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Diastereoselective Yang Photocyclization Reactions in Solution. Synthesis of Enantiopure Azetidin-3-ol Derivatives

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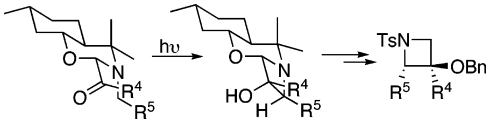

Chiral 2-acyl-3-allyl- or 2-acyl-3-benzyl-substituted perhydro-1,3-benzoxazines readily cyclized under irradiation to azetidin-3-ol derivatives. The diastereoselectivity of the cyclization is dependent on the nature of the substituents at the nitrogen atom. *N*-allyl-substituted derivatives yielded only two of the four possible diastereomers in moderate to good diastereomeric excess. The cyclization of *N*-benzyl derivatives was totally diastereoselective leading to a single diastereomer. The elimination of the menthol appendage lead to enantiopure 2,3-disubstituted azetidin-3-ol derivatives.

Introduction

Inter- and intramolecular hydrogen abstraction is one of the oldest and most extensively studied photochemical reactions of the carbonyl group.[1,2] The intramolecular process is not precluded by structural constrains and it occurs easily via a cyclic six-membered transition state with a strong preference for γ-hydrogen abstraction (Norrish Type II process). Five-, seven-, or eight-membered cyclic transition states involving β, δ, or ϵ-hydrogen atom abstraction are also expected to occur when no hydrogen atoms are available in the γ position of the carbonyl group,[3] but three- and four-membered transition states are highly unfavorable.

The initially formed 1-hydroxy-1,4-biradical intermediate in the γ-hydrogen abstraction can follow three competing pathways: (i) reverse hydrogen transfer to regenerate the ground state; (ii) cleavage of the single bond to give an enol and the corresponding alkene (Norrish Type II cleavage); and (iii) cyclization of the 1,4-hydroxybiradical to give four-membered rings such as cyclobutanols, oxetanols, or azetidinols (Yang cyclization).[4]

The mechanism of the hydrogen abstraction, and subsequent diradical transformation, has been extensively studied over recent decades and nowadays it is fairly well understood.[5] However, the synthetic utility of the Yang cyclization is limited to some strained molecules, the formation of which would be tedious or impossible by ground-state paths.[6]

In addition to the problem of chemoselectivity (α-cleavage versus intramolecular hydrogen abstraction process or Norrish II fragmentation versus cyclization) that often is the reason for the moderate yields, the major problem of the Yang cyclization is the lack of control over product selectivity and in particular, stereoselectivity in solution.

The level of regioselectivity in the crystalline state is high because the reaction occurs in a single conformer, but in solution, the equilibrium between different con-

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formers in the excited triplet state allows the formation of mixtures of regioisomers because the abstraction of different hydrogen atoms is possible. Owing to the reversibility of the hydrogen atom transfer, the final photoproducts formed do not necessarily reflect abstraction of the stereoelectronically favored hydrogen.[7,8]

With regard to the stereoselectivity, during the photocyclization of the biradical two new stereogenic centers are created if the two radical centers involved are prostereogenic. The relative configuration can be interpreted in terms of conformational preferences that preexist in the biradicals, steric repulsions when the two ends of the biradical approach each other to form the new C−C bond, and entropic factors related to intersystem crossing (ISC).[9]On the other hand, preexisting stereogenic centers in the chain can control the facial diastereoselectivity.[10,11]

In recent years, the enantioselective variant of this photocyclization has attracted considerable attention. Good levels of diastereoselection have been obtained by irradiation in crystalline state of achiral molecules that crystallize spontaneously in chiral space groups.[12] Alternatively, homochiral crystals can be obtained by tethering a covalent[13] or ionic[14] chiral auxiliary to the substrate being photolyzed. Enantioselective Yang photocyclizations have been also achieved by photochemical reactions in crystalline inclusion compounds of an achiral molecule with a chiral host.[15] Another successful approach consists of the use of zeolites as microreactors in which a certain proportion of the cage has been rendered chiral by preadsorption of an optically active inductor molecule,[16] and achiral zeolites have been used to force an interaction between a chiral auxiliary and a reactant center in the same molecule.[17]

However, there are a few examples in which enantiomerically pure or enriched products have been obtained by Yang reaction in solution.[18−20] Whereas in the solid state the diastereoselectivity is governed by the restricted motion of the chain connecting the radical centers in a chiral environment, in solution, the biradical is expected to have more freedom of rotation and therefore lower diastereoselectivities are achieved.

We have recently reported the utility of chiral perhydro-1,3-benzoxazines derived from (−)-8-aminomenthol in diastereoselective intramolecular [2+2] photocyclization reactions in solution.[21] We now report on the synthesis of enantiopure azetidin-3-ol derivatives by stereospecific Yang photocyclization in *N*-benzyl- and *N*-allyl-2-acyl-perhydro-1,3-benzoxazine derivatives.

Results and Discussion

Preparation of Starting Compounds. The starting perhydro-1,3-benzoxazines **10b**, **10c**, and **10e**−**h** were prepared as single diastereomers, in good to excellent yield, as summarized in Scheme 1. Compounds **10b** and **10c** were obtained by alkylation of 2-benzoylperhydrobenzoxazine **1**[22] with allyl bromide or 1-bromo-2-phenyl-2-pentene, respectively, and potassium carbonate in refluxing acetonitrile.

Condensation of *N*-benzyl-(−)-8-aminomenthol[23] **2** with 4-metoxyphenylglyoxal[24] hydrate in refluxing benzene furnished perhydrobenzoxazine **10e**. Treatment of perhydrobenzoxazine **3**[25] with *N*,*O*-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride in THF at room temperature gave the Weinreb amide **4** that was

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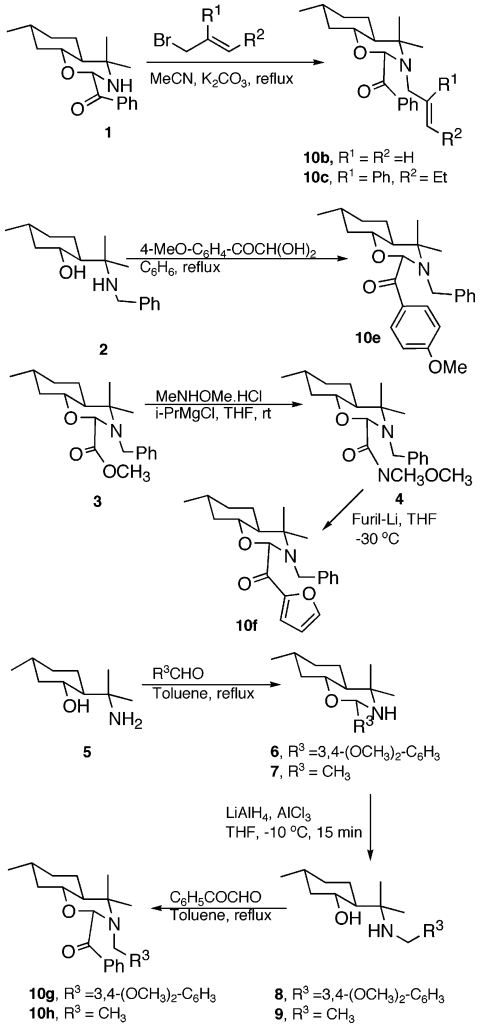
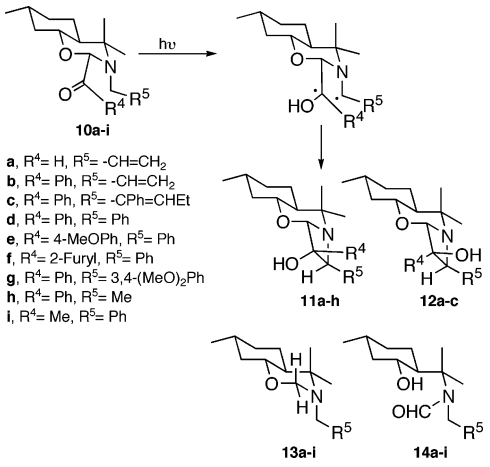
SCHEME 1. Synthesis of Perhydrobenzoxazines 10b−h



treated with 2-furyllithium in THF at −30 °C to yield perhydrobenzoxazine **10f**, while **10g** and **10h** were obtained in three steps from (−)-8-aminomenthol **5**.[26] Condensation of **5** with 3,4-dimethoxybenzaldehyde or acetaldehyde, in refluxing toluene, afforded nearly quantitatively perhydrobenzoxazines **6** and **7**, respectively, which were reduced to amino menthol derivatives **8** and **9** by treatment with aluminum hydride in THF at −10 °C. These compounds were converted into the final perhydrobenzoxazines **10g** and **10h** by heating with phenylglyoxal in toluene at reflux. The synthesis of perhydrobenzoxazines **10a**,[27] **10d**,[23] and **10i**[25] has been previously described.

