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Lewis acid mediated diastereoselective keto-ene cyclization on chiral perhydro-1,3-benzoxazines: synthesis of enantiopure *cis*-3,4-disubstituted 3-hydroxypyrrolidines

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ABSTRACT

Chiral 2-acyl-3-allyl-perhydro-1,3-benzoxazines derived from (−)-8-aminomenthol were easily cyclized in the presence of Lewis acids at 0 °C. The diastereoselectivity of the cyclization was dependent on the nature of the Lewis acid. The cyclization compounds can be transformed into enantiopure *cis*-3,4-disubstituted 3-hydroxypyrrolidines by ring opening of the N,O-acetal moiety and subsequent elimination of the menthol appendage.

1. Introduction

The 3-hydroxypyrrolidine subunit is found in a wide range of naturally occurring alkaloids[1] and optically active 3-pyrrolidinols are constituents of several bioactive compounds or they can be used as intermediates for the synthesis of other interesting biologically active molecules.[2] Consequently, several approaches to the stereoselective synthesis of 3-hydroxypyrrolidine and its derivatives have appeared.[3,4] Nevertheless, general and effective methods for the synthesis of enantioselective *cis*-4-substituted 3-hydroxypyrrolidines are noticeably rare.[5]

We have recently reported the utility of chiral perhydro-1,3-benzoxazines derived from (−)-8-aminomenthol in the synthesis of *cis*-3,4-disubstituted pyrrolidines by olefin-ene[6] and carbonyl-ene[7] intramolecular cyclizations. The thermally induced intramolecular carbonyl-ene cyclization of chiral 2-acyl-3-allyl-1,3-perhydrobenzoxazines took place in smooth conditions and total diastereoselectivity with formyl derivatives, but the cyclization of keto derivatives required high temperatures and the reaction showed a modest degree of stereoselection. Ketones are less reactive than aldehydes due to both steric and electronic effects. However, it is known that ene adducts can be isolated in smooth conditions in the intramolecular ene reaction of unsaturated ketones in the presence of Lewis acids.[8] Herein, we report on a versatile diastereoselective synthesis of enantiopure *cis*-4-substituted 3-hydroxypyrrolidines by Lewis acid induced intramolecular keto-ene[9,10] reactions on *2-acyl-3-allyl-substituted 1,3-perhydrobenzoxazines*.

2. Results and discussion

The starting chiral perhydro-1,3-benzoxazines were synthesized as summarized in Scheme 1. Compounds **3b**–**e** were prepared as single diastereomers in good to excellent yields by condensation of (−)-8-aminomenthol[11] with freshly prepared substituted aryl glyoxals[12] and subsequent alkylation with prenyl bromide of the resulting N-unsubstituted perhydrobenzoxazines. Compound **3f** was prepared by condensation of phenylglyoxal with the amino alcohol **2**, which was obtained by condensation of (−)-8-aminomenthol with *trans*-β-methylcinnamaldehyde[13] and reduction of the resulting perhydrobenzoxazine with aluminum hydride in THF. The isopropylketone **3h** was obtained by treatment of the Weinreb

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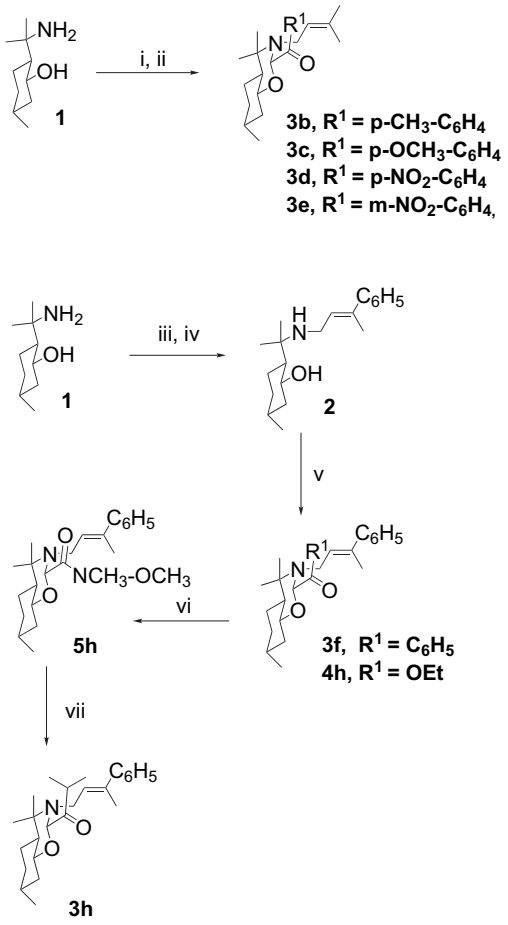
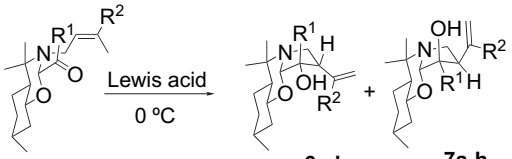
amide **5h** with isopropylmagnesium chloride, which was obtained by reaction of the ester **4h** with N,O-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride in THF. The ester **4h** was prepared by condensation of the amino alcohol **2** with ethyl glyoxylate. The synthesis of the perhydrobenzoxazines **3a** and **3g** has been previously described.[7]



Scheme 1. *Reagents and conditions*: (i) ArCOCHO, CH_2Cl_2, rt. (ii) Prenyl bromide, K_2CO_3, acetonitrile, rt, **3b** (82%), **3c** (87%), **3d** (66%), **3e** (68%). (iii) *trans*-3-methylcinnamaldehyde, CH_2Cl_2, rt. (iv) $LiAlH_4$, $AlCl_3$, THF, 0 °C, 88%. (v) PhCOCHO or EtO_2C-CHO, toluene, Dean–Stark, reflux, **3f** (52%), **4h** (60%). (vi) MeNHOMe·HCl, *i*-PrMgCl, THF, −20 °C to room temperature. (vii) *i*-PrMgCl, THF, rt, 61% from **4h**.

Keto-ene cyclization of ketones **3a**–**h** was tested under the influence of some Lewis acids of different hardness and the results are summarized in Scheme 2 and Table 1.



3a, R^1 = C_6H_5, R^2 = CH_3
3b, R^1 = p-CH_3-C_6H_4, R^2 = CH_3
3c, R^1 = p-OCH_3-C_6H_4, R^2 = CH_3
3d, R^1 = p-NO_2-C_6H_4, R^2 = CH_3
3e, R^1 = m-NO_2-C_6H_4, R^2 = CH_3
3f, R^1 = C_6H_5, R^2 = C_6H_5
3g, R^1 = ^{i}Pr, R^2 = CH_3
3h, R^1 = ^{i}Pr, R^2 = C_6H_5

Scheme 2. Diastereoselective keto-ene cyclization of compounds **3a**–**h**.

Table 1
Keto-ene reaction of **3a**–**h** in the presence of different Lewis acids

Entry	Ketone	Lewis acid (equiv)	Yield[a] (%)	Products[b] (ratio)
1	**3a**	$MgBr_2$ (2.0)[c]	90	**6a** (77), **7a** (23)
2	**3a**	$ZnCl_2$ (2.0)[c]	91	**6a** (79), **7a** (21)
3	**3a**	$BF_3{\cdot}OEt_2$ (2.0)[c]	34	**6a** (81), **7a** (19)
4	**3a**	$EtAlCl_2$ (2.0)[d]	70	**6a** (90), **7a** (10)
5	**3a**	Et_2AlCl (1.5)[d]	93	**6a** (96), **7a** (4)
6	**3a**	Me_2AlCl (1.5)[d]	94	**6a** (96), **7a** (4)
7	**3a**	$SnCl_4$ (1.5)[d]	81	**6a** (18), **7a** (82)
8	**3b**	Me_2AlCl (1.5)[d]	92	**6b** (91), **7b** (9)
9	**3b**	$SnCl_4$ (1.5)[d]	83	**6b** (20), **7b** (80)
10	**3c**	Et_2AlCl (1.5)[d]	93	**6c** (>97)
11	**3c**	$SnCl_4$ (1.5)[d]	76	**6c** (10), **7c** (90)
12	**3d**	Me_2AlCl (1.5)[d]	93	**6d** (90), **7d** (10)
13	**3d**	$SnCl_4$ (1.5)[d]	85	**6d** (85), **7d** (25)
14	**3e**	Me_2AlCl (1.5)[d]	90	**6e** (87), **7e** (13)
15	**3e**	$SnCl_4$ (1.5)[d]	81	**6e** (56), **7e** (44)
16	**3f**	Et_2AlCl (1.5)[d]	95	**6f** (96), **7f** (4)
17	**3f**	$SnCl_4$ (1.5)[d]	90	**6f** (21), **7f** (79)
18	**3g**	Me_2AlCl (1.5)[d]	92	**6g** (85), **7g** (15)
19	**3g**	$SnCl_4$ (1.5)[d]	84	**6g** (30), **7g** (70)
20	**3h**	Et_2AlCl (1.5)[d]	93	**6h** (83), **7h** (17)
21	**3h**	$SnCl_4$ (1.5)[d]	88	**6h** (14), **7h** (86)

[a] Chemical yields refer to pure compounds after column chromatography.
[b] Determined by ^{1}H NMR on the reaction mixtures.
[c] Et_2O was used as solvent.
[d] CH_2Cl_2 was used as solvent.

Different Lewis acids were initially explored using the phenylketone **3a**. In the presence of 2 equiv of $MgBr_2$ or $ZnCl_2$ in Et_2O, **3a** gave only two of the four possible ene adducts with an excellent yield and moderate stereoselectivity (entries 1 and 2 in Table 1). In contrast, in the presence of $BF_3{\cdot}OEt_2$ stereoselectivity was similar but the chemical yield was poor (entry 3). In these conditions significant amounts (30%) of oxetane **8** (Fig. 1) were isolated. This compound was presumably formed via a stepwise cyclization (Fig. 1).[14]

The use of aluminum derivatives as Lewis acids in the keto-ene cyclization improved the diastereomeric ratios (entries 4, 5, and 6). The best results were obtained when 1.5 equiv of Me_2AlCl or Et_2AlCl in CH_2Cl_2 were used instead of the stronger Lewis acid $EtAlCl_2$ (compare entries 5 and 6 vs 4). In these conditions unsaturated aromatic ketones **3a**–**f** (entries 5, 6, 8, 10, 12, 14, and 16) and aliphatic ketones **3g**, **h** (entries 18 and 20) reacted with high diastereoselectivity leading to a mixture of two hydroxypyrrolidine derivatives **6a**–**h** and **7a**–**h** in excellent yields. Electron-withdrawing nitro groups (entries 12 and 14) and electron-donor methoxy groups attached at the phenyl group of the aromatic ketones were tolerated (entry 10). The diastereoselectivity in cyclization of isopropyl ketones **3g** and **3h** (entries 18 and 20) was slightly lower than that observed for aromatic ketones **3a**–**f**.

