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Synthesis of enantiopure mono- and disubstituted tetrahydroisoquinolines by 6-*exo* radical cyclizations

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Abstract—2-(*o*-Bromophenyl)-3-allyl- and 2-allyl-3-(*o*-bromobenzyl)-substituted perhydrobenzoxazines, derived from (−)-8-amino menthol, readily cyclized stereoselectively by reaction with tributyltin hydride in the presence of AIBN. The cyclization compounds were transformed into enantiopure 4-alkyl tetrahydroisoquinolines by reductive ring opening of the N,O-acetal moiety with lithium aluminum hydride. Enantiopure 1,4- and 3,4-dialkyl-substituted tetrahydroisoquinolines were also prepared by reaction of the cyclized compounds with methylmagnesium iodide and subsequent elimination of the menthol appendage. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

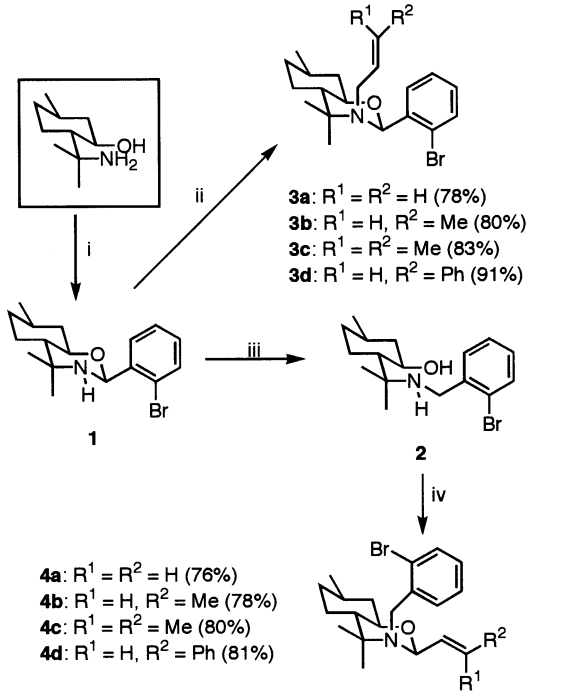
In previous papers we have described the stereoselective synthesis of pyrrolidines by 5-*exo* cyclization of 3-aza-5-hexenyl radicals derived from phenylseleno allylamines[1] and phenylseleno acrylamides.[2,3] Stereoselective 6-*exo* cyclizations of 6-heptenyl radicals, directed to the synthesis of alkaloids[4] or piperidine derivatives[5] have been also reported, although these processes are less selective because competitive intramolecular hydrogen atom abstraction,[6] ring expansion[7] or neophyl rearrangements[8] can appear, especially in reactions of aryl radicals.[9]

The interest of enantiopure 4-substituted[10] and disubstituted-1,2,3,4-tetrahydroisoquinolines[11] lead us to consider the stereoselective synthesis of these compounds by cyclization of 4-aza-6-heptenyl aryl radicals derived from (−)-8-amino menthol. On the other hand, we have previously reported that the regiochemistry of the cyclization in these substrates is dependent on the substitution at the double bond[12] or the relative position of the radical and the acceptor double bond.[13]

In this paper we wish to report in full on our progress along these lines. To this end, we studied radical cyclizations on positional isomeric 2-(*o*-bromophenyl)-3-allyl perhydrobenzoxazines **3a–d** and 2-vinyl-3-(*o*-bromobenzyl) perhydrobenzoxazines **4a–d**, promoted by tributyltin hydride in the presence of AIBN as initiator.

2. Results and discussion

The starting chiral perhydrobenzoxazines were synthesized as summarized in Scheme 1. Compounds **3a–d** were prepared in two steps from (−)-8-aminomenthol by condensation with *o*-bromobenzaldehyde to **1**, and subsequent alkylation with allyl-, crotyl-, prenyl-, and cinnamyl



Scheme 1. *Reagents and conditions*. (i) *o*-BrC_6H_4CHO, CH_2Cl_2, rt, 4 h. (ii) $R^1R^2C{=}CHCH_2Br$, K_2CO_3, MeCN, reflux. (iii) $NaBH_4$, $BF_3{\cdot}OEt_2$, THF, rt, 2 h. (iv) $R^1R^2C{=}CHCHO$, 120°C, sealed tube, 2 h.