Photocyclization Reactions. Yang cyclization of perhydro-1,3-benzoxazines **10a**−**i** was carried out using a water-cooled Pyrex immersion well photoreactor equipped with a 125 W mercury medium-pressure lamp. The argon-purged solution of **10a**−**i** (0.02 M) was irradiated until disappearance of the starting compound was observed, and the progress of the reaction was monitored by TLC or ^{1}H NMR. The results are summarized in Scheme 2 and Table 1.

SCHEME 2. Diastereoselective Photocyclization of 10a−i



Different reaction conditions were initially explored using the formyl derivative **10a** (entries 1−4 in Table 1). The irradiation of a methanolic solution of this compound yielded a very complex mixture, consisting of photolysis unidentified products and the starting aldehyde. No cyclization products could be detected. In contrast, the photocyclization of **10a** in benzene or acetonitrile solutions was highly diastereoselective, giving a mixture of only two, of the four possible, diastereomeric azetidin-3-ols **11a** and **12a**. In acetonitrile, both the chemical yield and diastereoselectivity were better than those observed in benzene. The temperature on the Yang photocyclization has no effect on the diastereomeric ratio (compare entries 3 and 4), but chemical yield in the cyclization at room temperature was better than at 5 °C.

The irradiation at room temperature in acetonitrile as the solvent proved to be the conditions of choice for the cyclization of perhydrobenzoxazines **10b**−**i**. Under these conditions, aromatic ketones cyclized much faster, and in higher yields, than the formyl derivative **10a**. An exception to this general behavior was the *N*-ethyl derivative **10h** that yielded a complex reaction mixture, and the cyclization product was isolated in only 6%. This result can be explained as a consequence of the better stabilization of an allylic or benzylic radical and the faster rate of intramolecular γ-hydrogen abstraction from a benzylic or allylic methylene group compared with a system bearing an alkyl group.[28] In this case, other undefined photodecomposition processes compete with the γ-hydrogen abstraction and cyclization, and formamide **14h**, probably formed by hydrolysis of the type I Norrish reaction intermediate, was the major compound detected in the reaction mixture.

Irradiation of perhydrobenzoxazine **10c** quickly cyclized to the corresponding azetidin-3-ols but only in 27% yield and to the unexpected cyclic enamine **15** (Scheme 3). This compound must arise from the intramolecular γ-hydrogen abstraction followed by the double-bond isomerization prior to the cyclization. In contrast, the formation of cyclic enamines by transposition of the double bond was not observed in the photocyclization of

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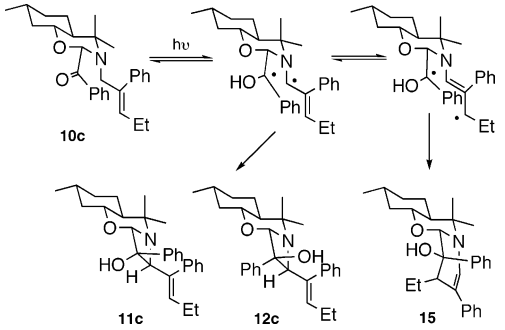
TABLE 1. Yang Photocyclization of Perhydrobenzoxazines 10a−i

entry	comp.	solvent	*T* (°C)	time (H)	yield[a] (%)	product ratio[b] (%)	byproducts
1	**10a**	MeOH	25	35			**13a**(15)**14a**(5)
2	**10a**	benzene	25	35	40	**11a**(68)**12a**(32)	**13a**(2)**14a**(9)
3	**10a**	MeCN	25	35	50	**11a**(82)**12a**(18)	**13a**(2)**14a**(8)
4	**10a**	MeCN	5	56	32	**11a**(83)**12a**(17)	**13a**(2)**14a**(16)
5	**10b**	MeCN	25	7	56	**11b**(79)**12b**(21)	**14b**(20)
6	**10c**	MeCN	25	5	27[c]	**11c**(94) **12c** (6)	**14c**(4)
7	**10d**	MeCN	25	4	60	**11d**(>96)[d]	**14d**(6)
8	**10e**	MeCN	25	5	58	**11e**(>96)[d]	**14e**(11)
9	**10f**	MeCN	25	3	55	**11f**(>96)[d]	**14f**(7)
10	**10g**	MeCN	25	4	56	**11g**(>96)[d]	**14g**(13)
11	**10h**	MeCN	25	9	6		**14h**(40)
12	**10i**	MeCN	25	43			**14i**(25)

[a] Yields refer to pure diastereomers (**11** and **12**) after flash chromatography. [b] Determined by integration of the signals in the ^{1}H NMR spectra of the reaction mixtures. [c] 29% of enamine **15** was isolated (see Scheme 3). [d] Only one diastereomer was detected by ^{1}H NMR.

SCHEME 3. Photocyclization of Compound 10c



allyl derivatives **10a** and **10b**. The irradiation of methyl ketone **10i** proceeded sluggishly and the only product identified was formamide **14i**; no cyclization products were detected.

Interestingly, the diastereoselectivity of the Yang cyclization is dependent on the nature of the 1-hydroxy-1,4-biradical. Benzylic radicals cyclized with high stereoselectivity to give a single diastereomer (entries 6−10) whereas allylic radicals yielded a mixture of only two of the four possible diastereomers, but in moderate to good diastereoselection (entries 2−5 in Table 1). In addition, different amounts of Norrish I fragmentation byproduct **13a**, or formamides **14a**−**i**, were formed during the reactions, but no Norrish II cleavage products were detected.

Stereochemical Determination. Azetidin-3-ols **11a**−**h** and **12a**−**c** were isolated and their stereochemistry was determined from NOESY experiments. For instance, the trans relationship between the allyl and hydroxyl groups in **11a** was assigned on the basis of the cross-peaks between the signals of hydrogen at C-1 and C-7a; it can also be observed as cross-peaks for signals of hydrogen at C-1 and the hydrogen of the hydroxylic group and between the hydrogen at C-2 and the α-hydrogen of the vinyl substituent. In addition, no cross-peaks were observed for signals of hydrogens at C-1 and C-2a (see Figure 1). In contrast, NOESY experiment for **12a** showed the same cross signals for hydrogen at C-1 and hydrogen at C-7a and hydrogens of the equatorial methyl group at C-8, but the absence of the cross signal between hydrogen at C-2 and the α-hydrogen of the double bond points to a relative cis disposition between hydrogens at C-1 and C-2. The estructure, including the absolute configuration of compound **11b**, was established

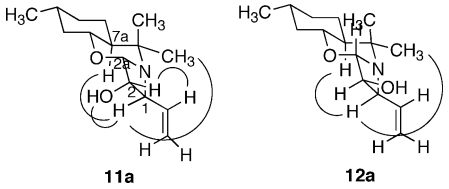


FIGURE 1. ^{1}H NOESY contacts recorded for compounds **11a** and **12a**.

by X-ray diffraction analysis,[29] confirming the proposed stereochemistry for major products.

Synthesis of Azetidin-3-ols. Elimination of the menthol appendage in photoproducts **11a**−**g** yielded enantiopure azetidin-3-ol derivatives. These compounds have attracted a great deal of attention because of their synthetic interest[30] and pharmacological properties,[31] and they are found in nature as the sphingosine type alkaloids.[32] Transformation of photocyclization products **11a**−**g** into the final enantiopure azetidin-derivatives **17a**−**g** was achieved as depicted in Scheme 4. Benzyl protection of the hydroxyl group as benzyl ether by deprotonation with sodium hydride and treatment with benzyl bromide, followed by reductive ring opening of the *N*,*O*-ketal moiety by aluminum hydride in THF at reflux, leads to the menthol derivatives **16a**−**g** in good chemical yields. X-ray diffraction analysis confirmed the absolute stereochemistry of compound **16e**.[29] The elimination of the menthol appendage in these derivatives was effected by oxidation with PCC in CH_2Cl_2 at room temperature to 8-aminomenthone derivatives, which, without isolation, were treated with KOH in H_2O−THF−MeOH, leading

(29) Crystallographic data can be obtained from the Cambridge Crystallographic Data Center, 12, union Road, Cambridge CB2 1EZ, UK. E-mail: deposit@ccdc.cam.ac.uk.