Interestingly, when the cyclization was carried out in CH_2Cl_2 at 0 °C in the presence of $SnCl_4$ and larger reaction times, the stereoselection was reversed and the diastereoisomers **7a**–**c**,**f**–**h** were obtained as majority products (entries 7, 9, 11, 17, 19, and 21). The chemical yields and diastereoselectivity were lower when reaction was carried out using $SnCl_4$ than in the presence of Me_2AlCl or Et_2AlCl. An exception to this behavior was the cyclization of ketones

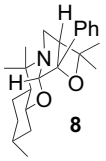


Figure 1.

3d and **3e** bearing a nitro group in the aromatic ring (entries 13 and 15). However, the 3-hydroxypyrrolidine derivatives **7d** and **7e** can be obtained as majority products in a thermally induced keto-ene cyclization. In this way, the heating of **3d** or **3e** in refluxing acetonitrile for 1.5 h, led to **6d** and **7d** in a ratio of 23:77 (92% yield) and **6e** and **7e** in a ratio of 25:75 (86% yield), respectively.

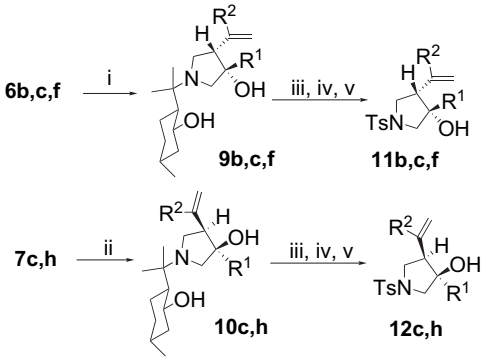
It is known that the nature of the Lewis acid can affect the reactivity and simple diastereoselectivity in a carbonyl-ene reaction.[15] In our case, it is noteworthy that the carbonyl-ene cyclization of **3a**–**h** showed complete simple diastereoselectivity for the formation of the *cis*-3,4-disubstituted products. However, the induced diastereoselectivity is dramatically affected by the nature of the Lewis acid.

Probably, the difference in the induced diastereoselectivity observed by changing the Lewis acid from tin(IV) chloride to aluminum reagents is due to their acid–base nature. Me_2AlCl is a strong Lewis acid but it is also a Bronsted base due to the basic alkyl groups.[16] The alcohol/Me_2AlCl complex intermediate formed in the cyclization reaction decomposes rapidly to give methane and an aluminum alkoxide making the cyclization irreversible. On the other hand, $SnCl_4$ behaves only as Lewis acid and in the reaction conditions, cyclization is reversible. An ^1H NMR study of the cyclization course of **3a** in the presence of $SnCl_4$ shows that at 60 min of reaction (ca. 85% conversion) a mixture 36:64 of products **6a**:**7a** was formed. After 3 h (100% of conversion) the ratio of the reaction products **6a**:7**a** changed to 23:77 and to 18:82 after 8 h of reaction time. This behavior is not observed in the reaction of **3a** in the presence of Me_2AlCl. The ratio of the products **6a**:**7a** remains invariable with the reaction time. On the other hand, the isolated diastereomer **6a** was transformed into a mixture of **6a**:**7a** in a ratio of 34:65 by stirring in CH_2Cl_2 at 0 °C for 6 h in the presence of 1.5 equiv of $SnCl_4$, whereas the diastereomer **7a** remained unchanged in the same conditions. Neither **6a** nor **7a** was interconverted when Me_2AlCl was used.

From the experimental results, it suggested that the energy potential of this cyclization reaction can be described as Scheme 3. The product **6a** is kinetic product due to lower activation energy, while product **7a** is thermodynamic product with higher stability. For the aluminum complex, it is not only a Lewis acid but also a strong Bronsted base. The kinetic product **6a** rapidly decomposed to methane and aluminum alkoxide. This makes the pathway I irreversible. So the product **6a** is major product with aluminum as Lewis acid. And tin complex acts only as Lewis acid, the pathway I is reversible. So the thermodynamic product **7a** was obtained as major product at the end while increasing the experimental time.

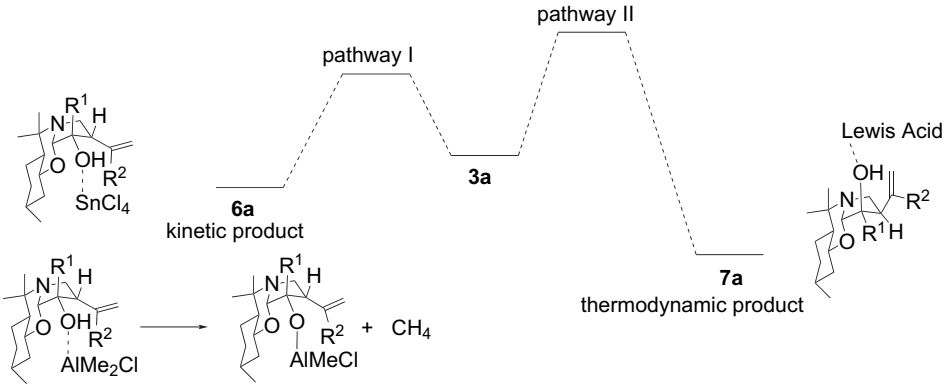
Diastereoisomers formed in each reaction were separated by flash chromatography and their stereochemistry was assigned on the basis of NOESY experiments for compounds **6b**–**d**, **6h**, and **7b**–**d**. On the other hand, the hydrogen (H-2) attached to the carbon that supports the vinyl group in adducts **7** resonates downfield of the same proton in diastereomers **6** (ca. 0.6 ppm in adducts derived from aromatic ketones and 0.20–0.35 ppm in adducts derived from isopropyl ketones). The resonance for the hydrogen H-9a attached to the N,O-acetalic carbon is shifted upfield (ca. 0.15 ppm) in adducts **7** with respect to the same proton in compounds **6**, except for adducts **6g** and **7g**, which have the same chemical shift. This general trend allowed the assignation of the stereochemistry for all these compounds.

The transformation of some ene adducts into the final *cis*-3,4-disubstituted-3-hydroxypyrrolidines was carried out in two steps as depicted in Scheme 4.



Scheme 4. *Reagents and conditions*: (i) $LiAlH_4$, $AlCl_3$, THF, −10 °C, **9b** (92%), **9c** (95%), **9f** (90%). (ii) $NaBH_3CN$, MeOH, HCl 0.1 M (pH ~ 4), 60 °C, **10c** (86%), **10h** (85%). (iii) PCC, CH_2Cl_2, 4 Å molecular sieves, rt. (iv) KOH, H_2O/MeOH/THF, rt. (v) TsCl, *i*-Pr_2NEt, AcOEt, rt, **11b** (54%), **11c** (46%), **11f** (50%), **12c** (52%), **12h** (46%).

Treatment of adducts **6b**,**c**,**f** with aluminum hydride in THF at −10 °C for 10 min led to amino alcohols **9b**,**c**,**f** in good yields. In the same conditions, adducts **7c**,**h** provided alcohols **10c**,**h**, in poor chemical yields. Better yields were obtained when the reductive ring opening of the N,O-acetal moiety was carried out by treatment with sodium cyanoborohydride in acidic media.[17] The elimination of the menthol appendage was carried out by oxidation with PCC of the amino alcohols to the aminomenthone derivatives, followed by elimination with a solution of KOH in THF/MeOH/H_2O[18] leading to the final enantiopure 3-hydroxypyrrolidines in moderate yields. These compounds were isolated and characterized as *N*-tosyl derivatives **11b**,**c**,**f** and **12c**,**h** by treatment with tosyl chloride and diisopropylethylamine in ethyl acetate. The absolute stereochemistry of compound **11f** was established by X-ray diffraction analysis,[19] corroborating the absolute configuration of the ene-cyclization product **6f**. As expected, the 3-hydroxypyrrolidines **11c** and **12c** were enantiomers.



Scheme 3.

3. Conclusion

In summary, this paper describes an efficient access to enantiopure *cis*-3,4-disubstituted 3-hydroxypyrrolidines through Lewis acid induced intramolecular carbonyl-ene cyclization reaction of 2-acyl-3-allyl-perhydro-1,3-benzoxazine derivatives.

A dramatic changeover in the diastereoselectivity of the cyclization was observed by changing the Lewis acid from aluminum reagents to tin(IV) chloride, which permits us to obtain both enantiomers of the final product by the judicious choice of the Lewis acid employed starting from the same perhydrobenzoxazine.

4. Experimental

4.1. General

All reactions were carried out in anhydrous solvents under an argon atmosphere and in oven-dried glassware. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were registered in $CDCl_3$ as solvent and chemical shifts are given relative to TMS as an internal reference. Specific rotations were determined on a digital polarimeter using a Na lamp and concentration is given in g per 100 mL. Melting points were determined in open capillary tubes and are uncorrected. Solvents were dried by standard methods. TLC was performed on glass-backed plates coated with silica gel 60 with F254 indicator; the chromatograms were visualized under UV light and/or by staining with a Ce/Mo reagent. Flash chromatography was carried out on silica gel 60 (230–240 mesh).

Compounds **3a**, **3g**, **6a**, **6g**, **7a**, and **7g** have been previously described.[7]

4.2. (1*R*,2*S*,5*R*)-5-Methyl-2-[1-[(*E*)-3-phenylbut-2-enylamino]-1-methylethyl]-cyclohexanol (2)

Dry $AlCl_3$ (2.0 g, 15.0 mmol) was added, in portions, to a suspension of $LiAlH_4$ (1.71 g, 45.0 mmol) in anhydrous THF (40 mL) cooled to −10 °C. The mixture was stirred for 15 min at −10 °C and a solution of the benzoxazine obtained by condensation of (−)-8-aminomenthol and *trans*-β-methylcinnamaldehyde[13] (4.5 g, 15.0 mmol) in dry THF (25 mL) was slowly added. The reaction mixture was stirred for 10 min at 0 °C and quenched by the addition of a 10% aqueous solution of NaOH (4.0 mL). The resulting mixture was filtered, the solid was washed with hot EtOAc, and the organic layer was dried over anhydrous $MgSO_4$. The solvent was eliminated under reduced pressure and the residue was chromatographed on silica gel using a mixture of hexane/EtOAc 3:1 as eluent. Yield: 88%. Colorless solid. Mp: 106–107 °C (from hexane). $[\alpha]_D^{25}$ −26.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ: 0.88–1.9 (m, 5H); 0.91 (d, 3H, *J*=6.5 Hz); 1.15 (s, 3H); 1.17 (s, 3H); 1.30 (m, 1H); 1.42 (m, 1H); 1.61–1.69 (m, 2H); 1.95 (m, 1H); 2.05 (s, 3H); 3.37 (dd, 1H, J_1=12.8, Hz, J_2=6.8 Hz); 3.43 (dd, 1H, J_1=12.8, Hz, J_2=6.8 Hz); 3.63 (td, 1H, J_1=10.4 Hz, J_2=4.0 Hz); 5.79 (t, 1H, *J*=6.8 Hz); 7.19–7.38 (m, 5H). ^{13}C NMR δ: 15.8 (CH_3); 21.4 (CH_3); 22.0 (CH_3); 25.6 (CH_2); 26.1 (CH_3); 30.9 (CH); 34.9 (CH_2); 39.3 (CH_2); 44.3 (CH_2); 49.6 (CH); 56.6 (C); 72.4 (CH); 125.3 (CH); 125.5 (2 CH); 126.9 (CH); 128.0 (2 CH); 137.1 (C); 142.8 (C). IR (Nujol dispersion): 3260 (broad), 3040, 1595, 750, 700 cm^{-1}. HRMS: calcd for $C_{20}H_{32}NO$ $[M+H]^+$ 302.2484, found 302.2467.