Keywords: radical cyclizations; stereoselection; asymmetric synthesis; isoquinolines.

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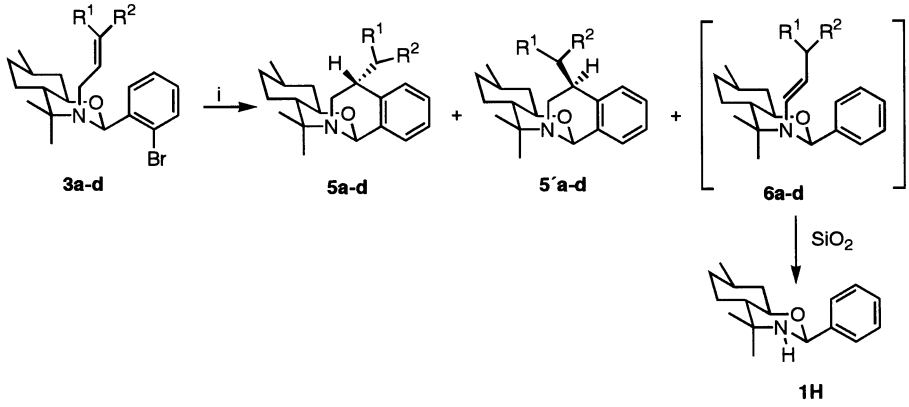


Scheme 2. *Reagents and conditions*. (i) Bu_3SnH, AIBN, benzene, reflux, 13–44 h.

Table 1. Radical cyclization of perhydrobenzoxazines **3a–d**

Start. Mat.	R^1	R^2	Conc.	time (h)	Products (%)[a]	Ratio **5/5′**
3a	H	H	0.02 M	13	**1H** (14):**5** (71)	**5a/5′a**(3/2)
3a	H	H	0.1 M	13	**1H** (20):**5** (67)	**5a/5′a**(3/2)
3b	H	Me	0.02 M	21	**1H** (4):**5** (76)	**5b/5′b**(3/2)
3b	H	Me	0.1 M	21	**1H** (4):**5** (76)	**5b/5′b**(3/2)
3c	Me	Me	0.02 M	20	**1H** (12):**5** (70)	**5c/5′c**(3/2)
3c	Me	Me	0.1 M	20	**1H** (16):**5** (64)	**5c/5′c**(3/2)
3d	H	Ph	0.02 M	44	**1H** (25):**5** (68)	**5d/5′d**(3/2)
3d	H	Ph	0.1 M	44	**1H** (38):**5** (58)	**5d/5′d**(3/2)

[a] Numbers in parentheses refer to the yield of products after isolation and purification.

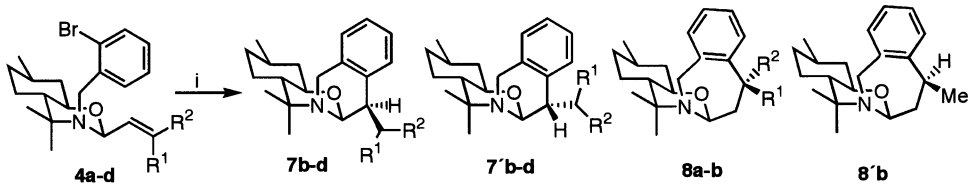
bromides, respectively, with potassium carbonate in acetonitrile at reflux. Compounds **4a–d** were also obtained in good yields by condensation of 8-(*o*-bromobenzylamino) menthol **2**, prepared by reductive ring opening of **1** with sodium borohydride and boron trifluoride in THF, with acrolein, crotonaldehyde, 3,3-dimethylacrolein and cinnamaldehyde in a sealed tube at 120°C.