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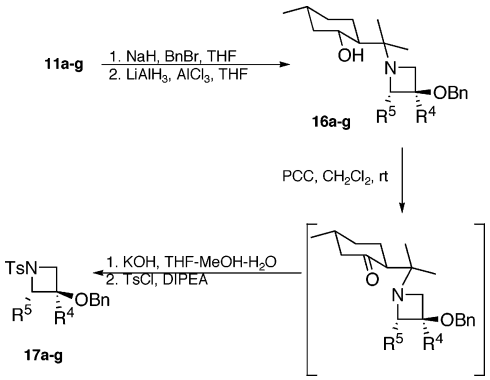
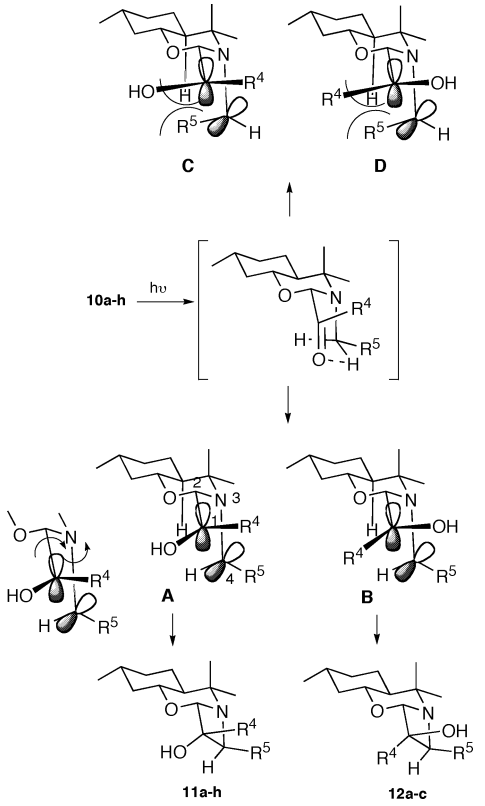
SCHEME 4. Transformation of 11a−g into Azetidin-3-ols 17a−g



SCHEME 5. Proposed Mechanism for the Photocyclization of 10a−h



to the enantiopure azetidine derivatives. These compounds were isolated and characterized as *N*-tosyl derivatives **17a**−**g** by treatment with tosyl chloride and diisopropylethylamine in ethyl acetate. The absolute stereochemistry of compound **17d** was established by X-ray diffraction analysis,[29] corroborating the absolute configuration of photoproduct **11d** and that no racemization occurred during the elimination of the chiral auxiliary.

Mechanistic Discussion. The diastereoselective formation of only two (from **10a**−**c**) or one (from **10d**−**h**) of the four possible isomers can be explained on the basis of the accepted mechanism for these photocyclizations (Scheme 5). The hydrogen-transfer process must be initiated in a chairlike conformation after electronic excitation and ISC.[33] The stereochemistry at C-4 in the final azetidin-3-ols reflects that, in the transfer process, the diastereotopic hydrogens of the methylene group attached to the nitrogen atom are perfectly differentiated[10g] and that the abstraction occurs in the most stable chairlike conformation where the pro-R hydrogen atom is the only one transferred because the substituent (R^5) occupies an equatorial disposition.

The triplet 1,4-biradical has relatively long lifetimes[34] to enable conformational flexibility at room temperature. To favor an efficient ISC to a singlet state and to allow C−C bond formation, a geometry of the triplet biradical in which the axes of the p orbitals at the radical center are oriented perpendicular to each other is required for strong spin−orbit coupling (SOC).[35] Since the lifetime of singlet biradicals is usually quite short to allow significant molecular motions, specially bond rotation, the ISC is expected to proceed in a concerted fashion with the formation of the new bond. Therefore, the stereoselectivity of the reaction can be attributed to the conformation memory effects during ISC of the triplet 1,4-biradical.[36]

Four conformations of the triplet biradical (**A**−**D**) can fulfill the Salem−Rowland requirement and are able to undergo ISC to singlet state and C−C bond formation. Whereas the major products **11a**−**h** were formed from conformation **A** by combination of the two radical centers from the Re face of the radical at C-4 and the Si face of the radical at C-1, and minor products **12a**−**c** were formed from conformation **B** by combination of the two radicals from the Re−Re face, conformers **C** and **D** were sterically less favorable because of steric hindrance between R^5 and the benzoxazine framework, and no products were formed from these conformations. On the other hand, a possible intramolecular hydrogen-bonding interaction between the hydroxyl group and the oxygen of the perhydrobenzoxazine can contribute enough to stabilize confomer **A** and explain the high facial discrimination.

Semiempirical calculations using PM3/UHF method with the program PC Spartan Plus of the two relevant 1,4-biradical conformers **A** and **B** from **10d** resulted in absolute differences of approximately 2.8 kcal/mol in favor of the most stable conformation **A**. The same calculation at UHF/3-21G level shows that biradical **10a**−**A** is more stable than **10a**−**B** with approximately 2.1 kcal/mol.[37] Higher differences in energy have been proposed for related 1,4-biradicals by DFT calculations.[38] The hydrogen bond distance O···H−O for **10a**−**A** and **10d**−**A** were 2.04 and 1.88 Å, respectively.

On the other hand, the differences in reactivity between aliphatic **10i** and aromatic carbonyl **10b**−**g** substrates are probably due to differences in the excited states (singlet/triplet). Because of rapid intersystem crossing from the singlet state, the aromatic carbonyl compounds generally reflect pure T_1 (n-π^*) photochem-

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istry[39] whereas the corresponding aliphatic carbonyls have lower k_{isc} and therefore they can react from S_1 as well as T_1. Although the hydrogen abstraction occurs from both the singlet and triplet nπ^* states, the singlet efficiency in hydrogen abstraction and Norrish-type II reaction of aliphatic compounds are generally lower than from triplet state.[40]

In summary, the irradiation, in benzene or acetonitrile solution, of 3-allyl or 3-benzyl-2-acyl disubstituted perhydrobenzoxazines yielded azetidin-3-ol derivatives in moderate chemical yields (50−60%) and good to excellent diastereoselection (64→96%). Only two or one of the four possible diastereomers were formed, and the stereochemistry of the major isomer can be explained by assuming the selective hydrogen transfer from diastereotopic γ-CH, followed by biradical cyclization with *retention* at both radical centers. The use of the chiral template in this diastereoselective cyclization enlarges the synthetic utility of the Norrish−Yang reaction.

Experimental Section

General Procedure for Yang Photocyclization Reactions. A 0.02 M solution of the appropriate benzoxazine (3 mmol) in acetonitrile (150 mL) was poured into a water-cooled Pyrex immersion well photoreactor, degassed by bubbling argon through the solution for 15 min, and then irradiated under argon atmosphere with a medium-pressure mercury lamp (125 W) until disappearance of the starting amide (TLC). The solvent was removed under vacuum and the residue was purified by flash chromatography on silica gel using hexanes−ethyl acetate as eluent.

(1*S*,2*S*,2a*S*,3a*R*,5*R*,7a*S*)-5,8,8-Trimethyl-2-vinyloctahydro-1*H*,3a*H*-azeto[2,1-b][1,3]benzoxazin-2-ol (11a). Colorless oil. $[\alpha]_D^{25} = +14.46$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (δ): 0.89 (s, 3H); 0.95 (d, 3H, $J = 6.5$ Hz); 0.97−1.09 (m, 3H); 1.03 (s, 3H); 1.38−1.55 (m, 2H); 1.60 (m, 1H); 1.72 (m, 1H); 1.96 (m, 1H); 3.10 (broad, s, 1H); 3.48 (td, 1H, $J_1 = 10,4$ Hz, $J_2 = 4.4$ Hz); 3.81 (m, 1H); 4.05 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 5.1$ Hz); 5.04 (dd, 1H, $J_1 = 10.3$ Hz, $J_2 = 1.4$ Hz); 5.05 (d, 1H, $J = 3.7$ Hz); 5.21 (dd, 1H, $J_1 = 17.6$ Hz, $J_2 = 1.4$ Hz); 5.91 (ddd, 1H, $J_1 = 17.6$ Hz, $J_2 = 10.3$ Hz, $J_3 = 7.8$ Hz). ^{13}C NMR (δ): 20.9; 22.2; 24.7; 24.9; 31.1; 34.9; 41.4; 44.8; 51.5; 68.9; 70.8; 71.4; 84.9; 115.5; 140.4. IR (film): 3450 (broad); 3080; 2930; 1735; 1710; 1640; 770; 645 cm^{-1}. Anal. calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.51; 9.89; N, 5.69.

(1*S*,2*R*,2a*S*,3a*R*,5*R*,7a*S*)-5,8,8-Trimethyl-2-vinyloctahydro-1*H*,3a*H*-azeto[2,1-b][1,3]benzoxazin-2-ol (12a). Colorless oil. $[\alpha]_D^{25} = +16.31$ ($c = 0.75$, $CHCl_3$). ^{1}H NMR (δ): 0.86−1.14 (m, 3H); 0.90 (s, 3H); 0.92 (d, 3H, $J = 6.6$ Hz); 1.04 (s, 3H); 1.18−1.47 (m, 2H); 1.60 (m, 1H); 1.69 (m, 1H); 1.91 (m, 1H); 2.70 (broad, s, 1H); 3.36 (td, 1H, $J_1 = 10.4$ Hz, $J_2 = 4.4$ Hz); 3.92 (d, 1H, $J = 5.2$ Hz); 4.64 (dd, 1H, $J_1 = 6.5$ Hz, $J_2 = 5.2$ Hz); 4.86 (s, 1H); 5.32 (dd, 1H, $J_1 = 10.4$ Hz, $J_2 = 1.0$ Hz); 5.43 (dd, 1H, $J_1 = 17.1$ Hz, $J_2 = 1.0$ Hz); 5.93 (ddd, 1H, $J_1 = 17.1$ Hz, $J_2 = 10.4$ Hz, $J_3 = 6.5$ Hz). ^{13}C NMR (δ): 20.8; 22.2; 24.7 (2C); 31.0; 34.9; 41.4; 44.5; 52.0; 63.9; 70.7; 71.7; 89.1; 118.5; 137.2. IR (film): 3305 (broad); 2953; 1725; 1660; 845 cm^{-1}. Anal. calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.51; H, 10.18; N, 5.46.