4.3. Synthesis of ketones 3b, 3c, 3d, and 3e

A mixture of (−)-8-aminomenthol (2.5 g, 15 mmol) and the appropriate arylglioxal derivative (15 mmol) in dichloromethane (60 mL) was stirred for 24 h at room temperature. The solvent was removed under vacuum and the residue was dissolved in dry acetonitrile (8 mL). Potassium carbonate (4.3 g, 31.0 mmol) and prenyl bromide (2.5 mL, 21.2 mmol) were added and the mixture was stirred at room temperature for 120–150 h. The reaction mixture was diluted with ethyl acetate and the solid was separated by filtration and washed with hot ethyl acetate (3×25 mL). The solvents were evaporated under vacuum and the residue was purified by flash chromatography on silica gel, using a mixture of hexane/EtOAc 25:1 as eluent.

*4.3.1. (2S,4aS,7R,8aR)-[3-(3-Methylbut-2-enyl)-4,4,7-trimethyloctahydro-2H-benzo[e][1,3]oxazin-2-yl]-p-tolyl ketone (**3b**).* Yield: 82%. Colorless oil. $[\alpha]_D^{25}$ +4.3 (*c* 2.4, $CHCl_3$). ^{1}H NMR δ: 0.86–1.11 (m, 2H); 0.94 (d, 3H, *J*=6.4 Hz); 1.18 (s, 3H); 1.23 (m, 1H); 1.30 (s, 3H); 1.36 (s, 3H); 1.40 (s, 3H); 1.43–1.58 (m, 2H); 1.63 (m, 1H); 1.72 (m, 1H); 2.03 (m, 1H); 2.37 (s, 3H); 3.18 (dd, 1H, J_1=16.6 Hz, J_2=6.1 Hz); 3.31 (dd, 1H, J_1=16.6 Hz, J_2=6.1 Hz); 3.56 (td, 1H, J_1=10.5 Hz, J_2=4.0 Hz); 4.75 (t, 1H, *J*=6.1 Hz); 5.64 (s, 1H); 7.24 (d, 2H, *J*=8.1 Hz); 8.10 (d, 2H, *J*=8.1 Hz). ^{13}C NMR δ: 17.5 (CH_3); 19.9 (CH_3); 21.5 (CH_3); 22.1 (CH_3); 24.9 (CH_2); 25.3 (CH_3); 26.7 (CH_3); 31.2 (CH); 34.8 (CH_2); 41.2 (CH_2); 42.3 (CH_2); 46.1 (CH); 57.4 (C); 76.1 (CH); 88.5 (CH); 126.2 (CH); 128.4 (2 CH); 129.2 (2 CH); 130.4 (C); 132.9 (C); 143.2 (C); 194.1(C). IR (Neat): 2925, 2870, 1700, 1610, 755, 735, 665 cm^{-1}. HRMS: calcd for $C_{24}H_{35}NO_2Na$ $[M+Na]^+$ 392.2565, found 392.2552.

*4.3.2. (2S,4aS,7R,8aR)-[3-(3-Methylbut-2-enyl)-4,4,7-trimethyloctahydro-2H-benzo[e][1,3]oxazin-2-yl]-(4-methoxyphenyl) ketone (**3c**).* Yield: 87%. Colorless solid. Mp: 113–114 °C (from EtOH). $[\alpha]_D^{25}$ +16.6 (*c* 0.5, $CHCl_3$). ^{1}H NMR δ: 0.90–1.05 (m, 2H); 0.94 (d, 3H, *J*=6.4 Hz); 1.19 (s, 3H); 1.22 (m, 1H) 1.32 (s, 3H); 1.35 (s, 3H); 1.40 (s, 3H); 1.47–1.60 (m, 2H); 1.67 (m, 1H); 1.71 (m, 1H); 2.02 (m, 1H); 3.18 (dd, 1H, J_1=16.6 Hz, J_2=5.8 Hz); 3.25 (dd, 1H, J_1=16.6 Hz, J_2=5.8 Hz); 3.56 (td, 1H, J_1=10.5 Hz, J_2=4.0 Hz); 3.85 (s, 3H); 4.78 (t, 1H, *J*=5.8 Hz); 5.61 (s, 1H); 6.87 (d, 2H, *J*=8.8 Hz); 8.22 (d, 2H, *J*=8.8 Hz). ^{13}C NMR δ: 17.5 (CH_3); 19.6 (CH_3); 22.1 (CH_3); 24.9 (CH_2); 25.3 (CH_3); 26.6 (CH_3); 31.2 (CH); 34.8 (CH_2); 41.2 (CH_2); 42.3 (CH_2); 46.1 (CH); 55.2 (CH_3); 57.4 (C); 76.0 (CH); 88.7 (CH); 112.9 (2 CH); 126.2 (CH); 128.4 (C); 130.3 (C); 131.5 (2 CH); 163.0 (C); 193.2 (C). IR (Nujol dispersion): 1690, 1595, 855, 660, 615 cm^{-1}. HRMS: calcd for $C_{24}H_{35}NO_3Na$ $[M+Na]^+$ 408.2515, found 408.2503.

*4.3.3. (2S,4aS,7R,8aR)-[3-(3-Methylbut-2-enyl)-4,4,7-trimethyloctahydro-2H-benzo[e][1,3]oxazin-2-yl]-(4-nitrophenyl) ketone (**3d**).* Yield: 66%. Yellow solid. Mp: 105–106 °C (from EtOH). $[\alpha]_D^{25}$ −1.4 (*c* 0.8, $CHCl_3$). ^{1}H NMR δ: 0.92–1.07 (m, 2H); 0.94 (d, 3H, *J*=6.4 Hz); 1.17 (s, 3H); 1.20 (m, 1H); 1.23 (s, 3H); 1.30 (s, 3H); 1.37 (s, 3H); 1.43–1.60 (m, 2H); 1.69–1.75 (m, 2H); 2.01 (m, 1H); 3.09 (dd, 1H, J_1=16.0 Hz, J_2=6.4 Hz); 3.32 (dd, 1H, J_1=16.0, Hz, J_2=6.4 Hz); 3.58 (td, 1H, J_1=10.5 Hz, J_2=4.0 Hz); 4.61 (t, 1H, *J*=6.4 Hz); 5.44 (s, 1H); 8.24 (dd, 2H, J_1=7.1 Hz, J_2=1.6 Hz); 8.43 (dd, 2H, J_1=7.1 Hz, J_2=1.6 Hz). ^{13}C NMR δ: 17.5 (CH_3); 17.8 (CH_3); 22.0 (CH_3); 24.8 (CH_2); 25.2 (CH_3); 26.7 (CH_3); 31.1 (CH); 34.6 (CH_2); 41.1 (CH_2); 42.0 (CH_2); 47.1 (CH); 57.6 (C); 76.0 (CH); 89.8 (CH); 122.8 (2 CH); 125.6 (CH); 130.3 (2 CH); 132.6 (C); 139.8 (C); 149.6 (C); 192.8 (C). IR (Nujol dispersion): 3080, 3110, 3055, 1705, 1600, 720, 690 cm^{-1}. HRMS: calcd for $C_{23}H_{33}N_2O_4$ $[M+H]^+$ 401.2440, found 401.2438.

*4.3.4. (2S,4aS,7R,8aR)-[3-(3-Methylbut-2-enyl)-4,4,7-trimethyloctahydro-2H-benzo[e][1,3]oxazin-2-yl]-(3-nitrophenyl) ketone (**3e**).* Yield: 68%. Yellow solid. Mp: 113–114 °C (from EtOH). ^{1}H NMR δ: 0.86–1.08 (m, 2H); 0.94 (d, 3H, *J*=6.4 Hz); 1.16 (s, 3H); 1.21 (m, 1H); 1.24 (s, 3H); 1.33 (s, 3H); 1.36 (s, 3H); 1.43–1.67 (m, 2H); 1.70–1.79 (m, 2H); 2.01 (m, 1H); 3.09 (dd, 1H, J_1=16.1 Hz, J_2=6.5 Hz); 3.33 (dd, 1H, J_1=16.1 Hz, J_2=6.5 Hz); 3.58 (td, 1H, J_1=10.6 Hz, J_2=4.1 Hz); 4.60 (t, 1H, *J*=6.5 Hz); 5.46 (s, 1H); 7.60 (t, 1H, *J*=8.0 Hz); 8.35 (m, 1H); 8.52 (m, 1H); 9.25 (t, 1H, *J*=1.9 Hz). ^{13}C NMR δ: 17.5 (CH_3); 17.9 (CH_3); 22.1 (CH_3); 25.0 (CH_2); 25.2 (CH_3); 26.8 (CH_3); 31.2 (CH); 34.7 (CH_2); 41.1 (CH_2); 42.1 (CH_2); 47.2 (CH); 57.6 (C); 76.1 (CH); 89.8 (CH); 124.8 (CH); 125.6 (CH);

126.8 (CH); 128.8 (CH); 132.6 (C); 134.7(CH); 136.5 (C); 147.6 (C); 192.4 (C). IR (Nujol dispersion): 3120, 1700, 1603, 1526, 710, 685 cm^{-1}. HRMS: calcd for $C_{23}H_{32}N_2O_4Na$ $[M+Na]^+$ 423.2260, found 423.2253.

4.4. Synthesis of oxazines 3f and 4h

A mixture of alcohol **2** (2.4 g, 8.0 mmol), phenyglyoxal (1.3 g, 9.7 mmol) or ethyl glyoxalate (1.9 mL of a commercial 50% solution in toluene, 9.7 mmol), and toluene (60 mL) was heated at reflux with a Dean–Stark trap for 38 h. The solvent was evaporated under vacuum and the residue was chromatographed on silica gel using a mixture of hexane/EtOAc 15:1 as eluent.