The cyclization of **3a–d** was carried out by slow addition (6–8 h, syringe pump) of a solution of tributyltin hydride (1.2 equiv.) and AIBN (0.2 equiv.) in benzene, to a solution of the corresponding compound in boiling dry degassed benzene, and the reflux was continued until the starting perhydrobenzoxazine has been consumed. The stannane byproducts were removed by treatment with 10% solution of potassium fluoride in water and the solids were eliminated by filtration through a pad of celite. To check the effect of the concentration on the products distribution, the reactions were carried out in two different concentrations (0.02 M and 0.1 M) of the initial solution of perhydrobenzoxazines, and the results are summarized in Scheme 2 and Table 1.

From these results it can be deduced that the reactions occurred regioselectively to the 6-*exo* cyclization products obtained, in good to moderate yields, as a mixture (3/2) of diastereoisomers **5a–d** and **5′a–d** at the newly created stereocenter. It is noteworthy that the ratio of diastereoisomers is independent on both the nature of substituents and the dilution conditions, and the major diastereoisomers have *R* configuration as determined by NOESY experiments after isolation of the pure compounds and comparison of the spectroscopical properties for the known **10a**.[14] The cyclization products were contaminated with different amounts of N-vinyl perhydrobenzoxazines **6a–d**, resulting from the 1,5-hydrogen shift in the intermediate radical.[5] These compounds were only observed in the reaction mixtures by ^{1}H NMR, because they were hydrolysed to 2-phenyl perhydrobenzoxazine **1H** and the corresponding aldehyde when the reaction mixtures were subjected to purification by flash chromatography on silica gel. On the other hand, the hydrogen translocation products increased with the concentration of the reaction, and the stabilization of the rearranged radical. In this way, the benzylic character of the radical forced the rearrangement in the initial intermediate formed from **3d** to occur in the greatest extension (25–38%). It is also interesting to note that no direct reduction products were formed in the reactions.

Previously we had demonstrated that the 1,5-hydrogen migration products were not formed when the radicals were generated at the alkyl substituent on the nitrogen atom and the acceptor double bond was placed at the acetallic carbon.[5] On the basis of that fact, and trying to improve both the chemical yields and the stereodifferentiation of the processes, we studied the cyclization, in the above experimental conditions, of regioisomeric 2-allyl-N-(*o*-bromobenzyl) perhydrobenzoxazines **4a–d** (Scheme 3 and Table 2).

To our surprise, the parent 2-allyl-substituted derivative **4a** was regiospecifically transformed into the 7-*endo* cyclization product **8a** after refluxing for 10 h in benzene with tributyltin hydride (1.2 equiv.) and AIBN (0.2 equiv.),[13] independently of the concentration of the reaction. The presence of susbtituents at the outer position of the accepting double bond disfavored the 7-*endo* cyclization,[15] and in this way, the crotyl derivative **4b** yielded an equimolar mixture of the six-membered **7b** and **7′b** and seven-membered derivatives **8b** and **8′b**, whereas **4c**, with two methyl groups β in the double bond lead regiospecifically to the 6-*exo* cyclization product **7c**. The cinnamyl derivative **4d** also gave the six-membered derivatives **7d** and **7′d** probably as a consequence of the benzylic character of the intermediate cyclized radical. As expected, no products resulting from 1,5-hydrogen shift were found because the radicals formed from **4a–d** are unable to adopt the chair-like conformation required for migration.[5]



Scheme 3. *Reagents and conditions*. (i) Bu_3SnH, AIBN, benzene, reflux, 8–13 h.

Table 2. Radical cyclization of perhydrobenzoxazines **4a–d**

Start. Mat.	R^1	R^2	Conc.	time (h)	Prod (%)[a]	Ratio **7,8/7′,8′**
4a	H	H	0.02 M	10	**8a** (70)	
4a	H	H	0.1 M	10	**8a** (70)	
4b	H	Me	0.02 M	9	**7b** (34)	(**7b/7′b**: 3/1)
					8b (34)	(**8b/8′b**: 3/1)
4b	H	Me	0.1 M	9	**7b** (34)	(**7b/7′b**: 3/1)
					8b (34)	(**8b/8′b**: 3/1)
4c	Me	Me	0.02 M	8	**7c** (70)[b]	
4c	Me	Me	0.1 M	8	**7c** (70)[b]	
4d	H	Ph	0.02 M	13	**7d** (75)	(**7d/7′d**: 2/1)
4d	H	Ph	0.1 M	13	**7d** (75)	(**7d/7′d**: 2/1)

[a] Numbers in parentheses refer to the yield of products after isolation and purification.
[b] The corresponding epimeric compound **7′c** was not detected by ^1H NMR on the reaction mixture.

