental conditions, **2b** (with two methyl groups at the end of the double bond) did not cyclize and only gave debrominated compound **H-2b** after 15 h of reaction, and the crotyl derivative (**2d**) gave the reduction product **H-2d** in 95% yield and 2-azabenzonorbornane **8d** (5%) after 24 h of stirring. On the contrary, the methallyl derivative **2e** led to a mixture of **H-2e** (65%) and 2-azabenzonorbornane **8e** (35%) after 24 h of reaction. **2a**, after 8 h of stirring at room temperature, furnished a mixture of debrominated 2-phenyl-substituted perhydrobenzoxazine **H-2a** (12%), 6-*exo* cyclization compound **5′a** (8%), and 2-azabenzonorbornane **8a** (80%) as the only diastereoisomer. Moreover, **2c** immediately cyclizes (0.3 h.) to a mixture of diastereoisomers **8c** and **8′c** in a 77/23 ratio and 90% total yield, and **2h** led to 2-azabenzonorbornane **8h** as a single diastereoisomer in 95% yield, after 1 h of reaction. In this case, compound **2i** also participates in the cyclization process giving, after 2 h, a mixture of **5i** (11%) and diastereomeric 2-azabenzonorbornanes **8i** and **8′i** in a 73/11 ratio and 80% yield; the formation of traces (^{1}H NMR) of an isomeric azabicyclic system was observed from the reaction mixture in this case.

The stereochemistry of the stereocenters created in the reaction, C-4 at the tetrahydroisoquinoline system for 6-*exo* carbocyclization and C-1, C-4, and C-7 at the 2-azabenzonorbornane derivatives, was established by NOESY experiments and confirmed by X-ray diffraction analysis for compound **8h** (Figure 1) and **8d**, **8e**, and **11c**.[19] In this respect, the major 6-*exo* cyclization compounds **5c**,**f**,**g** have configuration *R* at C-4 in the THIQ system, which is maintained in the 2-azabenzonorbornane derivatives (C-4). Furthermore, the configurations of the stereocenters are 1*S*, 4*R* for **8a** and **8e**, 1*S*, 4*R*, 7*R* for **8c**, **8h**, and **8i**, and 1*S*, 4*R*, 7*S* for **8d** (the change of the configuration at C-7 in this case is due to the change of the priority of the substituents).

Both chemical and stereochemical outcome of these reactions could be interpreted as summarized in Scheme 5. In this respect, it is clear that the formation of the aryllithium (**A**) by bromine−lithium interchange is a fast process, but the 6-*exo* cyclization

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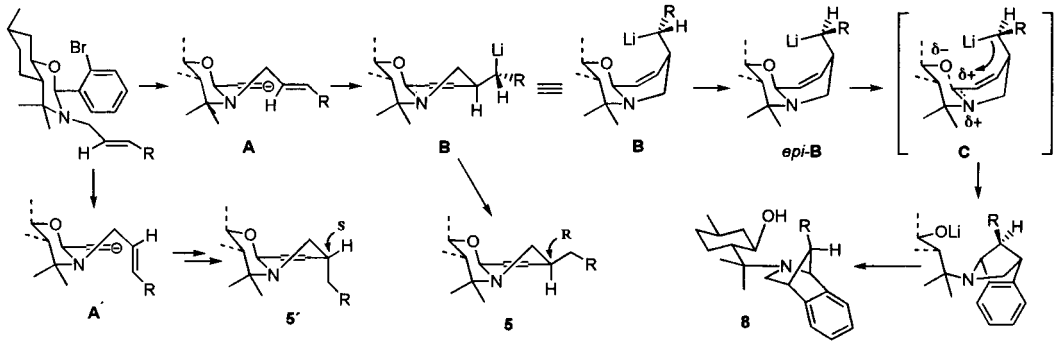
(19) See Supporting Information.

Scheme 5



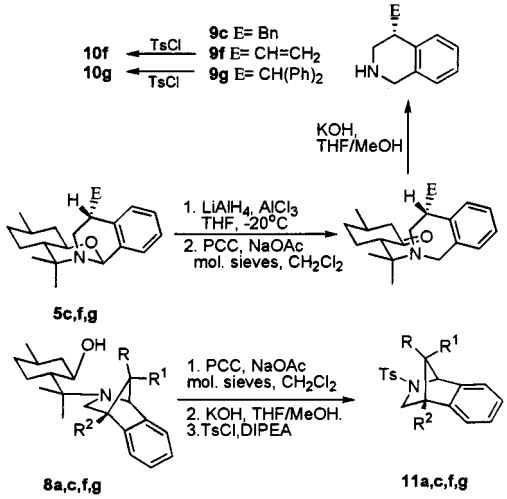
is slower than the 5-*exo* reaction,[11,20] and only occurs quickly if the terminal alkene carbon bears either a phenyl group (**2c**) that is able to stabilize the alkyllithium (**B** in Scheme 5) generated in the cyclization or a good leaving group that directs the process to an S_N2' reaction.[17] Interestingly, in the absence of strong chelating TMEDA, the 6-*exo* cyclization followed by nucleophilic intramolecular ring opening of the *N*,*O*-acetal system is a fast process. This points to the fact that the reactive species resembles more an alkyllithium than a carbanion,[21] and in this case the driving force for the initial cyclization could be the second nucleophilic reaction leading to the 2-azabenzonorbornane system.