*4.4.1. (2S,4aS,7R,8aR)-Phenyl-[3-[(E)-3-phenylbut-2-enyl]-4,4,7-trimethyloctahydro-2H-benzo[e][1,3]oxazin-2-yl] ketone (**3f**).* Yield: 52%. Colorless solid. Mp: 110–111 °C (from EtOH). $[\alpha]_D^{25}$ −25.2 (*c* 0.9, $CHCl_3$). ^1H NMR δ: 0.90–1.08 (m, 2H); 1.02 (d, 3H, *J*=6.4 Hz); 1.22 (s, 3H); 1.29 (m, 1H); 1.41 (s, 3H); 1.42–1.79 (m, 4H); 1.82 (s, 3H); 2.06 (m, 1H); 3.39 (dd, 1H, J_1=17.5 Hz, J_2=6.1 Hz); 3.52 (dd, 1H, J_1=17.5 Hz, J_2=6.1 Hz); 3.61 (td, 1H, J_1=10.5 Hz, J_2=4.1 Hz); 5.32 (t, 1H, *J*=6.1 Hz); 5.74 (s, 1H); 6.80–6.83 (m, 2H); 7.09–7.11 (m, 3H); 7.33–7.39 (m, 2H); 7.49 (m, 1H); 8.18–8.22 (m, 2H). ^{13}C NMR δ: 15.6 (CH_3); 20.0 (CH_3); 22.2 (CH_3); 25.0 (CH_2); 26.9 (CH_3); 31.3 (CH); 34.9 (CH_2); 41.2 (CH_2); 42.9 (CH_2); 46.2 (CH); 57.7 (C); 76.2 (CH); 88.5 (CH); 125.3 (2 CH); 126.3 (CH); 127.7 (2 CH); 128.0 (2 CH); 129.4 (2 CH); 130.0 (CH); 132.9 (CH); 133.1 (C); 135.2 (C); 143.3 (C); 194.7(C). IR (Nujol dispersion): 1700, 1600, 1575, 775, 755, 735, 700, 685 cm^{-1}. HRMS: calcd for $C_{28}H_{35}NO_2Na$ $[M+Na]^+$ 440.2565, found 440.2564.

*4.4.2. (2S,4aS,7R,8aR)-2-(Ethoxycarbonyl)-3-[(E)-3-phenylbut-2-enyl]-4,4,7-trimethyloctahydro-2H-benzo[e][1,3]oxazine (**4h**).* Yield: 60%. Colorless solid. Mp: 105–106 °C (from EtOH). $[\alpha]_D^{25}$ −27.3 (*c* 1.1, $CHCl_3$). ^1H NMR δ: 0.90–1.04 (m, 2H); 0.94 (d, 3H, *J*=6.5 Hz); 1.15 (m, 1H); 1.17 (t, 3H, *J*=6.1 Hz); 1.19 (s, 3H); 1.23 (s, 3H); 1.42–1.74 (m, 4H); 1.98 (s, 3H); 2.01 (m, 1H); 3.40–3.59 (m, 3H); 4.01–4.20 (m, 2H); 5.10 (s, 1H); 5.86 (t, 1H, *J*=5.6 Hz); 7.18 (m, 1H); 7.25–7.30 (m, 2H); 7.36–7.39 (m, 2H). ^{13}C NMR δ: 13.9 (CH_3); 15.6 (CH_3); 19.7 (CH_3); 22.1 (CH_3); 24.8 (CH_2); 26.5 (CH_3); 31.2 (CH); 34.7 (CH_2); 40.9 (CH_2); 43.5 (CH_2); 45.8 (CH); 57.1 (C); 61.2 (CH_2); 76.0 (CH); 85.7 (CH); 125.3 (2 CH); 126.4 (CH); 127.9 (2 CH); 130.1 (CH); 132.6 (C); 143.0 (C); 168.9 (C). IR (Nujol dispersion): 1750, 770, 765, 700 cm^{-1}. HRMS: calcd for $C_{24}H_{36}NO_3$ $[M+H]^+$ 386.2695, found 386.2695.

4.5. Synthesis of oxazine 3h

A solution of *i*-PrMgCl in diethyl ether (13.7 mL, 2 M) was slowly added (1 h) to a slurry of the ester **4h** (3.0 g, 7.8 mmol) and Me(MeO)NH·HCl (1.1 g, 11.7 mmol) in THF (35 mL), cooled to −20 °C. The mixture was stirred for 10 min at −20 °C and then for 15 min at room temperature. The reaction was quenched with a saturated solution of NH_4Cl, and the product was extracted with diethyl ether (4×20 mL). The organic layer was dried over MgSO4 and concentrated under vacuum to give an oily residue, which was purified by flash chromatography on silica gel with hexanes/ethyl acetate as eluent to yield 1.6 g of amide **5h** and 0.71 g of ketone **3h**.

A solution of *i*-PrMgCl (2.8 mL, 2 M) was slowly added at −40 °C to a solution of amide **5h** in THF (10 mL). The reaction mixture was stirred for 30 min and the mixture was treated as above to obtain 1.1 g of ketone **3h**.

*4.5.1. (2S,4aS,7R,8aR)-N-Methoxy-3-[(E)-3-phenylbut-2-enyl]-N,4,4,7-tetramethyloctahydro-2H-benzo[e][1,3]oxazine-2-carboxamide (**5h**).* Colorless oil. $[\alpha]_D^{25}$ −37.7 (*c* 1.3, $CHCl_3$). ^1H NMR (333 K) δ: 0.86–1.07 (m, 2H); 0.93 (d, 3H, *J*=6.4 Hz); 1.19 (s, 3H); 1.20 (m, 1H); 1.29 (s, 3H); 1.38–1.78 (m, 4H); 1.97 (s, 3H); 2.03 (m, 1H); 3.09 (br s, 3H); 3.38–3.57 (m, 2H); 3.65–3.83 (m, 4H); 5.53 (m, 1H); 5.81 (m, 1H); 7.13–7.39 (m, 5H). ^{13}C NMR δ: 15.7 (CH_3); 21.1 (CH_3); 22.1 (CH_3); 24.8 (CH_2); 26.8 (CH_3); 31.3 (CH); 32.3 (CH_3); 34.8 (CH_2); 41.0 (CH_2); 42.6 (CH_2); 45.0 (CH); 57.5 (C); 61.6 (CH_3); 76.6 (CH); 82.8 (CH); 125.4 (2 CH); 126.3 (CH); 128.0 (2 CH); 130.6 (CH); 132.4 (C); 143.6 (C); 170.0 (C). IR (Neat): 2975, 2920, 2865, 1685, 1680, 760, 730, 700 cm^{-1}. HRMS: calcd for $C_{24}H_{36}N_2O_3Na$ $[M+Na]^+$ 423.2624, found 423.2621.

*4.5.2. (2S,4aS,7R,8aR)-2-Methyl-1-[3-[(E)-3-phenylbut-2-enyl]-4,4,7-trimethyloctahydro-2H-benzo[e][1,3]oxazin-2-yl]propan-1-one (**3h**).* Yield: 61% from **4h**. Colorless oil. $[\alpha]_D^{25}$ −79.3 (*c* 1.1, $CHCl_3$). ^1H NMR δ: 0.85–1.05 (m, 2H); 0.94 (d, 3H, *J*=6.4 Hz); 1.00 (d, 3H, *J*=6.9 Hz); 1.10 (d, 3H, *J*=6.9 Hz); 1.17 (s, 3H); 1.26 (m, 1H); 1.29 (s, 3H); 1.48–1.61 (m, 2H); 1.66 (m, 1H); 1.73 (m, 1H); 1.93 (s, 3H); 2.04 (m, 1H); 3.12 (sep, 1H, *J*=6.9 Hz); 3.21 (dd, 1H, J_1=17.7, Hz, J_2=5.5 Hz); 3.48–3.56 (m, 2H); 5.21 (s, 1H); 5.79 (t, 1H, *J*=5.5 Hz); 7.18–7.40 (m, 5H). ^{13}C NMR δ: 15.9 (CH_3); 17.4 (CH_3); 19.5 (CH_3); 21.6 (CH_3); 22.2 (CH_3); 24.9 (CH_2); 26.6 (CH_3); 31.4 (CH); 35.0 (CH_2); 36.3 (CH); 41.1 (CH_2); 44.1 (CH_2); 44.8 (CH); 57.3 (C); 76.4 (CH); 88.5 (CH); 125.5 (2 CH); 126.6 (CH); 128.1 (2 CH); 130.7 (CH); 132.7 (C); 143.3 (C); 210.8 (C). IR (Neat): 2975, 2930, 2870, 1725, 1600, 735, 700 cm^{-1}. HRMS: calcd for $C_{25}H_{38}NO_2$ $[M+H]^+$ 384.2903, found 384.2899.

4.6. General procedure for keto-ene cyclization of 3a–3h in the presence of Me_2AlCl, Et_2AlCl or $SnCl_4$

A commercial solution of Me_2AlCl or Et_2AlCl in hexanes or $SnCl_4$ in CH_2Cl_2 (5.25 mL, solution 1 M) was slowly added to a solution of ketone **3a**–**h** (3.5 mmol) in anhydrous CH_2Cl_2 (70 mL) cooled to 0 °C. The mixture was stirred at this temperature for 1.5 h for the reactions in the presence of aluminum derivatives and 15 h for reactions in the presence of $SnCl_4$. Then the reaction was quenched by addition of a saturated aqueous solution NH_4Cl (40 mL). The organic layer was decanted and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash chromatography on silica gel using a mixture of hexane/EtOAc as eluent.

*4.6.1. (1R,2S,4aS,7R,8aR,9aS)-2-Isopropenyl-4,4,7-trimethyl-1-(p-tolyl)-decahydro-9-oxa-3a-azacyclopenta[b]naphthalen-1-ol (**6b**).* Colorless solid. Mp: 114–115 °C (from EtOH). $[\alpha]_D^{25}$ −24.0 (*c* 1.0, $CHCl_3$). ^1H NMR δ: 0.83–1.01 (m, 2H); 0.91 (d, 3H, *J*=6.5 Hz); 1.09 (m, 1H); 1.14 (s, 3H); 1.19 (s, 3H); 1.35–1.54 (m, 2H); 1.59 (s, 3H); 1.61 (m, 1H); 1.70 (m, 1H); 1.90 (m, 1H); 2.32 (s, 3H); 2.93 (dd, 1H, J_1=9.0 Hz, J_2=7.6 Hz); 3.08 (dd, 1H, J_1=8.1 Hz, J_2=7.6 Hz); 3.35 (dd, 1H, J_1=9.0 Hz, J_2=8.1 Hz); 3.43 (td, 1H, J_1=10.5 Hz, J_2=4.1 Hz); 3.69 (s, 1H); 4.58 (s, 1H); 4.69 (s, 1H); 4.86 (s, 1H); 7.12 (d, 2H, *J*=8.0 Hz); 7.54 (d, 2H, *J*=8.0 Hz). ^{13}C NMR δ: 20.0 (CH_3); 21.0 (CH_3); 22.2 (CH_3); 23.5 (CH_3); 24.7 (CH_2); 26.9 (CH_3); 31.1 (CH); 34.9 (CH_2); 41.1 (CH_2); 44.5 (CH); 46.9 (CH_2); 53.3 (C); 56.6 (CH); 74.9 (CH); 79.7 (C); 91.9 (CH); 111.1 (CH_2); 124.5 (2 CH); 128.4 (2 CH); 135.6 (C); 143.6 (C); 144.9 (C). IR (Nujol dispersion): 3545, 3080, 1645, 1510, 730, 700 cm^{-1}. HRMS: calcd for $C_{24}H_{36}NO_2$ $[M+H]^+$ 370.2746, found 370.2749.