The stereochemical outcome of the cyclization of **4a–d** is also noteworthy. The major cyclization stereoisomers also had *R* configuration at the created stereocenter as demonstrated by NOESY experiments, but the facial discrimination was better than for **3a–d**, and the diastereomeric excesses depend on the substituents at the double bond. The formation of the major diastereoisomer can be explained because the cyclization occurs in a chair-like transition state where the substituent lies on a pseudoequatorial conformation.[16] The formation of **7c** as a single diastereoisomer is a consequence of the 1,3-allylic strain acting in the radical formed from **4c** (as shown in Fig. 1).[17]

Major diastereoisomers **5a–d**, **7b–d**, and **8b** were isolated by flash chromatography and transformed into enantiopure (*R*)-4-alkyl substituted tetrahydroisoquinolines **10a–d** or (*R*)-5-methyl tetrahydro-2-benzazepine **11b**, respectively, in 66–72% yield as summarized in Scheme 4.

To this end, cyclized products **5a–d** were reacted with lithium aluminum hydride and aluminum chloride in THF at 0°C yielding quantitatively the amino menthol derivatives **9a–d**. The same reductive treatment on **7b–d** lead to **9b–d** demonstrating that the configuration at the stereocenter created in the cyclization reaction is coincident for both regioisomers. Aminomenthols **9a–d** were converted into tetrahydroisoquinolines **10a–d** by oxidation to the 8-aminomenthone derivatives with a buffered (sodium acetate) solution of PCC in CH_2Cl_2, followed by elimination of the menthol appendage by treatment with a solution of KOH in H_2O/MeOH/ THF at room temperature. When the oxidation was carried out in the absence of sodium acetate variable amounts of 3,4-dihydro isoquinolines were obtained. The sequential reductive ring opening-oxidation-elimination on **8b** gave tetrahydrobenzazepine **11b** in 71% overall yield.

The easy stereoselective ring opening of perhydrobenzoxazines by organometallics[18] opens the possibility to obtain enantiopure dialkyl substituted tetrahydro isoquinolines from cyclization products. In fact, **5a** and **5d** reacted with methylmagnesium iodide in Et_2O, at room temperature, yielding quantitatively **12a** and **12d** as single diastereoisomers. Oxidation of these aminomenthol derivatives with buffered solution of PCC in methylene chloride, and elimination with a solution of KOH lead to 1,4-disubstituted tetrahydroisoquinolines, which were isolated as tosylates **13a** and **13d** in 57% and 59% overall yield by reaction with tosyl chloride in the presence of diisopropyl amine (Scheme 5).