(1*S*,2*S*,2a*S*,3a*R*,5*R*,7a*S*)-2-Phenyl-5,8,8-trimethyl-1-vinyloctahydro-1*H*,3a*H*-azeto[2,1-b][1,3]benzoxazin-2-ol (11b). Colorless solid. Mp: 104−105 °C (from hexanes−EtOAc). $[\alpha]_D^{25} = +53.32$ ($c = 0.9$, $CHCl_3$). ^{1}H NMR (δ): 0.90 (s, 3H); 0.91−1.02 (m, 2H); 0.95 (d, 3H, $J = 6.5$ Hz); 1.13 (s, 3H); 1.16 (m, 1H); 1.48−1.52 (m, 2H); 1.61 (m, 1H); 1.72 (m, 1H); 1.97 (m, 1H); 3.58 (td, 1H, $J_1 = 10.4$ Hz, $J_2 = 4.4$ Hz); 4.01 (s, 1H); 4.35 (d, 1H, $J = 8.4$ Hz); 4.80 (dd, 1H, $J_1 = 10.1$ Hz, $J_2 = 1.9$ Hz); 5.05 (dd, 1H, $J_1 = 17.2$ Hz, $J_2 = 1.9$ Hz); 5.12 (s, 1H); 5.31 (ddd, 1H, $J_1 = 17.2$ Hz, $J_2 = 10.1$ Hz, $J_3 = 8.4$ Hz); 7.21−7.35 (m, 3H); 7.64−7.67 (m, 2H). ^{13}C NMR (δ): 21.1; 22.3; 24.7; 25.1; 31.1; 34.9; 41.4; 44.6; 51.7; 71.7; 74.6; 75.1; 88.6; 116.3; 125.7 (2C); 127.0; 127.6 (2C); 138.8; 139.3. IR (Nujol): 3527; 3480 (broad); 3055; 1835; 1690; 1655; 1640; 1605; 780; 755; 700; 655 cm^{-1}. Anal. calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 77,21; H, 9.05; N, 4.39.

(1*S*,2*R*,2a*S*,3a*R*,5*R*,7a*S*)-2-Phenyl-5,8,8-trimethyl-1-vinyloctahydro-1*H*,3a*H*-azeto[2,1-b][1,3]benzoxazin-2-ol (12b). Colorless oil. $[\alpha]_D^{25} = -4.97$ ($c = 0.5$, $CHCl_3$). ^{1}H NMR (δ): 0.83−1.06 (m, 2H); 0.94 (d, 3H, $J = 6.6$ Hz); 1.07 (s, 3H); 1.14 (s, 3H); 1.17 (m, 1H); 1.25 (s, 1H); 1.52−1.61 (m, 2H); 1.70−1.75 (m, 2H); 1.98 (m, 1H); 3.83 (td, 1H, $J_1 = 10.8$ Hz, $J_2 = 4.1$ Hz); 4.42 (d, 1H, $J = 7.5$ Hz); 4.86 (dd, 1H, $J_1 = 10.2$ Hz, $J_2 = 2.2$ Hz); 5.12 (dd, 1H, $J_1 = 17.2$ Hz, $J_2 = 2.2$ Hz); 5.17 (s, 1H); 5.41 (ddd, 1H, $J_1 = 17.2$ Hz, $J_2 = 10.2$ Hz, $J_3 = 7.5$ Hz); 7.24−7.36 (m, 3H); 7.60−7.64 (m, 2H). ^{13}C NMR (δ): 18.2; 22.1; 25.5; 31.0; 31.4; 34.8; 42.0; 48.8; 51.9; 73.4; 74.5; 76.8; 88.4; 116.7; 125.5 (2C); 126.9; 127.6 (2C); 138.2; 139.6. IR (Film): 3400 (broad); 3065; 1725; 1600; 700 cm^{-1}. Anal. calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 77.19; H, 8.82; N, 4.06.

(1*S*,2*S*,2a*S*,3a*R*,5*R*,7a*S*)-2-Phenyl-1-(*trans*-1-phenyl-but-1-enyl)-5,8,8-trimethyl-1*H*,3a*H*-azeto[2,1-b][1,3]benzoxazin-2-ol (11c). Colorless oil. $[\alpha]_D^{25} = +139.5$ ($c = 1.1$, $CHCl_3$). ^{1}H NMR (δ): 0.54 (t, 3H, $J = 7.4$ Hz); 0.87−1.18 (m, 3H); 0.92 (d, 3H, $J = 6.5$ Hz); 0.97 (s, 3H); 1.23 (s, 3H); 1.44−1.50 (m, 2H); 1.59−1.79 (m, 4H); 1.97 (m, 1H); 3.60 (td, 1H, $J_1 = 10.5$ Hz, $J_2 = 4.3$ Hz); 4.04 (s, 1H); 4.55 (s, 1H); 5.22 (s, 1H); 5.59 (dd, 1H, $J_1 = 8.1$ Hz, $J_2 = 7.2$ Hz); 6.93−6.96 (m, 2H); 7.13−7.30 (m, 6H); 7.53−7.56 (m, 2H). ^{13}C NMR (δ): 14.5; 21.7; 22.1; 22.7; 25.2 (2C); 31.5; 35.4; 41.8; 44.9; 52.4; 71.9; 76.6; 77.8; 88.6; 126.7; 126.8 (2C); 127.3; 127.6 (2C); 128.1 (2C); 128.9 (2C); 133.2; 136.3; 139.3; 140.8. IR (Film): 3525 (broad); 3060; 3030; 1600; 1575; 760; 700; 615 cm^{-1}. Anal. calcd for $C_{29}H_{37}NO_2$: C, 80.70; H, 8.64; N, 3.25. Found: C, 80.59; H, 8.46; N, 3.39.

(1*S*,2*R*,2a*S*,3a*R*,5*R*,7a*S*)-2-Phenyl-1-(*trans*-1-phenyl-but-1-enyl)-5,8,8-trimethyl-1*H*,3a*H*-azeto[2,1-b][1,3]-benzoxazin-2-ol (12c). Colorless oil. $[\alpha]_D^{25} = +116.8$ ($c = 0.71$, $CHCl_3$). ^{1}H NMR (δ): 0.50 (t, 3H, $J = 7.5$ Hz); 0.79−1.19 (m, 3H); 0.99 (d, 3H, $J = 4.8$ Hz); 1.00 (s, 3H); 1.22 (s, 3H); 1.53−1.79 (m, 4H); 2.04−2.17 (m, 2H); 2.42 (m, 1H); 3.70 (td, 1H, $J_1 = 10.3$ Hz, $J_2 = 4.3$ Hz); 4.20 (s, 1H); 4.83 (s, 1H); 5.39 (t, 1H, $J = 7.4$ Hz); 5.66 (s, 1H); 7.28−7.58 (m, 10H). ^{13}C NMR (δ): 13.6; 19.9; 21.8; 22.3; 23.9; 24.7; 31.2; 35.0; 41.4; 44.1; 52.0; 71.8; 75.5; 76.5; 86.6; 126.1; 126.9 (2C); 127.1 (2C); 127.3; 127.7 (2C); 128.1 (2C); 136.0; 137.9; 139.0; 145.1. IR (film): 3510 (broad); 3060; 3030; 1600; 780; 760; 700 cm^{-1}. Anal. calcd for $C_{29}H_{37}NO_2$: C, 80.70; H, 8.64; N, 3.25. Found: C, 80.56; H, 8.77; N, 3.32.

(1*S*,2*S*,2a*S*,3a*R*,5*R*,7a*S*)-1,2-Diphenyl-5,8,8-trimethyl-1*H*,3a*H*-azeto[2,1-b][1,3]benzoxazin-2-ol (11d). Colorless solid. Mp: 121−122 °C (from pentane). $[\alpha]_D^{25} = +127.1$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (δ): 0.78 (s, 3H); 1.04 (d, 3H, $J = 6.5$ Hz); 1.04−1.11 (m, 2H); 1.29 (m, 1H); 1.31 (s, 3H); 1.62−1.69 (m, 3H); 1.81 (m, 1H); 2.12 (m, 1H); 3.74 (td, 1H, $J_1 = 10.4$ Hz, $J_2 = 4.1$ Hz); 4.23 (s, 1H); 5.06 (s, 1H); 5.51 (s, 1H); 7.02−7.17 (m, 8H); 7.34−7.36 (m, 2H). ^{13}C NMR (δ): 21.2; 22.3; 24.8; 25.0; 31.2; 35.0; 41.5; 44.5; 51.8; 71.8; 75.9; 76.2; 87.7; 126.2 (2C); 126.4; 126.7; 127.0 (4C); 127.1 (2C); 138.1; 139.8. IR (Nujol): 3520 (broad); 3070; 1600; 780; 755; 700; 670 cm^{-1}. Anal. calcd for $C_{25}H_{31}NO_2$: C, 79.54; H, 8.28; N, 3.71. Found: C, 79.70; H, 8.42; N, 3.57.