*4.6.2. (1R,2S,4aS,7R,8aR,9aS)-2-Isopropenyl-4,4,7-trimethyl-1-(4-methoxyphenyl)decahydro-9-oxa-3a-azacyclopenta[b]naphthalen-1-ol (**6c**).* Colorless oil. $[\alpha]_D^{25}$ −6.9 (*c* 0.9, $CHCl_3$). ^1H NMR δ: 0.89–0.99 (m, 2H); 0.91 (d, 3H, *J*=6.4 Hz); 1.07 (m, 1H); 1.14 (s, 3H); 1.19 (s, 3H); 1.34–1.57 (m, 2H); 1.61 (s, 3H); 1.62 (m, 1H); 1.70 (m, 1H); 1.90 (m, 1H); 2.91 (dd, 1H, J_1=8.9 Hz, J_2=8.2 Hz); 3.08 (dd, 1H, J_1=8.2 Hz, J_2=7.8 Hz); 3.34 (dd, 1H, J_1=8.9 Hz, J_2=7.8 Hz); 3.44

(td, 1H, J_1=10.4 Hz, J_2=4.1 Hz); 3.68 (s, 1H); 3.79 (s, 3H); 4.58 (s, 1H); 4.69 (s, 1H); 4.86 (s, 1H); 6.85 (d, 2H, J=8.4 Hz); 7.57 (d, 2H, J=8.4 Hz). ^{13}C NMR δ: 19.8 (CH_3); 22.1 (CH_3); 23.3 (CH_3); 24.6 (CH_2); 26.8 (CH_3); 31.0 (CH); 34.8 (CH_2); 40.9 (CH_2); 44.3 (CH); 46.8 (CH_2); 53.2 (C); 54.8 (CH_3); 56.4 (CH); 74.8 (CH); 79.4 (C); 91.7 (CH); 111.0 (CH_2); 112.9 (2 CH); 125.6 (2 CH), 139.8 (C); 143.4 (C); 157.9 (C). IR (Neat): 3525, 3080, 2975, 2930, 2860, 1645, 1610, 1580, 835, 735 cm^{-1}. HRMS: calcd for $C_{24}H_{36}NO_3$ $[M+H]^+$ 386.2695, found 386.2686.

*4.6.3. (1R,2S,4aS,7R,8aR,9aS)-2-Isopropenyl-4,4,7-trimethyl-1-(4-nitrophenyl)decahydro-9-oxa-3a-azacyclopenta[b]naphthalen-1-ol (**6d**).* Colorless solid. Mp: 100–101 °C (from EtOH). $[\alpha]_D^{25}$ −12.2 (c 0.9, $CHCl_3$). ^{1}H NMR δ: 0.88–1.04 (m, 2H); 0.93 (d, 3H, J=6.5 Hz); 1.11 (m, 1H); 1.18 (s, 3H); 1.23 (s, 3H); 1.41–1.81 (m, 4H); 1.59 (s, 3H); 1.91 (m, 1H); 2.90 (dd, 1H, J_1=9.0 Hz, J_2=8.0 Hz); 3.14 (dd, 1H, J_1=8.0 Hz, J_2=7.7 Hz); 3.41 (dd, 1H, J_1=9.0 Hz, J_2=7.7 Hz); 3.49 (td, 1H, J_1=10.4 Hz, J_2=4.1 Hz); 3.83 (s, 1H); 4.61 (s, 1H); 4.70 (s, 1H); 4.89 (s, 1H); 7.87 (d, 2H, J=8.8 Hz); 8.17 (d, 2H, J=8.8 Hz). ^{13}C NMR δ: 20.4 (CH_3); 22.1 (CH_3); 23.3 (CH_3); 24.7 (CH_2); 26.9 (CH_3); 31.1 (CH); 34.8 (CH_2); 41.0 (CH_2); 44.1 (CH); 47.1 (CH_2); 53.5 (C); 57.1(CH); 75.2 (CH); 80.0 (C); 91.1 (CH); 112.0 (CH_2); 123.1 (2 CH); 125.6 (2 CH), 142.6 (C); 146.5 (C); 155.5 (C). IR (Nujol dispersion): 3500, 3065, 1645, 1595, 1510, 760, 720, 710 cm^{-1}. HRMS: calcd for $C_{23}H_{33}N_2O_4$ $[M+H]^+$ 401.2440, found 401.2437.

*4.6.4. (1R,2S,4aS,7R,8aR,9aS)-2-Isopropenyl-4,4,7-trimethyl-1-(3-nitrophenyl)decahydro-9-oxa-3a-azacyclopenta[b]naphthalen-1-ol (**6e**).* Yellow oil. $[\alpha]_D^{25}$ −41.6 (c 1.0, $CHCl_3$). ^{1}H NMR δ: 0.85–1.01 (m, 2H); 0.94 (d, 3H, J=6.5 Hz); 1.13 (m, 1H); 1.19 (s, 3H); 1.23 (s, 3H); 1.38–1.68 (m, 3H); 1.61 (s, 3H); 1.73 (m, 1H); 1.93 (m, 1H); 2.90 (dd, 1H, J_1=9.0 Hz, J_2=7.7 Hz); 3.15 (dd, 1H, J_1=8.1 Hz, J_2=7.7 Hz); 3.40 (dd, 1H, J_1=9.0 Hz, J_2=8.1 Hz); 3.49 (td, 1H, J_1=10.5 Hz, J_2=4.1 Hz); 3.81 (s, 1H); 4.60 (s, 1H); 4.71 (s, 1H); 4.89 (s, 1H); 7.50 (t, 1H, J=7.9 Hz); 8.02–8.11 (m, 2H); 8.58 (t, 1H, J=1.9 Hz). ^{13}C NMR δ: 20.3 (CH_3); 22.1 (CH_3); 23.3 (CH_3); 24.7 (CH_2); 26.8 (CH_3); 31.1 (CH); 34.8 (CH_2); 41.0 (CH_2); 44.1 (CH); 47.0 (CH_2); 53.5 (C); 56.8 (CH); 75.2 (CH); 79.7 (C); 91.2 (CH); 112.0 (CH_2); 120.0 (CH); 121.4 (CH); 128.7 (CH); 130.9 (CH); 142.6 (C); 148.0 (C); 150.2 (C). IR (Neat): 3515, 3085, 2925, 2870, 1650, 1530, 730, 700, 685 cm^{-1}. HRMS: calcd for $C_{23}H_{33}N_2O_4$ $[M+H]^+$ 401.2440, found 401.2422.

*4.6.5. (1R,2S,4aS,7R,8aR,9aS)-1-Phenyl-2-(1-phenylvinyl)-4,4,7-trimethyldecahydro-9-oxa-3a-azacyclopenta[b]naphthalen-1-ol (**6f**).* Colorless oil. $[\alpha]_D^{25}$ −9.4 (c 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.90–1.09 (m, 2H); 0.99 (d, 3H, J=6.5 Hz); 1.19 (m, 1H); 1.25 (s, 3H); 1.28 (s, 3H); 1.51 (m, 1H); 1.60–1.75 (m, 2H); 1.80 (m, 1H); 1.99 (m, 1H); 3.38 (t, 1H, J=7.8 Hz); 3.47–3.65 (m, 3H); 3.79 (s, 1H); 4.75 (s, 1H); 5.31 (s, 1H); 5.50 (s, 1H); 7.06–7.16 (m, 5H); 7.18–7.29 (m, 3H); 7.54–7.59 (m, 2H). ^{13}C NMR δ: 20.5 (CH_3); 22.2 (CH_3); 24.7 (CH_2); 26.9 (CH_3); 31.1 (CH); 34.9 (CH_2); 41.1 (CH_2); 44.2 (CH); 49.6 (CH_2); 53.4 (C); 54.6 (CH); 75.0 (CH); 79.6 (C); 91.7 (CH); 114.4 (CH_2); 124.6 (2 CH); 126.1 (CH); 126.5 (2 CH); 126.6 (CH); 127.5 (4 CH); 142.7 (C); 147.2 (2 C). IR (Neat): 3520, 3050, 2975, 2925, 2870, 1605, 765, 700 cm^{-1}. HRMS: calcd for $C_{28}H_{36}NO_2$ $[M+H]^+$ 418.2746, found 418.2742.

*4.6.6. (1S,2S,4aS,7R,8aR,9aS)-1-Isopropyl-2-(1-phenylvinyl)-4,4,7-trimethyldecahydro-9-oxa-3a-azacyclopenta[b]naphthalen-1-ol (**6h**).* Colorless solid. Mp: 73–74 °C (from EtOH). $[\alpha]_D^{25}$ +13.9 (c 0.9, $CHCl_3$). ^{1}H NMR δ: 0.72 (d, 3H, J=6.8 Hz); 0.80 (d, 3H, J=6.8 Hz); 0.87–1.04 (m, 2H); 0.93 (d, 3H, J=6.5 Hz); 1.10 (m, 1H); 1.10 (s, 3H); 1.13 (s, 3H); 1.44–1.54 (m, 2H); 1.55–1.76 (m, 3H); 1.96 (m, 1H); 3.21 (s, 3H); 3.23 (s, 1H); 3.50 (td, 1H, J_1=10.5 Hz, J_2=4.0 Hz); 4.56 (s, 1H); 5.30 (s, 1H); 5.40 (s, 1H); 7.19–7.37 (m, 5H). ^{13}C NMR δ: 17.4 (CH_3); 17.8 (CH_3); 20.6 (CH_3); 22.3 (CH_3); 24.9 (CH_2); 26.6 (CH_3); 31.3 (CH); 35.1 (CH_2); 35.9 (CH); 41.4 (CH_2); 43.9 (CH); 47.3 (CH); 51.8 (CH_2); 53.2 (C); 74.9 (CH); 81.8 (C); 87.1 (CH); 116.1 (CH_2); 126.8 (CH); 126.9 (2 CH); 128.0 (2 CH); 144.7 (C); 148.7 (C). IR (Nujol dispersion): 3515, 3080, 3050, 2935, 775, 700 cm^{-1}. HRMS: calcd for $C_{25}H_{38}NO_2$ $[M+H]^+$ 384.2903, found 384.2897.

*4.6.7. (1S,2R,4aS,7R,8aR,9aS)-2-Isopropenyl-4,4,7-trimethyl-1-(p-tolyl)decahydro-9-oxa-3a-azacyclopenta[b]naphthalen-1-ol (**7b**).* Colorless oil. $[\alpha]_D^{25}$ −91.4 (c 1.5, $CHCl_3$). ^{1}H NMR δ: 0.86–1.10 (m, 3H); 0.89 (d, 3H, J=6.5 Hz); 1.16 (s, 3H); 1.17 (s, 3H); 1.35 (m, 1H); 1.47–1.61 (m, 2H); 1.49 (s, 3H); 1.70 (m, 1H); 1.81 (m, 1H); 2.32 (s, 3H); 2.85 (s, 1H); 3.08 (dd, 1H, J_1=9.0 Hz, J_2=6.4 Hz); 3.27 (td, 1H, J_1=10.4 Hz, J_2=4.0 Hz); 3.38 (dd, 1H, J_1=9.9 Hz, J_2=9.0 Hz); 3.53 (dd, 1H, J_1=9.9 Hz, J_2=6.4 Hz); 4.43 (s, 1H); 4.85 (s, 1H); 4.88 (s, 1H); 7.12 (d, 2H, J=8.1 Hz); 7.56 (d, 2H, J=8.1 Hz). ^{13}C NMR δ: 21.0 (CH_3); 22.1 (CH_3); 22.3 (CH_3); 23.9 (CH_3); 24.8 (CH_2); 26.2 (CH_3); 31.2 (CH); 35.1 (CH_2); 41.2 (CH_2); 43.0 (CH); 46.6 (CH_2); 51.3 (CH); 53.3 (C); 74.5 (CH); 81.4 (C); 93.3 (CH); 112.5 (CH_2); 127.0 (2 CH); 128.0 (2 CH); 136.2 (C); 136.7 (C); 143.1 (C). IR (Neat): 3505, 3080, 2925, 2870, 1640, 1515, 820, 735 cm^{-1}. HRMS: calcd for $C_{24}H_{36}NO_2$ $[M+H]^+$ 370.2746, found 370.2755.