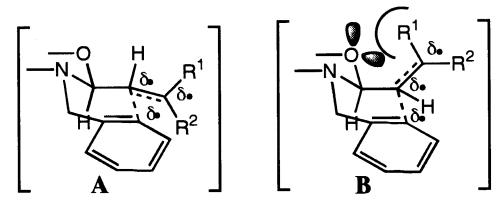
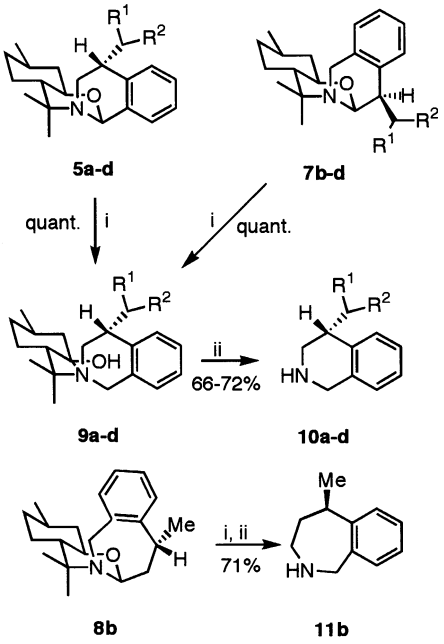
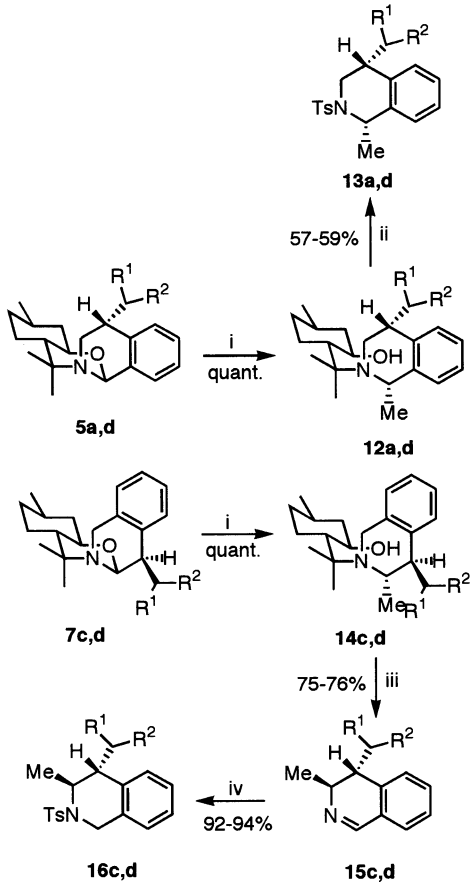


Figure 1. T.E. proposed for the formation of major and minor **7b–d** and **7′b–d**.



Scheme 4. *Reagents and conditions*. $LiAlH_4$, $AlCl_3$, THF, −20°C, 0.5 h. (ii) PCC, NaOAc, 3Å molecular sieves, CH_2Cl_2, rt, 2 h., then KOH, MeOH/ THF/H_2O.



Scheme 5. *Reagents and conditions.* (i) MeMgI, OEt_2, 0°C, then, NH_4Cl, H_2O. (ii) PCC, NaOAc, 3Å molecular sieves, CH_2Cl_2, rt, 2 h., then KOH, MeOH/THF/H_2O, then TsCl, $(i\text{-Pr})_2NH$. (iii) $NaBH_4$, EtOH, rt, then TsCl, $(i\text{-Pr})_2NH$.

The stereochemistry of final 1,4-disubstituted tetrahydroisoquinolines was established on the basis of their ^1H NMR data. The values of the measured and calculated[19,20] coupling constants between protons at C-3 and C-4 showed a *cis* relationship of substituents at C-1 and C-4, and consequently *S* configuration for C-1. This fact was also in agreement with the stereochemical outcome in the ring opening reaction of the N,O-acetal moiety by magnesium derivatives.[18]

Compounds **7c** and **7d** were also transformed into 3,4-disubstituted tetrahydroisoquinolines in the same way. Reaction with methylmagnesium iodide yielded aminomenthol derivatives **14c** and **14d**, which were subjected to oxidation with a buffered solution of PCC in CH_2Cl_2 leading directly to 3,4-disubstituted-3,4-dihydro isoquinolines **15c** and **15d**. Reaction of dihydroderivatives with sodium borohydride in ethanol lead to the final 3,4-disubstituted tetrahydro isoquinolines isolated as tosylates **16c** and **16d** by treatment with tosyl chloride and diisopropylamine. The stereochemistry of the final terahydro isoquinolines was also established by ^1H NMR data, because the 0 Hz coupling constant for hydrogens at C-3 and C-4 points to that the dihedral angle between these protons is 90° only possible if both are in a *trans* relationship. The configuration at C-3 was then established to be *S*.

3. Experimental

All solvents employed were distilled prior to use. Benzene was dried by distillation over sodium/benzophenone. All commercially available products were used without purification. TLC was performed on silica gel 60 F254 plates. Flash chromatography was conducted using 240–300 mesh silica gel. Melting points were determined on capillary open tubes, and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a sodium lamp (254 nm). Proton and carbon magnetic resonance spectra were recorded on a Bruker AC-300 or Bruker ARX-300 (300 MHz for proton, 75.2 MHz for carbon) using $CDCl_3$ as solvent; chemical shifts (δ) are given in ppm related to tetramethylsilane (TMS) as internal reference (δ=0 for TMS). Mass spectra were obtained on a Hewlett–Packard 5988 A spectrometer by chemical ionization. Infrared spectra were registered on a Philips PU9706 apparatus, neat or as a nujol dispersion.