From the stereochemical standpoint the results can be interpreted by accepting that the major or single isomer is formed from the initial coordination of the lithium atom to the alkene π-bond, followed by syn insertion across the double bond[22] in a chairlike transition state formed from **A** (Scheme 5), where the double bond is in the pseudoequatorial disposition. In this way, alkyllithium intermediate **B** will be formed, leading to the 4-substituted THIQ ring with configuration *R* at C-4 upon hydrolysis. Minor diastereoisomers will be formed, also through a chairlike transition state, from **A′** where the double bond is oriented in a pseudoaxial disposition.

The formation of the azabicyclic system is also stereochemically noteworthy. The formation of the final product as a single diastereoisomer or as a mixture in the same ratio in which are formed the 6-*exo* cyclization compounds shows that the formation of the bicyclic system accurs from alkyllithium **B**, by intramolecular attack of the lithium alkyl to the early iminium ion (**C**) formed during the *N*,*O*-acetal opening.[14] This reaction could occur with inversion of configuration at the organolithium center or, most probably, through *epi*-**B**, as a result of a previous epimerization of this carbon due to its benzylic character.[12, 23]

Enantiopure 4-substituted tetrahydro isoquinoline derivatives **9c**,**f**,**g** were obtained from major diastereoisomers **5c**,**f**,**g** isolated from the reaction mixtures by flash chromatography. Reductive ring opening of these compounds with a mixture of H_4AlLi and $AlCl_3$ in THF at −20 °C led to the corresponding (8)-aminomenthol derivatives, which were converted into 8-amino menthones by oxidation with a buffered (NaOAc) solution of PCC in CH_2Cl_2 in the presence of molecular sieves.[24] Finally, amino

Scheme 6



menthones, without isolation, were transformed into the final products by elimination promoted by KOH in THF/MeOH. In this way (*R*)-4-benzyl tetrahydroisoquinoline **9c**, (*R*)-4-vinyl tetrahydroisoquinoline **9f**, and (*R*)-4-diphenylmethyl tetrahydroisoquinoline **9g**, isolated as tosylates **10f** and **10g**, respectively, were obtained in 62−68%. Amino menthol derivatives **8a**,**c**,**h**,**i** were also transformed into tosylates of 7-substituted 2-azabenzonorbornanes **11a**,**c**,**h**,**i** in 68−74%. Oxidation of starting aminomenthols with PCC in the above conditions yielded 8-amino menthone derivatives, which were transformed, without isolation, into 2-azabenzonorbornane derivatives by elimination with KOH in THF/MeOH, and derivatized as tosylates by treatment with tosyl chloride in DIPEA (Scheme 6).

Conclusions

The present work shows for the first time the synthetic utility of anionic 6-*exo* cyclizations of unactivated alkenes. The reaction easily occurs if the cyclized lithium derivative is moderately stable or if the lithium intermediate can evolve to a stable final compound by elimination of a good leaving group or intramolecular ring opening of the *N*,*O*-acetallic system. On the contrary, the cyclization of **2b** with two methyl groups at the terminal olefinic bond was not possible, and cyclization of **2d**, with one methyl group at the same position, led to the 2-azabenzonorbonane derivative in only 5% yield. This fact has been previously observed in the formation of five-membered rings by 5-*exo* cyclization processes,[1b,3] and could be explained because the cyclization leads to unstable tertiary or secondary

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(24) Modification of the method described in: Andrés C.; Nieto J.; Pedrosa R.; Vicente M. *J. Org. Chem.* **1998**, *63*, 8570.

cyclized lithium intermediates. Whereas the intramolecular 6-*exo* carbolithiation allows the preparation of enantiopure 4-substituted tetrahydroisoquinolines, the tandem process constitutes an unprecedented[25] stereoselective synthesis of enantiopure 7-substituted 2-azabenzonorbornane derivatives.

Experimental Section

Anionic Cyclization: General Method. To a deoxygenated solution of the corresponding perhydrobenzoxazine **2a**−**i** (8 mmol) in diethyl ether (80 mL), cooled to −90 °C, was slowly added a 1.5 M solution of *t*-BuLi in pentane (11.7 mL); the mixture was stirred for 10 min at −90 °C, then TMEDA (16 mmol) was slowly added at that temperature, the cooling bath was removed, and the reaction mixture was allowed to reach room temperature. After being stirred for 20 min the reaction was quenched with a saturated solution of ammonium chloride, the phases were decanted, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The organic layer was washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed. The products were purified by flash chromatography (silica gel, EtOAc/hexane 1/60). In the reaction *without TMEDA*, the same experimental procedure, except for the addition of the cosolvent, was followed.