(1*S*,2*S*,2a*S*,3a*R*,5*R*,7a*S*)-2-(4-Methoxyphenyl)-1-phenyl-5.8,8-trimethyl-1*H*,3a*H*-azeto[2,1-b][1,3]benzoxazin-2-ol (11e). Colorless oil. $[\alpha]_D^{25} = +142.24$ ($c = 0.98$, $CHCl_3$). ^{1}H NMR (δ): 0.79 (s, 3H); 1.05 (d, 3H, $J = 6.4$ Hz); 1.07−1.15 (m, 2H); 1.28 (m, 1H); 1.30 (s, 3H); 1.62−1.69 (m, 3H); 1.80 (m,

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1H); 2.13 (m, 1H); 3.69 (s, 3H); 3.73 (td, 1H, J_1 = 10.0 Hz, J_2 = 4.6 Hz); 4.23 (s, 1H); 5.05 (s, 1H); 5.49 (s, 1H); 6.70 (d, 2H, J = 8.8 Hz); 7.03−7.15 (m, 5H); 7.29 (d, 2H, J = 8.8 Hz). ^{13}C NMR (δ): 21.1; 22.2; 24.6; 25.0; 31.0; 34.9; 41.4; 44.4; 51.6; 54.8; 71.7; 75.8; 75.9; 87.8; 112.4 (2C); 126.4; 126.9 (4C); 127.3 (2C); 130.4; 139.9; 158.2. IR (film): 3525 (broad); 3065; 3030; 1615; 1585; 765; 735; 700; 650; 620 cm^{-1}. Anal. calcd for $C_{26}H_{33}NO_3$: C, 76.62; H, 8.16; N, 3.44. Found: C, 76.71; H, 8.29; N, 3.56.

(1*S*,2*S*,2a*S*,3a*R*,5*R*,7a*S*)-2-(2-Furyl)-1-phenyl-5,8,8-trimethyl-1*H*,3a*H*-azeto[2,1-b][1,3]benzoxazin-2-ol (11f). Colorless solid. Mp: 148−149 °C (from hexane). $[\alpha]_D^{25}$ = +85.6 (c = 0.99, $CHCl_3$). ^{1}H NMR (δ): 0.74 (s, 3H); 0.99−1.13 (m, 2H); 1.03 (d, 3H, J = 6.5 Hz); 1.23 (s, 3H); 1.27 (m, 1H); 1.59−1.65 (m, 3H); 1.80 (m, 1H); 2.10 (m, 1H); 3.70 (td, 1H, J_1 = 10.4 Hz, J_2 = 4.3 Hz); 4.05 (broad, s, 1H); 4.98 (s, 1H); 5.50 (s, 1H); 6.08 (dd, 1H, J_1 = 3.2 Hz, J_2 = 0.6 Hz); 6.17 (dd, 1H, J_1 = 3.2 Hz, J_2 = 1.8 Hz); 7.12−7.27 (m, 6H). ^{13}C NMR (δ): 20.9; 22.2; 24.6; 24.7; 31.0; 34.8; 41.3; 44.5; 51.4; 71.6; 73.3; 74.5; 86.4; 107.4; 109.2; 126.7 (3C); 127.1 (2C); 139.9; 141.6; 151.6. IR (Nujol): 3380 (broad); 3100; 3070; 3030; 1595; 1585; 1550; 770; 735; 710; 700 cm^{-1}. Anal. calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.28; H, 8.09; N, 3.70.

(1*S*,2*S*,2a*S*,3a*R*,5*R*,7a*S*)-1-(3,4-Dimethoxyphenyl)-2-phenyl-5,8,8-trimethyl-1*H*,3a*H*-azeto[2,1-b][1,3]-benzoxazin-2-ol (11g). Colorless oil. $[\alpha]_D^{25}$ = +96.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (δ): 0.71 (s, 3H); 0.89−1.08 (m, 2H); 0.97 (d, 3H, J = 6.6 Hz); 1.22 (s, 3H); 1.25 (m, 1H); 1.50−1.65 (m, 3H); 1.72 (m, 1H); 2.06 (m, 1H); 3.56 (s, 3H); 3.64 (td, 1H, J_1 = 10.3 Hz, J_2 = 4.3 Hz); 3.70 (s, 3H); 4.16 (broad, s, 1H); 4.92 (s, 1H); 5.47 (s, 1H); 6.50−6.55 (m, 2H); 6.65 (m, 1H); 7.04−7.15 (m, 3H); 7.30−7.33 (m, 2H). ^{13}C NMR (δ): 21.4; 22.3; 24.8; 25.1; 31.2; 35.0; 41.5; 44.5; 51.8; 55.5 (2C); 71.9; 75.5; 76.4; 87.6; 109.7; 110.7; 119.4; 126.5 (2C); 126.9; 127.3 (2C); 132.7; 138.3; 147.6; 147.8. IR (film): 3535; 3450 (broad); 3065; 3030; 1610; 1590; 770; 735; 700; 650 cm^{-1}. Anal. calcd for $C_{27}H_{35}NO_4$: C, 74.11; H, 8.06; N, 3.20. Found: C, 74.22; H, 8.21; N, 3.33.

(1*S*,2*S*,2a*S*,3a*R*,5*R*,7a*S*)-2-Phenyl-1,5,8,8-tetramethyl-1*H*,3a*H*-azeto[2,1-b][1,3]benzoxazin-2-ol (11h). Colorless oil. $[\alpha]_D^{25}$ = −2.50 (c = 0.4, EtOAc). ^{1}H NMR (δ): 0.65 (d, 3H, J = 6.1 Hz); 0.90−1.04 (m, 3H); 0.92 (d, 3H, J = 6.5 Hz); 0.93 (s, 3H); 1.07 (s, 3H); 1.39−1.48 (m, 2H); 1.58 (m, 1H); 1.67 (m, 1H); 1.92 (m, 1H); 3.51 (td, 1H, J_1 = 10.4 Hz, J_2 = 4.4 Hz); 3.80 (s, 1H); 3.96 (q, 1H, J = 6.1 Hz); 5.04 (s, 1H); 7.18−7.32 (m, 3H); 7.60−7.63 (m, 2H). ^{13}C NMR (δ): 18.5; 21.1; 22.2; 24.8; 25.2; 31.2; 35.0; 41.5; 44.6; 51.3; 67.6; 71.6; 73.4; 89.1; 125.9 (2C); 126.9; 127.6 (2C); 139.4. IR (film): 3530; 3345 (broad); 3065; 3030; 1725; 1675; 1600; 1580; 765; 700 cm^{-1}. Anal. calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.29; H, 9.14; N, 4.38.

(3*R*,4a*R*,5a*S*,6*R*,7*S*,11a*S*)-6,8-Diphenyl-7-ethyl-3,11,11-trimethyl-2,3,4,4a,6,7,11,11a-octahydro-*1 H,5aH*-pyrido-[2,1-b][1,3]benzoxazin-6-ol (15). Colorless solid. Mp: 142−143 °C (from EtOH). $[\alpha]_D^{25}$ = +176.87 (c = 0.8, $CHCl_3$). ^{1}H NMR (δ): 0.42 (t, 3H, J = 7.5 Hz); 0.84 (d, 3H, J = 6.5 Hz); 0.88−1.00 (m, 3H); 1.08 (s, 3H); 1.21−1.33 (m, 3H); 1.37 (s, 3H); 1.59−1.74 (m, 4H); 3.04 (m, 1H); 3.18 (s, 1H); 3.31 (td, 1H, J_1 = 10.5 Hz, J_2 = 4.2 Hz); 4.61 (s, 1H); 6.39 (s, 1H); 7.11−7.36 (m, 8H); 7.53 (d, 2H, J = 7,3 Hz). ^{13}C NMR (δ): 13.8; 17.8; 20.2; 21.9; 25.0; 26.1; 30.9; 34.4; 40.6; 46.8; 49.1; 57.0; 74.6; 75.6; 86.1; 117.4; 125.0; 125.6 (2C); 126.3 (3C); 127.6 (3C); 128.0 (2C); 141.9; 144.5. IR (Nujol): 3560 (broad); 3040; 1620; 1590; 760; 700 cm^{-1}. Anal. calcd for $C_{29}H_{37}NO_2$: C, 80.70; H, 8.64; N, 3.25. Found: C, 80.56; H, 8.51; N, 3.23.