*4.6.8. (1S,2R,4aS,7R,8aR,9aS)-2-Isopropenyl-4,4,7-trimethyl-1-(4-methoxyphenyl)decahydro-9-oxa-3a-azacyclopenta[b]naphthalen-1-ol (**7c**).* Colorless oil. $[\alpha]_D^{25}$ −105.5 (c 1.5, $CHCl_3$). ^{1}H NMR δ: 0.83–0.95 (m, 2H); 0.90 (d, 3H, J=6.5 Hz); 1.04 (m, 1H); 1.16 (s, 3H); 1.17 (s, 3H); 1.28–1.51 (m, 2H); 1.49 (s, 3H); 1.56 (m, 1H); 1.70 (m, 1H); 1.82 (m, 1H); 2.85 (s, 1H); 3.07 (dd, 1H, J_1=9.0 Hz, J_2=6.3 Hz); 3.29 (td, 1H, J_1=10.5 Hz, J_2=4.0 Hz); 3.37 (dd, 1H, J_1=9.9 Hz, J_2=9.1 Hz); 3.50 (dd, 1H, J_1=9.9 Hz, J_2=6.3 Hz); 3.70 (s, 3H); 4.43 (s, 1H); 4.84 (s, 1H); 4.89 (s, 1H); 6.85 (d, 2H, J=8.8 Hz); 7.59 (d, 2H, J=8.8 Hz). ^{13}C NMR δ: 22.0 (CH_3); 22.2 (CH_3); 23.8 (CH_3); 24.7 (CH_2); 26.1 (CH_3); 31.1 (CH); 35.1 (CH_2); 41.2 (CH_2); 42.9 (CH); 46.5 (CH_2); 51.3 (CH); 53.2 (C); 54.9 (CH_3); 74.4 (CH); 81.2 (C); 93.2 (CH); 112.5 (CH_2+2 CH); 128.2 (2 CH), 131.8 (C); 142.9 (C); 158.3 (C). IR (Neat): 3505, 3080, 2930, 1640, 1610, 1585, 830, 740 cm^{-1}. HRMS: calcd for $C_{24}H_{36}NO_3$ $[M+H]^+$ 386.2695, found 386.2684.

*4.6.9. (1S,2R,4aS,7R,8aR,9aS)-2-Isopropenyl-4,4,7-trimethyl-1-(4-nitrophenyl)decahydro-9-oxa-3a-azacyclopenta[b]naphthalen-1-ol (**7d**).* Colorless oil. $[\alpha]_D^{25}$ −96.8 (c 0.6, $CHCl_3$). ^{1}H NMR δ: 0.88–1.10 (m, 3H); 0.89 (d, 3H, J=6.5 Hz); 1.16 (s, 3H); 1.20 (s, 3H); 1.33–1.66 (m, 3H); 1.47 (s, 3H); 1.68–1.82 (m, 2H); 3.01 (s, 1H); 3.11 (dd, 1H, J_1=9.1 Hz, J_2=6.2 Hz); 3.38 (td, 1H, J_1=10.5 Hz, J_2=4.0 Hz); 3.42 (dd, 1H, J_1=9.7 Hz, J_2=9.1 Hz); 3.52 (dd, 1H, J_1=9.7 Hz, J_2=6.2 Hz); 4.46 (s, 1H); 4.82 (s, 1H); 4.89 (s, 1H); 7.90 (d, 2H, J=9.1 Hz); 8.15 (d, 2H, J=9.1 Hz). ^{13}C NMR δ: 21.3 (CH_3); 22.1 (CH_3); 23.5 (CH_3); 24.6 (CH_2); 26.1 (CH_3); 31.0 (CH); 34.9 (CH_2); 41.0 (CH_2); 43.2 (CH); 46.2 (CH_2); 52.2 (CH); 53.4 (C); 74.6 (CH); 81.3 (C); 93.1 (CH); 113.1 (CH_2); 122.1 (2 CH); 128.1 (2 CH), 141.9 (C); 146.6 (C); 147.9 (C). IR (Neat): 3515, 3085, 2965, 1640, 1600, 730, 700 cm^{-1}. HRMS: calcd for $C_{23}H_{33}N_2O_4$ $[M+H]^+$ 401.2440, found 401.2435.

*4.6.10. (1S,2R,4aS,7R,8aR,9aS)-2-Isopropenyl-4,4,7-trimethyl-1-(3-nitrophenyl)decahydro-9-oxa-3a-azacyclopenta[b]naphthalen-1-ol (**7e**).* Yellow solid. Mp: 154–155 °C (from MeOH). $[\alpha]_D^{25}$ −86.3 (c 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.83–1.15 (m, 3H); 0.90 (d, 3H, J=6.5 Hz); 1.16 (s, 3H); 1.19 (s, 3H); 1.43 (m, 1H); 1.50 (s, 3H); 1.51–1.68 (m, 2H); 1.70–1.85 (m, 2H); 2.95 (s, 1H); 3.10 (dd, 1H, J_1=8.9 Hz, J_2=6.1 Hz); 3.29 (td, 1H, J_1=10.4 Hz, J_2=4.0 Hz); 3.43 (dd, 1H, J_1=9.7 Hz, J_2=8.9 Hz); 3.51 (dd, 1H, J_1=9.7 Hz, J_2=6.1 Hz); 4.45 (s, 1H); 4.82 (s, 1H); 4.90 (s, 1H); 7.46 (t, 1H, J=8.0 Hz); 8.01–8.08 (m, 1H); 8.09–8.12 (m, 1H); 8.62 (t, 1H, J=1.9 Hz). ^{13}C NMR δ: 21.6 (CH_3); 22.2 (CH_3); 23.7 (CH_3); 24.7 (CH_2); 26.2 (CH_3); 31.2 (CH); 35.0 (CH_2); 41.0 (CH_2); 43.2 (CH);

46.5 (CH_2); 52.1 (CH); 53.5 (C); 74.7 (CH); 81.1 (C); 93.1 (CH); 113.4 (CH_2); 121.8 (CH); 122.6 (CH), 127.9 (CH); 133.5 (CH); 142.0 (C); 142.6 (C); 147.7 (C). IR (Nujol dispersion): 3480, 3085, 1635, 1580, 720, 700 cm^{-1}. HRMS: calcd for $C_{23}H_{33}N_2O_4$ $[M+H]^+$ 401.2440, found 401.2432.

*4.6.11. (1S,2R,4aS,7R,8aR,9aS)-1-Phenyl-2-(1-phenylvinyl)-4,4,7-trimethyldecahydro-9-oxa-3a-azacyclopenta[b]naphthalen-1-ol (**7f**).* Colorless solid. Mp: 98–99 °C (from EtOH). $[\alpha]_D^{25}$ −26.5 (*c* 0.9, $CHCl_3$). ^1H NMR δ: 0.86–1.01 (m, 3H); 0.89 (d, 3H, *J*=6.5 Hz); 1.12 (s, 3H); 1.16 (s, 3H); 1.39 (m, 1H); 1.48–1.63 (m, 2H); 1.71 (m, 1H); 1.81 (m, 1H); 2.94 (dd, 1H, J_1=9.2 Hz, J_2=7.3 Hz); 3.04 (s, 1H); 3.30 (td, 1H, J_1=10.4 Hz, J_2=4.0 Hz); 3.52 (dd, 1H, J_1=9.9 Hz, J_2=9.2 Hz); 4.12 (dd, 1H, J_1=9.9 Hz, J_2=7.3 Hz); 4.54 (s, 1H); 5.29 (s, 1H); 5.37 (s, 1H); 7.10–7.22 (m, 8H); 7.56–7.60 (m, 2H). ^{13}C NMR δ: 21.7 (CH_3); 22.2 (CH_3); 24.7 (CH_2); 26.2 (CH_3); 31.2 (CH); 35.0 (CH_2); 41.2 (CH_2); 43.3 (CH); 48.4 (CH); 48.9 (CH_2); 53.3 (C); 74.5 (CH); 81.5 (C); 93.6 (CH); 115.7 (CH_2); 126.6 (CH); 126.7 (2 CH); 126.8 (CH); 127.1 (4 CH); 127.8 (2 CH); 139.4 (C); 143.1 (C); 146.1 (C). IR (Nujol dispersion): 3488, 2927, 2860, 1605, 699 cm^{-1}. HRMS: calcd for $C_{28}H_{35}NO_2Na$ $[M+Na]^+$ 440.2565, found 440.2548.

*4.6.12. (1R,2R,4aS,7R,8aR,9aS)-1-Isopropyl-2-(1-phenylvinyl)-4,4,7-trimethyldecahydro-9-oxa-3a-azacyclopenta[b]naphthalen-1-ol (**7h**).* Colorless oil. $[\alpha]_D^{25}$ −6.2 (*c* 1.3, $CHCl_3$). ^1H NMR δ: 0.71 (d, 3H, *J*=6.8 Hz); 0.83–1.00 (m, 2H); 0.88 (d, 3H, *J*=6.8 Hz); 0.92 (d, 3H, *J*=6.5 Hz); 1.05 (m, 1H); 1.10 (s, 3H); 1.18 (s, 3H); 1.40–1.53 (m, 2H); 1.59 (m, 1H); 1.72 (m, 1H); 1.81–1.94 (m, 2H); 2.27 (s, 1H); 2.89 (dd, 1H, J_1=8.6 Hz, J_2=5.6 Hz); 3.35 (td, 1H, J_1=10.4 Hz, J_2=4.0 Hz); 3.43 (dd, 1H, J_1=10.0 Hz, J_2=5.6 Hz); 3.56 (dd, 1H, J_1=10.0 Hz, J_2=8.6 Hz); 4.55 (s, 1H); 5.39 (s, 1H); 5.55 (s, 1H); 7.20–7.39 (m, 5H). ^{13}C NMR δ: 17.6 (CH_3); 18.4 (CH_3); 22.3 (2 CH_3); 24.8 (CH_2); 26.3 (CH_3); 31.3 (CH); 32.1 (CH); 35.1 (CH_2); 41.5 (CH_2); 42.9 (CH); 47.0 (CH); 53.1 (C); 53.4 (CH_2); 74.5 (CH); 83.9 (C); 92.7 (CH); 115.9 (CH_2); 126.6 (2 CH); 127.0 (CH); 128.1 (2 CH); 144.3 (C); 149.2 (C). IR (Neat): 3530, 3085, 3060, 3025, 2925, 1610, 775, 700 cm^{-1}. HRMS: calcd for $C_{25}H_{38}NO_2$ $[M+H]^+$ 384.2903, found 384.2893.