3.1. 2α-(*o*-Bromophenyl)-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 1

A solution of (−)-8-aminomenthol (5 g, 29.2 mmol) and 2-bromobenzaldehyde (6 g, 32.2 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature until the starting aminoalcohol had disappeared (by TLC). Then sodium sulfate was added to the solution and the mixture was stirred for 10 min, the solid was filtered off and the solvent was removed under vacuum. The resulting perhydrobenzoxazine was purified by recrystallization. 98% yield. White solid (from ethanol); mp 74–76°C. $[\alpha]_D^{25}$=+63.7 (c=0.9, $CHCl_3$). ^1H NMR (δ): 0.90–1.05 (2H, m); 0.93 (3H, d, *J*=6.5 Hz); 1.10 (3H, s); 1.10–1.20 (1H, m); 1.24 (3H, s); 1.45–1.60 (2H, m); 1.65–1.80 (2H, m); 1.92–2.02 (1H, m); 3.61 (1H, td, *J*=4.1 Hz, 10.4 Hz); 5.64 (1H, s); 7.08–7.60 (4H, m). ^{13}C NMR (δ): 19.4; 22.3; 25.2; 29.8; 31.3; 35.0; 41.6; 51.6; 52.2; 76.7; 83.4; 122.5; 127.1; 127.6; 129.4; 132.8; 139.8. IR (nujol): 3300, 2920, 750 cm^{-1}. MS (*m/z*, %): 338 (M+1, 100), 340 (M+3, 94). Anal. Calcd for $C_{17}H_{24}BrNO$: C, 60.36; H, 7.15; N. 4.14. Found: C, 60.48; H, 7.09; N. 4.03.

3.2. *N*-(*o*-Bromobenzyl)-8-aminomenthol 2

To a cooled (0°C) suspension of sodium borohydride (1.90 g, 50 mmol) and $BF_3{\cdot}OEt_2$ (100 mL, 1 M solution) in dry THF (60 mL) was slowly added a solution of perhydrobenzoxazine **1** (8.45 g., 25 mmol) in THF (30 mL). The reaction mixture was stirred at room temperature for two hours and then quenched by slow addition of methanol (20 mL), and stirred for additional 30 minutes. The volatiles were eliminated in a rotavapor and the resulting solid was treated with a 20% solution of NaOH (20 mL) and solid NaOH (2 g) and refluxed for 1 h. The mixture was cooled and extracted with chloroform (5×75 mL), washed with brine, dried over sodium sulfate and the solvent removed. The resulting solid was recrystallized from hexanes to afford **2** in 98% yield. White solid (from hexanes); mp 90–91°C. $[\alpha]_D^{25}$=−25.2 (c=1.2, $CHCl_3$). ^1H NMR (δ): 0.85–1.12 (3H, m); 0.91 (3H, d, *J*=6.5 Hz); 1.21 (3H, s); 1.26 (3H, s); 1.27–1.52 (2H, m); 1.63–1.73 (2H, m); 1.89–1.98 (1H, m); 3.65 (1H, dt, *J*=4.1 Hz, 10.4 Hz); 3.84 (1H, d_{AB}, *J*=11.8 Hz);

3.86 (1H, d_{AB}, J=11.8 Hz); 7.08–7.52 (4H, m). ^{13}C NMR (δ): 21.2; 22.1; 25.7; 26.0; 31.0; 35.0; 44.3; 45.8; 49.9; 57.2; 72.4; 123.9; 127.9; 128.9; 130.7; 132.6; 138.3. IR (nujol): 3200, 2920, 740 cm^{-1}. MS (*m*/*z*, %): 340 (M+1, 100), 342 (M+3, 94). Anal. calcd. for $C_{17}H_{26}BrNO$: C, 60.00; H, 7.70; N, 4.12. Found: C, 59.87; H, 7.89; N, 4.26.