Synthesis of Amino Alcohols 16a−g. General Method. To a slurry of NaH (72.0 mg, 3.0 mmol) in THF (15 mL) was added a solution of the appropriate azetidin-3-ol **11a−g** (1.5 mmol) in THF (8 mL). The mixture was stirred for 25 min at room temperature and then a solution of benzyl bromide (0.27 mL, 2.25 mmol) in THF (4 mL) was added. The stirring was continued at room temperature for 70−90 h (an additional reflux for 1 h was necessary for protection of compound **11g**). The reaction was quenched by addition of water, and the product was extracted with EtOAc (4 × 25 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated under vacuum. The residue was redissolved in THF (10 mL) and slowly added to a suspension of $LiAlH_4$ (0.57 g, 15.0 mmol) and $AlCl_3$ (0.67 g, 5.0 mmol) in THF (35 mL) cooled to −10 °C. The reaction mixture was stirred at room temperature for 5 h and then heated at reflux for 2−3 h (TLC). The mixture was allowed to reach room temperature and was quenched by an addition of 10% aqueous solution of NaOH (4 mL). The mixture was filtered, the solid was washed with hot EtOAc, and the organic layer was dried over $MgSO_4$. The solvent was eliminated under vacuum, and the residue was chomatographed on silica gel using hexanes/EtOAc 8:1 as eluent.

(2*S*,3*R*)-*N*-(8-Mentholyl)-3-benzyloxy-2-vinyl-azetidine (16a). Yield 75%. Colorless oil. $[\alpha]_D^{25}$ = +14.30 (c = 1.0, $CHCl_3$). ^{1}H NMR (δ): 0.78−0.98 (m, 3H); 0.89 (d, 3H, J = 6.5 Hz); 0.94 (s, 3H); 1.00 (s, 3H); 1.08 (m, 1H); 1.39 (m, 1H); 1.53 (m, 1H); 1.63 (m, 1H); 1.90 (m, 1H); 2.96 (dd, 1H, J_1 = 7.1 Hz, J_2 = 6.1 Hz); 3.45 (dd, 1H, J_1 = 6.1 Hz, J_2 = 5.5 Hz); 3.57 (td, 1H, J_1 = 10.6 Hz, J_2 = 4.1 Hz); 3.77−3.87 (m, 2H); 4.40 (d, 1H, J = 11.7 Hz); 4.50 (d, 1H, J = 11.7 Hz); 5.06 (dd, 1H, J_1 = 10.2 Hz, J_2 = 1.2 Hz); 5.23 (dd, 1H, J_1 = 17.4 Hz, J_2 = 1.2 Hz); 5.91 (ddd, 1H, J_1 = 17.4 Hz, J_2 = 10.2 Hz, J_3 = 7.6 Hz); 7.24−7.38 (m, 5H); 8.33 (broad, s, 1H). ^{13}C NMR (δ): 18.5; 20.0; 22.0; 25.2; 30.8; 34.8; 44.0; 47.8; 50.6; 59.6; 68.3; 71.2; 72.6; 73.2; 116.3; 127.8 (3C); 128.3 (2C); 137.4; 140.1.IR (film): 3170 (broad); 3085; 3065; 3030; 1640; 790; 735; 700 cm^{-1}. Anal. calcd for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68; N, 4.08. Found: C, 77.08; H, 9.76; N, 3.98.

(2*S*, 3*R*)-*N*-(8-Mentholyl)-3-benzyloxy-3-phenyl-2-vinyl-azetidine (16b). Yield 65%. Colorless oil. $[\alpha]_D^{25}$ = −20.5 (c = 0.60, $CHCl_3$). ^{1}H NMR (δ): 0.62−0.90 (m, 3H); 0.72 (d, 3H, J = 6.5 Hz); 0.74 (s, 3H); 0.94 (s, 3H); 1.05 (m, 1H); 1.21 (m, 1H); 1.35−1.49 (m, 2H); 1.77 (m, 1H); 3.23 (d, 1H, J = 8.1 Hz); 3.40 (td, 1H, J_1 = 10.6 Hz, J_2 = 4.1 Hz); 3.78 (d, 1H, J = 8.1 Hz); 3.93 (d, 1H, J = 11.4 Hz); 3.98 (d, 1H, J = 11.4 Hz); 4.03 (d, 1H, J = 6.8 Hz); 4.64 (m, 1H); 4.85−4.96 (m, 2H); 7.03−7.28 (m, 10H); 7.87 (broad, s, 1H). ^{13}C NMR (δ): 18.2; 20.4; 22.0; 25.2; 30.8; 34.8; 44.2; 47.9; 52.3; 59.9; 65.6; 71.3; 72.3; 79.7; 117.5; 127.1 (2C); 127.4 (3C); 127.5; 128.3 (2C); 128.5 (2C); 137.4; 138.0; 138.5. IR (film): 3185 (broad); 3065; 3030; 1640; 1605; 1585; 780; 735; 710 cm^{-1}. Anal. calcd for $C_{28}H_{37}NO_2$: C, 80.15; H, 8.89; N, 3.34. Found: C, 80.33; H, 9.02; N, 3.48.

(2*S*, 3*R*)-*N*-(8-Mentholyl)-3-benzyloxy-3-phenyl-2-(*trans*-1-phenyl-but-1-enyl)-azetidine (16c). Yield 78%. Colorless oil. $[\alpha]_D^{25}$ = +41.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (δ): 0.56 (t, 3H, J = 7.4 Hz); 0.95−1.22 (m, 3H); 1.00 (d, 3H, J = 6.4 Hz); 1.08 (s, 3H); 1.18 (s, 3H); 1.34−1.49 (m, 2H); 1.65−1.87 (m, 4H); 2.12 (m, 1H); 3.50 (d, 1H, J = 8.2 Hz); 3.77 (td, 1H, J_1 = 10.4 Hz, J_2 = 4.1 Hz); 4.01 (d, 1H, J = 8.2 Hz); 4.24 (d, 1H, J = 11.9 Hz); 4.31 (d, 1H, J = 11.9 Hz); 4.61 (s, 1H); 5.43 (dd, 1H, J_1 = 8.4 Hz, J_2 = 6.8 Hz); 7.09−7.50 (m, 15H); 8.19 (broad s, 1H). ^{13}C NMR (δ): 13.5; 17.7; 20.5; 22.0; 22.1; 25.4; 30.8; 34.9; 44.1; 47.8; 51.9; 60.5; 66.1; 72.3; 72.8; 82.0; 126.3; 126.8 (2C); 127.1; 127.3; 127.6; 127.7 (2C); 128.1 (2C); 128.2 (3C); 128.6 (2C); 135.0; 135.5; 137.5; 138.4; 140.2. IR (film): 3180 (broad); 3060; 3030; 1600; 755; 730; 700 cm^{-1}. Anal. calcd for $C_{36}H_{45}NO_2$: C, 82.56; H, 8.66; N, 2.67. Found: C, 82.28; H, 8.56; N, 2.80.

(2*S*, 3*R*)-*N*-(8-Mentholyl)-3-benzyloxy-2,3-diphenyl-azetidine (16d). Yield 72%. Colorless solid. Mp: 64−65 °C (from pentane). $[\alpha]_D^{25}$ = −12.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (δ): 0.72 (s, 3H); 0.79−1.07 (m, 3H); 0.94 (d, 3H, J = 6.4 Hz); 1.20 (s, 3H); 1.27−1.42 (m, 2H); 1.60−1.70 (m, 2H); 2.04 (m, 1H); 3.50 (d, 1H, J = 8.4 Hz); 3.65 (td, 1H, J_1 = 10.4 Hz, J_2 = 4.0 Hz); 4.09−4.18 (m, 3H); 4.89 (s, 1H); 6.98−7.35 (m, 15H); 8.38 (s, 1H). ^{13}C NMR (δ): 17.6; 20.4; 22.0; 25.2; 30.6; 34.8; 44.1; 47.8; 51.6; 60.1; 65.9; 72.2; 73.0; 81.2; 126.8; 127.1; 127.3 (4C); 127.6 (3C); 127.8 (3C); 128.1 (3C); 136.4; 138.0; 138.8. IR

(Nujol): 3180 (broad); 3065; 3030; 1605; 1585; 795; 780; 735; 700 cm^{-1}. Anal. calcd for $C_{32}H_{39}NO_2$: C, 81.83; H, 8.37; N, 2.98. Found: C, 81.66; H, 8.43; N, 3.06.