*4.6.13. Oxetane (**8**).* Yellow oil. ^1H NMR δ: 0.84–1.00 (m, 2H); 0.87 (d, 3H, *J*=6.3 Hz); 0.94 (s, 3H); 1.18 (m, 1H); 1.25 (s, 3H); 1.28 (s, 3H); 1.30 (m, 1H); 1.45 (m, 1H); 1.53 (s, 3H); 1.61–1.72 (m, 2H); 1.85 (m, 1H); 2.59 (d, 1H, *J*=6.1 Hz); 2.77 (dd, 1H, J_1=10.1 Hz, J_2=6.1 Hz); 3.18 (d, 1H, *J*=10.1 Hz); 3.23 (td, 1H, J_1=10.4 Hz, J_2=4.2 Hz); 3.98 (s, 1H); 7.21–7.48 (m, 5H). ^{13}C NMR δ: 10.7 (CH_3); 22.0 (2 CH_3); 24.5 (CH_2); 26.5 (CH_3); 30.6 (CH_3); 31.3 (CH); 34.7 (CH_2); 41.0 (CH_2); 41.8 (CH_2); 48.1 (CH); 49.4 (CH); 54.6 (C); 76.5 (CH); 81.8 (C); 85.1 (C); 93.1 (CH); 125.0 (2 CH); 126.7 (CH); 127.8 (2 CH); 143.4 (C). IR (Neat): 2950, 1600, 1450, 1380, 990, 750, 690 cm^{-1}. HRMS: calcd for $C_{23}H_{34}NO_2$ $[M+H]^+$ 356.2590, found 356.2572.

4.7. Synthesis of amino alcohols 9b, 9c, and 9f

Dry $AlCl_3$ (0.67 g, 5 mmol) was added, in portions, to a suspension of $LiAlH_4$ (0.57 g, 15 mmol) in anhydrous THF (40 mL) cooled to −10 °C. The mixture was stirred for 10 min and a solution of the corresponding adduct (3 mmol) in dry THF (20 mL) was slowly added. The reaction mixture was stirred for 8 min at −10 °C and quenched by addition of H_2O (4 mL). The resulting mixture was filtered, the solid was washed with EtOAc, and the organic layer was dried ($MgSO_4$). The solvent was eliminated under reduced pressure and the residue was chromatographed on silica gel with hexane/EtOAc 3:1 as eluent.

*4.7.1. (3R,4S)-4-Isopropenyl-1-(8-mentholyl)-3-p-tolylpyrrolidin-3-ol (**9b**).* Yield: 92%. Colorless oil. $[\alpha]_D^{25}$ +5.4 (*c* 0.7, $CHCl_3$). ^1H NMR (333 K) δ: 0.79–1.11 (m, 3H); 0.89 (d, 3H, *J*=6.5 Hz); 1.04 (s, 3H); 1.21 (s, 3H); 1.24–1.50 (m, 2H); 1.33 (s, 3H); 1.52–1.70 (m, 2H); 1.94 (m, 1H); 2.29 (s, 3H); 2.50 (br s, 1H); 2.98–3.19 (m, 4H); 3.33 (m, 1H); 3.65 (td, 1H, J_1=10.4 Hz, J_2=4.0 Hz); 4.83 (s, 1H); 4.95 (s, 1H); 7.10 (d, 2H, *J*=8.1 Hz); 7.36 (d, 2H, *J*=8.1 Hz); 8.41 (br s, 1H). ^{13}C NMR (333 K) δ: 17.0 (CH_3); 20.6 (CH_3); 21.3 (CH_3); 21.8 (CH_3); 24.0 (CH_3); 25.5 (CH_2); 30.8 (CH); 35.0 (CH_2); 44.2 (CH_2); 48.4 (CH_2); 48.7 (CH); 56.0 (CH); 59.3 (C); 62.2 (CH_2); 72.7 (CH); 79.1 (C); 113.4 (CH_2); 124.9 (2 CH); 128.6 (2 CH); 136.0 (C); 141.2 (C); 141.3 (C). IR (Neat): 3530, 3260, 3085, 2920, 1640, 1510, 730, 645 cm^{-1}. HRMS: calcd for $C_{24}H_{38}NO_2$ $[M+H]^+$ 372.2903, found 372.2890.

*4.7.2. (3R,4S)-4-Isopropenyl-1-(8-mentholyl)-3-(4-methoxyphenyl)pyrrolidin-3-ol (**9c**).* Yield: 95%. Colorless oil. ^1H NMR (333 K) δ: 0.86–1.14 (m, 3H); 0.89 (d, 3H, *J*=6.5 Hz); 1.03 (s, 3H); 1.21 (s, 3H); 1.23–1.50 (m, 2H); 1.35 (s, 3H); 1.56–1.67 (m, 2H); 1.93 (m, 1H); 2.34 (br s, 1H); 3.00–3.16 (m, 4H); 3.31 (m, 1H); 3.66 (td, 1H, J_1=10.3 Hz, J_2=4.0 Hz); 3.77 (s, 3H); 4.85 (s, 1H); 4.98 (s, 1H); 6.84 (d, 2H, *J*=8.8 Hz); 7.35 (br s, 1H); 7.40 (d, 2H, *J*=8.8 Hz). ^{13}C NMR (333 K) δ: 17.1 (CH_3); 21.4 (CH_3); 21.9 (CH_3); 24.2 (CH_3); 25.6 (CH_2); 31.0 (CH); 35.1 (CH_2); 44.3 (CH_2); 48.5 (CH_2); 48.9 (CH); 55.1 (CH_3); 56.1 (CH); 59.5 (C); 62.3 (CH_2); 72.9 (CH); 79.1 (C); 113.6 (2 CH); 113.7 (CH_2); 126.2 (2 CH); 136.3 (C); 141.5 (C); 158.7 (C). HRMS: calcd for $C_{24}H_{38}NO_3$ $[M+H]^+$ 388.2852, found 388.2851.

*4.7.3. (3R,4S)-1-(8-Mentholyl)-3-phenyl-4-(1-phenylvinyl)pyrrolidin-3-ol (**9f**).* Yield: 90%. Colorless oil. $[\alpha]_D^{25}$ +8.2 (*c* 1.1, $CHCl_3$). ^1H NMR (333 K) δ: 0.71–1.00 (m, 3H); 0.81 (d, 3H, *J*=6.5 Hz); 0.98 (s, 3H); 1.15 (s, 3H); 1.32 (m, 1H); 1.46–1.62 (m, 2H); 1.72 (m, 1H); 1.87 (m, 1H); 2.50 (br s, 1H); 3.02–3.21 (m, 2H); 3.34 (m, 1H); 3.51–3.68 (m, 3H); 5.21 (s, 1H); 5.26 (s, 1H); 6.79–6.81 (m, 2H); 6.87–7.02 (m, 6H); 7.17–7.20 (m, 3H). ^{13}C NMR (333 K) δ: 17.1(CH_3); 21.4(CH_3); 21.9(CH_3); 25.6(CH_2); 31.0(CH); 35.1(CH_2); 44.3(CH_2); 48.8 (CH); 49.9 (CH_2); 54.3 (CH); 59.5 (C); 62.3 (CH_2); 72.8 (CH); 79.7 (C); 116.4 (CH_2); 125.0 (2 CH); 126.4 (CH); 126.5 (2 CH); 126.9 (CH); 127.7 (4 CH); 142.1 (C); 143.6 (C); 145.6 (C). IR (Neat): 3275, 3050, 3025, 2945, 1605, 760, 730, 700 cm^{-1}. HRMS: calcd for $C_{28}H_{38}NO_2$ $[M+H]^+$ 420.2903, found 420.2896.

4.8. Synthesis of amino alcohols 10c and 10h

$NaBH_3CN$ (0.52 g, 8.3 mmol) was added to a solution of **7c** or **7h** (3 mmol) in methanol (50 mL) cooled to 0 °C and acidified to pH ~4 by an aqueous solution of HCl 0.1 M. The mixture was heated at 60 °C and the pH maintained at 4 by periodic addition of 0.1 M HCl until the reaction was completed (TLC). The solvents were eliminated under reduced pressure, the residue dissolved in CH_2Cl_2 (40 mL), and an aqueous solution of KOH 2.5 M (25 mL) was added. The mixture was stirred for 30 min, the organic layer was decanted, and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash chromatography on silica gel using a mixture of hexane/EtOAc 3:1 as eluent.

*4.8.1. (3S,4R)-4-Isopropenyl-1-(8-mentholyl)-3-(4-methoxyphenyl)pyrrolidin-3-ol (**10c**).* Yield: 86%. Colorless solid. Mp: 138–139 °C (from Hexane). $[\alpha]_D^{25}$ −65.8 (*c* 0.4, $CHCl_3$). ^1H NMR (333 K) δ: 0.78–1.11 (m, 3H); 0.84 (d, 3H, *J*=6.5 Hz); 0.96 (s, 3H); 1.08 (s, 3H); 1.29 (s, 3H); 1.35–1.66 (m, 4H); 1.92 (m, 1H); 2.25 (br s, 1H); 2.90 (dd, 1H, J_1=10.8 Hz, J_2=7.8 Hz); 2.93–3.21 (m, 4H); 3.61 (td, 1H, J_1=10.6 Hz, J_2=4.1 Hz); 3.70 (s, 3H); 4.74 (s, 1H); 4.92 (s, 1H); 6.76 (d, 2H, *J*=8.8 Hz); 7.31 (d, 2H, *J*=8.8 Hz); 8.12 (br s, 1H). ^{13}C NMR (333 K) δ: 17.7 (CH_3); 21.0 (CH_3); 22.0 (CH_3); 24.1 (CH_3); 25.9 (CH_2); 31.1 (CH); 35.2 (CH_2); 44.4 (CH_2); 48.2 (CH_2); 48.7 (CH); 55.2 (CH_3);

56.8 (CH); 59.3 (C); 63.1 (CH_2); 72.9 (CH); 78.6 (C); 113.7 (2 CH); 113.8 (CH_2); 125.9 (2 CH); 137.6 (C); 141.8 (C); 158.6 (C). IR (Nujol dispersion): 3340, 3080, 1640, 1610, 1580, 770, 755, 685 cm^{-1}. HRMS: calcd for $C_{24}H_{38}NO_3$ $[M+H]^+$ 388.2852, found 388.2845.