3.3. *N*-Alkylation of perhydrobenzoxazine 1. General method

A mixture of perhydrobenzoxazine **1** (1.69 g, 5.0 mmol), potassium carbonate (0.69 g, 7 mmol) and the corresponding allyl bromide (7.5 mmol), in acetonitrile (8 mL) was refluxed with stirring until the reaction was finished (12–48 h) (TLC). When the reaction was completed, the solid was separated by filtration, the solid was washed with hot EtOAc (25 mL), and the solvents were eliminated on rotavapor. The residue was purified by recrystallization in the appropriate solvent.

3.3.1. *N*-Allyl-2α-(*o*-bromophenyl)-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 3a. 78% yield. White solid (from ethanol); mp 78–79°C. $[\alpha]_D^{25}$=+23.4 (c=1.0, $CHCl_3$). ^{1}H NMR (δ): 0.90–1.05 (2H, m); 0.94 (3H, d, J=6.4 Hz); 1.10–1.25 (1H, m); 1.16 (3H, s); 1.36 (3H, s); 1.43–1.58 (2H, m); 1.62–1.77 (2H, m); 1.92–1.98 (1H, m); 3.00 (1H, dd, J=5.4 Hz, 17.5 Hz); 3.28 (1H, dd, J=5.4 Hz, 17.5 Hz); 3.64 (1H, dt, J=4.1 Hz, 10.5 Hz); 4.60 (1H, dd, J=1.8 Hz, 9.3 Hz); 4.77 (1H, dd, J=1.8 Hz, 17.1 Hz); 5.39–5.52 (1H, m); 5.83 (1H, s); 7.08–7.66 (4H, m). ^{13}C NMR (δ): 18.8; 22.3; 25.0; 27.0; 31.3; 35.1; 41.5; 45.5; 47.0; 57.6; 76.3; 86.9; 112.8; 123.4; 126.9; 129.0; 130.2; 132.3; 139.2; 140.0; IR (nujol): 3060, 2920, 750 cm^{-1}. MS (*m*/*z*, %): 378 (M+1, 100), 380 (M+3, 92). Anal. Calcd for $C_{20}H_{28}BrNO$: C, 63.49; H, 7.46; N, 3.70. Found: C, 63.63; H, 7.42; N, 3.78.

3.3.2. *N*-Crotyl-2α-(*o*-bromopheny)-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 3b. 80% yield. White solid (from ethanol); mp 51–53°C. $[\alpha]_D^{25}$=+28.8 (c=1.0, $CHCl_3$). ^{1}H NMR (δ): 0.90–1.05 (2H, m); 0.95 (3H, d, J=6.5 Hz); 1.08–1.25 (1H, m); 1.18 (3H, s); 1.33 (3H, s); 1.39 (3H, d, J=4.8 Hz); 1.45–1.60 (2H, m); 1.62–1.78 (2H, m); 1.92–2.00 (1H, m); 2.87–2.94 (1H, m); 3.15–3.24 (1H, m); 3.63 (1H, dt, J=4.1 Hz, 10.5 Hz); 4.99–5.07 (2H, m); 5.80 (1H, s); 7.06–7.70 (4H, m). ^{13}C NMR (δ): 17.6; 18.2; 22.3; 25.0; 27.1; 31.3; 35.0; 41.5; 44.9; 47.4; 57.5; 76.1; 87.0; 123.4 (2 C); 126.8; 129.0; 130.4; 132.2; 132.6; 139.2. IR (nujol): 3060, 2920, 750 cm^{-1}. MS (*m*/*z*, %): 392 (M+1, 100), 394 (M+3, 84). Anal. Calcd for $C_{21}H_{30}BrNO$: C, 64.28; H, 7.71; N, 3.57. Found: C, 64.43; H, 7.56; N, 3.65.