(2*S*, 3*R*)-*N*-(8-Mentholyl)-3-benzyloxy-3-(4-methoxyphenyl)-2-phenyl-azetidine (16e). Yield 82%. Colorless solid. Mp: 161−162 °C (from hexanes−EtOAc). $[\alpha]_D^{25} = +10.50$ ($c = 1.0$, $CHCl_3$). ^1H NMR (δ): 0.74 (s, 3H); 0.90−1.10 (m, 2H); 0.97 (d, 3H, $J = 6.3$ Hz); 1.22 (s, 3H); 1.23 (m, 1H); 1.40−1.43 (m, 2H); 1.62−1.72 (m, 2H); 2.07 (m, 1H); 3.50 (d, 1H, $J = 7.9$ Hz); 3.65 (m, 1H); 3.68 (s, 3H); 4.12−4.20 (m, 3H); 4.88 (s, 1H); 6.73 (d, 2H, $J = 8.6$ Hz); 6.98−7.04 (m, 5 H); 7.13 (d, 2H, $J = 8.6$ Hz); 7.27−7.33 (m, 5H); 8.44 (s, 1H). ^{13}C NMR (δ): 17.8; 20.7; 22.2; 25.4; 30.9; 35.0; 44.3; 48.0; 52.0; 55.0; 60.2; 66.0; 72.5; 73.2; 81.2; 113.4 (2C); 127.0; 127.5 (4C); 127.9 (2C); 128.3 (3C); 128.6; 128.9 (2C); 138.3; 139.2; 158.8. IR (Nujol): 3130 (broad); 3070; 3035; 1615; 1585; 750; 730; 700; 670 cm^{-1}. Anal. calcd for $C_{33}H_{41}NO_3$: C, 79.32; H, 8.27; N, 2.80. Found: C, 79.50; H, 8.42; N, 2.72.

(2*S*, 3*R*)-*N*-(8-Mentholyl)-3-benzyloxy-3-(2-furyl)-2-phenyl-azetidine (16f). Yield 89%. Colorless oil. $[\alpha]_D^{25} = -37.37$ ($c = 1.0$, $CHCl_3$). ^1H NMR (δ): 0.71 (s, 3H); 0.88−1.17 (m, 3H); 0.94 (d, 3H, $J = 6.6$ Hz); 1.16 (s, 3H); 1.24−1.44 (m, 2H); 1.58−1.70 (m, 2H); 2.01 (m, 1H); 3.40 (d, 1H, $J = 7.7$ Hz); 3.65 (td, 1H, $J_1 = 10.5$ Hz, $J_2 = 4.4$ Hz); 3.92 (d, 1H, $J = 7.7$ Hz); 4.26 (d, 1H, $J = 11.6$ Hz); 4.29 (d, 1H, $J = 11.6$ Hz); 4.78 (s, 1H); 6.24 (dd, 1H, $J_1 = 3.1$ Hz, $J_2 = 1.7$ Hz); 6.43 (d, 1H, $J = 3.1$ Hz); 7.12−7.38 (m, 11H); 8.27 (s, 1H). ^{13}C NMR (δ): 17.9; 20.5; 22.1; 25.3; 30.8; 34.9; 44.1; 48.0; 53.0; 60.1; 67.0; 72.1; 72.3; 77.6; 109.9; 111.0; 127.4 (2C); 127.6; 127.7 (3C); 127.8 (2C); 128.3 (2C); 138.0; 139.2; 143.0; 150.8. IR (film): 3235 (broad): 3065; 3035; 1605; 1590; 740; 700; 695; 620 cm^{-1}. Anal. calcd for $C_{30}H_{37}NO_3$: C, 78.40; H, 8.11; N, 3.05. Found: C, 78.61; H, 8.32; N, 3.14.

(2*S*,3*R*)-*N*-(8-Mentholyl)-3-benzyloxy-3-phenyl-2-(3,4-dimethoxyphenyl)-azetidine (16g). Yield 80%. Colorless oil. $[\alpha]_D^{25} = -24.0$ ($c = 1.0$, $CHCl_3$). ^1H NMR (δ): 0.73 (s, 3H); 0.81−1.17 (m, 3H); 0.95 (d, 3H, $J = 6.6$ Hz); 1.22 (s, 3H); 1.26−1.44 (m, 2H); 1.61−1.71 (m, 2H); 2.04 (m, 1H); 3.49 (d, 1H, $J = 7.9$ Hz); 3.54 (s, 3H); 3.62 (td, 1H, $J_1 = 10.5$ Hz, $J_2 = 4.4$ Hz); 3.75 (s, 3H); 4.11 (d, 1H, $J = 11.0$ Hz); 4.16 (d, 1H, $J = 11.0$ Hz); 4.17 (d, 1H, $J = 7.9$ Hz); 4.81 (s, 1H); 6.30 (m, 1H); 6.56−6.60 (m, 2H); 7.13−7.43 (m, 10H); 8.20 (s, 1H). ^{13}C NMR (δ): 17.9; 20.5; 22.1; 25.4; 30.8; 34.9; 44.3; 48.0; 51.6; 55.5 (2C); 60.2; 66.2; 72.4; 72.9; 81.5; 109.8; 111.2; 120.2; 127.4; 127.6 (3C); 127.8 (2C); 128.2 (2C); 128.3 (2C); 131.9; 136.9; 138.2; 147.9; 148.0. IR (film): 3185 (broad); 3065; 3030; 1610; 1590; 765; 735; 700 cm^{-1}. Anal. calcd for $C_{34}H_{43}NO_4$: C, 77.09; H, 8.18; N, 2.64. Found: C, 76.88; H, 8.32; N, 2.78.

Elimination of the Menthol Appendage. General Method. A solution of the amino menthol derivative (1.48 mmol) and PPC (2.56 g, 11.9 mmol) in CH_2Cl_2 and 3 Å molecular sieves (1.5 g) was stirred under argon atmosphere until the oxidation was finished (TLC, 5−12 h). The solvent was eliminated under reduced pressure, the residue was dissolved in 10% aqueous solution of NaOH until pH = 12, and the resulting solution was extracted with $CHCl_3$ (5 × 25 mL). The organic layer was washed with brine, dried over $MgSO_4$, and the solvents were evaporated under vacuum. The residue was redissolved in a mixture of THF−MeOH−H_2O 2:1:1 (20 mL), cooled to 0 °C, and then KOH (4.0 g) was added. The solution was stirred at room temperature for 6−8 days. After elimination of the solvents under vacuum, H_2O (30 mL) was added, and the mixture was extracted with $CHCl_3$ (4 × 25 mL). The organic layer was washed with H_2O, dried over $MgSO_4$, and the solvent eliminated under vacuum. The residue was redissolved in EtOAc (10 mL), and diisopropyl-ethylamine (0.7 mL, 3.6 mmol) and tosyl chloride (0.4 g, 1.81 mmol) were added. The mixture was stirred at room temperature for 3 days and then was acidified by addition of 15% aqueous HCl (60 mL). The mixture was extracted with EtOAc (4 × 25 mL), washed with H_2O, dried over $MgSO_4$, and the solvent eliminated under vacuum. The residue was chomatographed on silica gel using hexanes/EtOAc 20:1 as eluent.

(2*S*,3*R*)-*N*-Tosyl-3-benzyloxy-2-vinyl-azetidine (17a). Yield 37%. Colorless oil. $[\alpha]_D^{25} = +94.64$ ($c = 0.56$, EtOAc). ^1H NMR (δ): 2.47 (s, 3H); 3.36 (dd, 1H, $J_1 = 7.7$ Hz, $J_2 = 6.3$ Hz); 3.82 (dd, 1H, $J_1 = 7.7$ Hz, $J_2 = 6.3$ Hz); 3.95 (dt, 1H, $J_1 = 6.3$ Hz, $J_2 = 5.3$ Hz); 4.07 (dd, 1H, $J_1 = 5.3$ Hz, $J_2 = 6.8$ Hz); 4.34 (d, 1H, $J = 11.7$ Hz); 4.40 (d, 1H, $J = 11.7$ Hz); 5.22 (d, 1H, $J = 10.4$ Hz); 5.34 (d, 1H, $J = 17.1$ Hz); 5.87 (ddd, 1H, $J_1 = 17.1$ Hz, $J_2 = 10.4$ Hz, $J_3 = 6.8$ Hz); 7.16−7.25 (m, 2H); 7.26−7.33 (m, 3H); 7.37 (d, 2H, $J = 8.1$ Hz); 7.70 (d, 2H, $J = 8.1$ Hz). ^{13}C NMR (δ): 21.7; 55.2; 71.5; 72.7; 72.9; 118.6; 127.8 (2C); 128.2; 128.5 (4C); 129.7 (2C); 131.6; 135.0; 136.8; 144.1. IR (film): 3065; 3030; 1645; 1600; 815; 750; 700; 670; 610 cm^{-1}. Anal. calcd for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08. Found: C, 66.22; H, 6.08; N, 4.21.

(2*S*,3*R*)-*N*-Tosyl-3-benzyloxy-3-phenyl-2-vinyl-azetidine (17b). Yield 45%. Colorless oil. $[\alpha]_D^{25} = +35.40$ ($c = 1.40$, EtOAc). ^1H NMR (δ): 2.51 (s, 3H); 3.72 (d, 1H, $J = 8.5$ Hz); 3.99 (d, 1H, $J = 11.4$ Hz); 4.15 (d, 1H, $J = 11.4$ Hz); 4.33 (d, 1H, $J = 8.5$ Hz); 4.38 (d, 1H, $J = 6.9$ Hz); 5.03 (d, 1H, $J = 10.0$ Hz); 5.11−5.31 (m, 2H); 7.03 (m, 2H); 7.27−7.45 (m, 10H); 7.77 (d, 2H, $J = 8.1$ Hz). ^{13}C NMR (δ): 21.7; 57.2; 66.2; 76.0; 79.8; 120.1; 127.0 (3C); 127.4 (2C); 127.8; 128.4; 128.6 (2C); 128.7 (3C); 129.8 (2C); 130.9; 133.0; 136.1; 137.2; 144.2. IR (film): 3060; 3030; 1600; 780; 735; 755; 710; 670; 610 cm^{-1}. Anal. calcd for $C_{25}H_{25}NO_3S$: C, 71.57; H, 6.01; N, 3.34. Found: C, 71.72; H, 5.89; N, 3.36.