Cyclized Compound 5c. 77% from **2c**. Oil. $[\alpha]_D^{25}$ −41.9 (*c* 1.7, $CHCl_3$). ^{1}H NMR (δ): 0.83−1.05 (2H, m); 0.95 (3H, d, J = 6.5 Hz); 0.99 (3H, s); 1.10 (3H, s); 1.10−1.21 (1H, m); 1.38−1.57 (2H, m); 1.64−1.73 (2H, m); 1.99−2.08 (1H, m); 2.55 (1H, dd, J = 3.1, 11.9 Hz); 2.93 (1H, dd, J = 3.1, 11.8 Hz); 3.03−3.10 (3H, m); 3.38 (1H, dt, J = 4.1, 10.6 Hz); 5.21 (1H, s); 7.13−7.46 (9H, m). ^{13}C NMR (δ): 13.9; 22.2; 25.1; 26.6; 31.3; 34.8; 40.6; 41.2; 41.4; 42.6; 48.6; 55.7; 75.7; 85.1; 125.9; 126.2; 127.2; 127.4; 127.7; 128.2; 128.4; 129.0; 129.2; 136.0; 139.0; 141.2. IR (neat): 3020, 2910 cm^{-1}. MS (*m*/*z*, %): 376 (M + 1, 100). Anal. Calcd for $C_{26}H_{33}NO$: C, 83.15; H, 8.86; N, 3.73. Found: C, 83.31; H, 8.99; N, 3.66.

Reductive Ring Opening of Compounds 5c,f,g. To a stirred suspension of $LiAlH_4$ (0.12 g, 3.2 mmol) and $AlCl_3$ (0.17 g, 1.3 mmol) in dry tetrahydrofuran (8 mL) at −10 °C was added the corresponding perhidrobenzoxazine **5c**,**f**,**g** (0.64 mmol) dissolved in tetrahydrofuran (5 mL). After 20 min at that temperature the reaction was quenched by slow addition of water and a 20% aqueous solution of NaOH. The solid was filtered and washed with chloroform, the organic solvents were dried over anhydrous sodium sulfate, and the solvent was removed under vacuum. The resulting amino alcohols were employed in the next step without further purification.

Elimination of the Menthol Appendage. To a stirred solution of the corresponding aminomenthol derivative (0.55 mmol) in dichloromethane (15 mL) was added PCC (2.1 mmol) sodium acetate (0.55 mmol) and 3 Å molecular sieves (0.20 g), and the mixture was stirred at room temperature for 2 h. The reaction was quenched with 2 M NaOH (20 mL) in an ice bath and stirred for 15 min. The organic layer was decanted and the aqueous extracted with chloroform (5 × 25 mL). The organic extracts were washed with brine and dried (sodium sulfate) and the solvents removed. The resulting slurry was redissolved in THF (6 mL), methanol (2 mL), and 2.5 M KOH (2 mL) and stirred overnight. The volatiles were eliminated and the residue was acidified with 1 N HCl and extracted with ether (2 × 25 mL). The aqueous layer was then made alkaline by careful addition of 2 M NaOH and extracted with chloroform (5 × 25 mL). The organic phases are washed, dried ,and concentrated. The free amines were purified by chromatography (compound **9c**), or directly transformed into the *N*-tosylamides (compounds **10f**−**g** and **11a**,**c**,**h**,**i**).[19]

***(R)*-4-Benzyl-1,2,3,4-tetrahydroisoquinoline 9c.** 62% from **5c**. Oil. $[\alpha]_D^{25}$ −32.86 (*c* 1.3, $CHCl_3$). Lit.[26] mp 179−180 °C for racemic hydrochloride. ^{1}H NMR (δ): 1.85 (1H, broad s); 2.86 (1H, dd, J = 9.3, 12.7 Hz); 2.94−3.00 (3H, m); 3.07 (1H, dd, J = 4.0, 12.7 Hz); 3.92 (2H, s); 6.99−7.32 (9H, m). ^{13}C NMR (δ): 39.1; 42.1; 46.9; 48.7; 126.0; 126.1 (2C); 128.4 (2C); 129.0; 129.2 (3C); 135.9; 138.5; 140.4. IR (neat): 3300, 3060, 2900, 1590 cm^{-1}. MS (*m*/*z*, %): 224 (M + 1, 100). Anal. Calcd for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 86.19; H, 7.81; N, 6.34.

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Supporting Information Available: Experimental details for preparation and physical and spectral properties for compounds **1**, **2a**−**i**, **3f**−**i**, **4f**−**i**, **5f**−**g**, **8a**−**i**, **10f**−**g**, and **11a**−**i**; NOESY experiments for compounds **8a**,**c**,**h**,**i** and X-ray diagrams, crystal data, and structure refinement for compounds **8d**, **8e**, **8h**. and **11c** including atomic coordinates, isotropic and anisotropic displacement parameter,s and a listing of bond angles and bond lengths (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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