*4.8.2. (3R,4R)-3-Isopropyl-1-(8-mentholyl)-4-(1-phenylvinyl)pyrrolidin-3-ol (**10h**).* Yield: 85%. Colorless oil. $[\alpha]_D^{25}$ −63.5 (*c* 1.1, $CHCl_3$). ^1H NMR (333 K) δ: 0.72 (d, 3H, *J*=6.8 Hz); 0.77 (d, 3H, *J*=6.8 Hz); 0.87–1.11 (m, 3H); 0.92 (d, 3H, *J*=6.5 Hz); 1.01 (s, 3H); 1.18 (s, 3H); 1.31–1.52 (m, 2H); 1.55–1.73 (m, 3H); 1.96 (m, 1H); 2.71 (d, 1H, *J*=10.4 Hz); 2.91 (m, 1H); 3.02 (d, 1H, *J*=10.4 Hz); 3,23–3.31 (m, 2H); 3.65 (td, 1H, J_1=10.0 Hz, J_2=4.0 Hz); 5.29 (s, 1H); 5.42 (s, 1H); 7.23–7.33 (m, 5H); 8.07 (br s, 1H). ^{13}C NMR (333 K) δ: 17.4 (CH_3); 17.5 (CH_3); 18.0 (CH_3); 21.1 (CH_3); 22.0 (CH_3); 25.9 (CH_2); 31.1 (CH); 35.2 (CH_2); 35.6 (CH); 44.5 (CH_2); 48.4 (CH); 48.5 (CH); 50.6 (CH_2); 54.6 (CH_2); 59.2 (C); 72.8 (CH); 81.2 (C); 117.0 (CH_2); 126.8 (2 CH); 127.5 (CH); 128.3 (2 CH); 143.4 (C); 146.9 (C). IR (Neat): 3400, 3055, 2950, 2875, 1625, 1600, 775, 735, 700 cm^{-1}. HRMS: calcd for $C_{25}H_{40}NO_2$ $[M+H]^+$ 386.3059, found 386.3053.

4.9. Elimination of the menthol appendage

A solution of amino derivatives **9b**, **9c**, **19f**, **10c** or **10h** (1.0 mmol) and PCC (1.3 g, 6 mmol) in CH_2Cl_2 (40 mL) and 4 Å molecular sieves (2 g) was stirred at room temperature until the oxidation was finished (TCL, 3–6 h). The solvent was eliminated under reduced pressure, the residue was dissolved in a 15% aqueous solution of NaOH (25 mL), and the resulting solution was extracted with EtOAc. The organic phase was washed with brine and dried over anhydrous magnesium sulfate. The solvents were eliminated under vacuum, the residue was taken up in a 2.5 M solution (16 mL) of KOH in THF/MeOH/H_2O (2:1:1), and the solution was stirred at room temperature for 5–6 h. After elimination of the solvents under reduced pressure, the residue was dissolved in 50 mL of CH_2Cl_2 and washed with H_2O. The organic layer was dried over $MgSO_4$ and filtered and the solvent was eliminated under vacuum to give an oily residue that was treated with an excess of tosyl chloride in diisopropylethylamine in ethyl acetate for 72 h. After elimination of the solvents, the residues were purified by flash chromatography on silica gel using a mixture of hexane/EtOAc 15:1 as eluent.

*4.9.1. (3R,4S)-4-Isopropenyl-3-(p-tolyl)-1-tosylpyrrolidin-3-ol (**11b**).* Yield: 54%. Colorless oil. $[\alpha]_D^{25}$ +8.5 (*c* 1.5, $CHCl_3$). ^1H NMR δ: 1.23 (s, 3H); 2.12 (br s, 1H); 2.31 (s, 3H); 2.44 (s, 3H); 3.11 (dd, 1H, J_1=11.5 Hz, J_2=7.3 Hz); 3.46 (dd, 1H, J_1=11.5 Hz, J_2=9.4 Hz); 3.59 (d, 1H, *J*=11.3 Hz); 3.67 (d, 1H, *J*=11.3 Hz); 3.74 (dd, 1H, J_1=9.4 Hz, J_2=7.3 Hz); 4.73 (s, 1H); 4.96 (s, 1H); 7.12 (d, 2H, *J*=8.2 Hz); 7.23 (d, 2H, *J*=8.2 Hz); 7.34 (d, 2H, *J*=8.2 Hz); 7.76 (d, 2H, *J*=8.2 Hz). ^{13}C NMR δ: 20.9 (CH_3); 21.6 (CH_3); 24.3 (CH_3); 50.1 (CH_2); 55.5 (CH); 62.7 (CH_2); 79.7 (C); 114.6 (CH_2); 124.8 (2 CH); 127.6 (2 CH); 129.0 (2 CH); 129.6 (2 CH); 133.9 (C); 137.2(C); 138.4 (C); 139.7 (C); 143.5 (C). IR (Neat): 3505, 3025, 2950, 2925, 1640, 1595, 735, 660 cm^{-1}. HRMS: calcd for $C_{21}H_{25}NO_3NaS$ $[M+Na]^+$ 394.1453, found 394.1457.

*4.9.2. (3R,4S)-4-Isopropenyl-3-(4-methoxyphenyl)-1-tosylpyrrolidin-3-ol (**11c**).* Yield: 46%. Colorless oil. $[\alpha]_D^{25}$ +18.2 (*c* 0.9 $CHCl_3$). ^1H NMR δ: 1.18 (s, 3H); 1.97 (s, 1H); 2.38 (s, 3H); 3.02 (dd, 1H, J_1=11.5 Hz, J_2=7.3 Hz); 3.38 (dd, 1H, J_1=11.5 Hz, J_2=9.4 Hz); 3.50 (d, 1H, *J*=11.3 Hz); 3.59 (d, 1H, *J*=11.3 Hz); 3.66 (dd, 1H, J_1=9.4 Hz, J_2=7.3 Hz); 3.71 (s, 3H); 4.65 (s, 1H); 4.90 (s, 1H); 6.77 (d, 2H, *J*=8.7 Hz); 7.19 (d, 2H, *J*=8.7 Hz); 7.28 (d, 2H, *J*=8.2 Hz); 7.69 (d, 2H, *J*=8.2 Hz). ^{13}C NMR δ: 21.6 (CH_3); 24.3 (CH_3); 50.0 (CH_2); 55.2 (CH_3); 55.4 (CH); 62.6 (CH_2); 79.5 (C); 113.6 (2 CH); 114.6 (CH_2); 126.1 (2 CH); 127.5 (2 CH); 129.6 (2 CH); 133.3 (C); 133.9 (C); 139.7 (C); 143.5 (C). 158.8 (C). IR (Neat): 3505, 3065, 2955, 1640, 1610, 1515, 830, 755, 660 cm^{-1}. HRMS: calcd for $C_{21}H_{25}NO_4NaS$ $[M+Na]^+$ 410.1402, found 410.1398.

*4.9.3. (3R,4S)-3-Phenyl-4-(1-phenylvinyl)-1-tosylpyrrolidin-3-ol (**11f**).* Yield: 50%. Colorless solid. Mp: 103–104 °C (from Hexane). $[\alpha]_D^{25}$ +15.15 (*c* 0.5 $CHCl_3$). ^1H NMR δ: 2.27 (br s, 1H); 2.45 (s, 3H); 3.51 (dd, 1H, J_1=11.5 Hz, J_2=9.2 Hz); 3.62 (d, 1H, *J*=11.3 Hz); 3.70 (dd, 1H, J_1=11.5 Hz, J_2=7.2 Hz); 3.75 (d, 1H, *J*=11.3 Hz); 3.90 (dd, 1H, J_1=9.2 Hz, J_2=7.2 Hz); 5.13 (s, 1H); 5.30 (s, 1H); 6.82–6.85 (m, 2H); 6.99–7.15 (m, 8H); 7.35 (d, 2H, *J*=8.2 Hz); 7.78 (d, 2H, *J*=8.2 Hz). ^{13}C NMR δ: 21.5 (CH_3); 51.2 (CH_2); 53.3 (CH); 62.6 (CH_2); 80.2 (C); 117.1 (CH_2); 124.9 (2 CH); 126.4 (2 CH); 127.1 (CH); 127.2 (CH); 127.5 (2 CH); 127.8 (2 CH); 127.9 (2 CH); 129.6 (2 CH); 133.7 (C); 140.6 (C); 141.4 (C); 143.5 (C); 143.7 (C). IR (Nujol dispersion): 3510, 3060, 3030, 2955, 2890, 1620, 1600, 760, 705, 670 cm^{-1}. HRMS: calcd for $C_{25}H_{25}NO_3NaS$ $[M+Na]^+$ 442.1453, found 442.1447.

*4.9.4. (3S,4R)-4-Isopropenyl-3-(4-methoxyphenyl)-1-tosylpyrrolidin-3-ol (**12c**).* Yield: 52%. Colorless oil. $[\alpha]_D^{25}$ −14.2 (*c* 1.1, $CHCl_3$). ^1H NMR, ^{13}C NMR and IR data are coincident with those reported for **11c**. HRMS: calcd for $C_{21}H_{25}NO_4NaS$ $[M+Na]^+$ 410.1402, found 410.1387.

*4.9.5. (3R,4R)-3-Isopropyl-4-(1-phenylvinyl)-1-tosylpyrrolidin-3-ol (**12h**).* Yield: 46%. Colorless oil. $[\alpha]_D^{25}$ −40.2 (*c* 1.3, $CHCl_3$). ^1H NMR δ: 0.53 (d, 3H, *J*=6.8 Hz); 0.78 (d, 3H, *J*=6.8 Hz); 1.27 (m, 1H); 1.51 (s, 1H); 2.45 (s, 3H); 3.23 (d, 1H, *J*=11.0 Hz); 3.26 (dd, 1H, J_1=11.5 Hz, J_2=6.9 Hz); 3.38 (dd, 1H, J_1=11.5 Hz, J_2=8.9 Hz); 3.46 (d, 1H, *J*=11.0 Hz); 3.78 (dd, 1H, J_1=8.9 Hz, J_2=6.9 Hz); 5.19 (s, 1H); 5.41 (s, 1H); 7.20–7.33 (m, 5H); 7.35 (d, 2H, *J*=8.2 Hz); 7.78 (d, 2H, *J*=8.2 Hz). ^{13}C NMR δ: 17.5 (CH_3); 17.8 (CH_3); 21.6 (CH_3); 34.4 (CH); 48.1 (CH); 52.1 (CH_2); 55.2 (CH_2); 82.5 (C); 117.4 (CH_2); 126.5 (2 CH); 127.5 (2 CH); 127.8 (CH); 128.5 (2 CH); 129.6 (2 CH); 133.9 (C); 142.6 (C); 143.4 (C); 144.3 (C). IR (Neat): 3515, 3060, 2960, 2880, 1620, 1600, 1495, 780, 735, 710, 665 cm^{-1}. HRMS: calcd for $C_{22}H_{27}NO_3NaS$ $[M+Na]^+$ 408.1609, found 408.1608.

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Supplementary data

Copies of ^1H NMR and ^{13}C NMR spectra for compounds **3b–f**, **3h**, **6b–f**, **6h**, **7b–f**, **7h**, **9b–c**, **9f**, **10c**, **10h**, **11b–c**, **11f**, **12c**, **12h** and copies of NOESY experiments for **6b–d**, **6h**, **7b–d**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.09.091.

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19. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 694507. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail deposit@ccdc.cam.ac.uk).