(2*S*,3*R*)-*N*-Tosyl-3-benzyloxy-3-phenyl-2-(*trans*-1-phenyl-but-1-enyl)-azetidine (17c). Yield 28%. Colorless oil. $[\alpha]_D^{25} = +32.25$ ($c = 0.40$, EtOAc). ^1H NMR (δ): 0.61 (t, 3H, $J = 7.4$ Hz); 1.62−1.75 (m, 2H); 2.47 (s, 3H); 3.85 (d, 1H, $J = 8.7$ Hz); 3.95 (d, 1H, $J = 11.8$ Hz); 4.11 (d, 1H, $J = 11.8$ Hz); 4.22 (d, 1H, $J = 8.7$ Hz); 4.83 (s, 1H); 5.73 (t, 1H, $J = 7.3$ Hz); 6.68−6.71 (m, 2H); 6.92−6.96 (m, 2H); 7.13−7.34 (m, 11H); 7.38 (d, 2H, $J = 8.1$ Hz); 7.80 (d, 2H, $J = 8.1$ Hz). ^{13}C NMR (δ): 13.8; 21.6; 21.7; 57.0; 66.2; 77.5; 81.4; 126.6; 127.0 (2C); 127.4 (2C); 127.5; 127.6 (2C); 127.9 (3C); 128.2 (2C); 128.7 (2C); 128.9 (2C); 129.7 (2C); 131.6; 132.5; 135.4; 136.2; 137.5; 137.7; 144.2. IR (film): 3060; 3030; 1600; 760; 740; 700; 665; 620 cm^{-1}. Anal. calcd for $C_{33}H_{33}NO_3S$: C, 75.69; H, 6.35; N, 2.67. Found: C, 75.81; H, 6.39; N, 2.48.

(2*S*,3*R*)-*N*-Tosyl-3-benzyloxy-2,3-diphenyl-azetidine (17d). Yield 34%. Colorless solid. Mp: 159−160 °C (from hexanes−EtOAc). $[\alpha]_D^{25} = +115.6$ ($c = 0.95$, EtOAc). ^1H NMR (δ): 2.50 (s, 3H); 3.84 (d, 1H, $J = 8.4$ Hz); 4.02 (d, 1H, $J = 11.4$ Hz); 4.14 (d, 1H, $J = 11.4$ Hz); 4.46 (d, 1H, $J = 8.4$ Hz); 5.04 (s, 1H); 7.02−7.31 (m, 15H); 7.38 (d, 2H, $J = 8.2$ Hz); 7.73 (d, 2H, $J = 8.2$ Hz). ^{13}C NMR (δ): 21.6; 56.9; 66.5; 77.2; 81.2; 127.2 (2C); 127.3 (2C); 127.5 (4C); 127.6; 127.8; 127.9; 128.0 (2C); 128.3 (2C); 128.8 (2C); 129.7 (2C); 130.7; 135.0; 135.3; 137.3; 144.3. IR (Nujol): 3055; 3035; 1600; 770; 760; 745; 720; 700; 680; 660 cm^{-1}. Anal. calcd for $C_{29}H_{27}NO_3S$: C, 74.17; H, 5.80; N, 2.98. Found: C, 74.36; H, 5.69; N, 2.80.

(2*S*,3*R*)-*N*-Tosyl-3-benzyloxy-3-(4-methoxyphenyl)-2-phenyl-azetidine (17e). Yield 25%. Colorless solid. Mp: 163−164 °C (from hexanes−EtOAc). $[\alpha]_D^{25} = +100.0$ ($c = 0.60$, EtOAc). ^1H NMR (δ): 2.50 (s, 3H); 3.72 (s, 3H); 3.80 (d, 1H, $J = 8.4$ Hz); 3.99 (d, 1H, $J = 11.5$ Hz); 4.11 (d, 1H, $J = 11.5$ Hz); 4.42 (d, 1H, $J = 8.4$ Hz); 5.01 (s, 1H); 6.68 (d, 2H, $J = 8.8$ Hz); 7.04−7.11 (m, 8H); 7.27−7.30 (m, 4H); 7.38 (d, 2H, $J = 8.1$ Hz); 7.72 (d, 2H, $J = 8.1$ Hz). ^{13}C NMR (δ): 21.6; 55.1; 57.0; 66.3; 77.4; 81.0; 113.3 (2C); 127.3; 127.5 (2C); 127.6 (4C); 127.7; 128.3 (2C); 128.6 (2C); 128.7 (3C); 129.6 (2C); 130.8; 135.2; 137.4; 144.2; 159.1. IR (Nujol): 3055; 3030; 1615; 1600; 1580; 765; 745; 730; 700; 680; 660 cm^{-1}. Anal. calcd for $C_{30}H_{29}NO_4S$: C, 72.12; H, 5.85; N, 2.80. Found: C, 72.28; H, 5.80; N, 2.66.

(2*S*,3*R*)-*N*-Tosyl-3-benzyloxy-3-(2-furyl)-2-phenyl-azetidine (17f). Yield 35%. Colorless solid. Mp: 160−161 °C (from hexanes−EtOAc). $[\alpha]_D^{25} = +83.75$ ($c = 0.56$, EtOAc). ^1H NMR (δ): 2.50 (s, 3H); 3.80 (d, 1H, $J = 8.4$ Hz); 4.10 (d,

1H, J = 11.4 Hz); 4.22 (d, 1H, J = 11.4 Hz); 4.32 (d, 1H, J = 8.4 Hz); 5.04 (s, 1H); 6.22 (s, 2H); 7.07−7.32 (m, 11H); 7.38 (d, 2H, J = 8.1 Hz); 7.73 (d, 2H, J = 8.1 Hz). ^{13}C NMR (δ): 21.6; 57.2; 67.1; 76.2; 77.2; 110.0; 111.2; 127.0 (2C); 127.6 (3C); 127.7; 127.8; 128.0; 128.3 (2C); 128.6 (2C); 129.7 (2C); 131.1; 135.3; 137.1; 143.3; 144.2; 149.2. IR (Nujol): 3060; 3030; 1600; 755; 740; 700; 675; 610 cm^{-1}. Anal. calcd for $C_{27}H_{25}N_4S$: C, 70.57; H, 5.48; N, 3.05. Found: C, 70.42; H, 5.31; N, 3.18.

(2*S*,3*R*)-*N*-Tosyl-3-benzyloxy-3-phenyl-2-(3,4-dimethoxyphenyl)-azetidine (17g). Yield 31%. Colorless solid. Mp: 135−136 °C (from hexanes−EtOAc). $[\alpha]_D^{25}$ = +92.2 (c = 0.45, EtOAc). ^{1}H NMR (δ): 2.49 (s, 3H); 3.54 (s, 3H); 3.77 (s, 3H); 3.80 (d, 1H, J = 8.4 Hz); 4.02 (d, 1H, J = 11.4 Hz); 4.13 (d, 1H, J = 11.4 Hz); 4.46 (d, 1H, J = 8.4 Hz); 4.94 (s, 1H); 6.32 (d, 1H, J = 1.8 Hz); 6.58 (d, 1H, J = 8.2 Hz); 6.66 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.8 Hz); 7.05−7.33 (m, 10H); 7.37 (d, 2H, J = 8.1 Hz); 7.70 (d, 2H, J = 8.1 Hz). ^{13}C NMR (δ): 21.6; 55.4; 55.6; 56.5; 66.6; 77.1; 81.4; 109.8; 110.4; 120.1; 127.4 (2C); 127.6 (3C); 127.8; 128.0; 128.1 (2C); 128.3 (2C); 128.7 (2C); 129.6 (2C); 130.9; 135.4; 137.2; 144.2; 148.0; 148.5. IR (Nujol): 3060; 3025; 1610; 1600; 770; 755; 740; 700; 665; 615 cm^{-1}. Anal. calcd for $C_{31}H_{31}NO_5S$: C, 70.30; H, 5.90; N, 2.64. Found: C, 70.42; H, 5.87; N, 2.79.

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Supporting Information Available: Full experimental conditions and characterization data for compounds **4**, **6**−**9**, **10b**, **10c**, **10e**−**h**, **16a**−**g**, and **17a**−**g**, copies of NOESY experiments for **11a** and **12a**, ORTEP representation of X-ray structures of **11b**, **16e**, and **17d**, and structures and coordinates of conformers **10a**−**A** and **10a**−**B** optimized at UHF/3-21G* and **10d**−**A** and **10d**−**B** optimized at UHF/PM3. This material is available free of charge via the Internet at http://pubs.acs.org.

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