3.3.3. *N*-Prenyl-2α-(*o*-bromophenyl)-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 3c. 83% yield. White solid (from ethanol); mp 63–64°C. $[\alpha]_D^{25}$=+36.5 (c=1.0, $CHCl_3$). ^{1}H NMR (δ): 0.90–1.05 (2H, m); 0.93 (3H, d, J=6.5 Hz); 1.10–1.20 (1H, m); 1.17 (3H, s); 1.21 (3H, s); 1.25 (3H, s); 1.41 (3H, s); 1.45–1.60 (2H, m); 1.65–1.75 (2H, m); 1.90–2.00 (1H, m); 2.95 (1H, dd, J=6.3 Hz, 16.8 Hz); 3.20 (1H, dd, J=4.1 Hz, 10.5 Hz); 3.62 (1H, td, J=4.1 Hz, 10.5 Hz); 4.82 (1H, t, J=5.9 Hz); 5.79 (1H, s); 7.03–7.69 (4H, m). ^{13}C NMR (δ): 17.3; 17.8; 22.3; 25.1; 25.5; 27.0; 29.7; 31.3; 35.0; 41.5; 47.6; 57.6; 76.1; 87.3; 123.3; 126.9; 128.5; 129.1; 130.5; 132.3; 139.0. IR (nujol): 3050, 2940, 760 cm^{-1}. MS (*m*/*z*, %): 406 (M+1, 100), 408 (M+3, 73). Anal. Calcd for $C_{22}H_{32}BrNO$: C, 65.02; H, 7.94; N, 3.45. Found: C, 64.89; H, 7.89; N, 3.51.

3.3.4. *N*-Cinnamyl-2α-(*o*-bromophenyl)-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 3d. 91% yield. Oil. $[\alpha]_D^{25}$=+31.5 (c=0.9, $CHCl_3$). ^{1}H NMR (δ): 0.90–1.05 (2H, m); 0.95 (3H, d, J=6.5 Hz); 1.10–1.20 (1H, m); 1.39 (6H, s); 1.45–1.60 (2H, m); 1.65–1.75 (2H, m); 1.95–2.05 (1H, m); 3.17 (1H, dd, J=5.2 Hz, 17.7 Hz); 3.42 (1H, m); 3.67 (1H, dt, J=4.1 Hz, 10.5 Hz); 5.85 (1H, m); 5.88 (1H, s); 6.07 (1H, d, J=15.9 Hz); 6.98–7.52 (9H, m). ^{13}C NMR (δ): 18.9; 22.4; 25.1; 27.1; 31.4; 35.1; 41.6; 45.1; 47.1; 57.6; 76.4; 87.0; 123.4; 126.6; 127.0; 127.5; 128.3; 129.3; 130.3; 132.4; 137.8; 138.8. IR (neat): 3050, 2940, 755, 695 cm^{-1}. MS (*m*/*z*, %): 454 (M+1, 100), 456 (M+3, 88). Anal. Calcd for $C_{26}H_{32}BrNO$: C, 68.72; H, 7.10; N, 3.08. Found: C, 68.79; H, 7.06; N, 3.17.

3.4. Synthesis of perhydrobenzoxazines 4a–h. General procedure

A mixture of aminoalcohol **2** (0.51 g, 1.5 mmol) and the corresponding aldehyde (3 mmol) were heated at 120°C in an oil bath in a sealed tube without solvent. When the reaction is finished (TLC) the mixture was dissolved in ethanol (50 mL) and the solvents were distilled under vacuum. The residues were purified by flash chromatography (silica gel, hexane/EtOAc: 10/1) or by recrystallization.

3.4.1. *N*-(*o*-Bromobenzyl)-2α-vinyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 4a. 76% yield. Oil. $[\alpha]_D^{25}$=−36.6 (c=2.0, $CHCl_3$). ^{1}H NMR (δ): 0.94 (3H, s); 0.95–1.05 (2H, m); 0.95 (3H, d, J=6.5 Hz); 1.11–1.23 (1H, m); 1.26 (3H, s); 1.40–1.80 (4H, m); 1.91–2.02 (1H, m); 3.57 (1H, dt, J=4.1 Hz, 10.6 Hz); 3.81 (1H, d_{AB}, J=10.4 Hz); 3.86 (1H, d_{AB}, J=10.4 Hz); 5.08 (1H, d, J=10.5 Hz); 5.14 (1H, d, J=3.9 Hz); 5.38 (1H, d, J=17.3 Hz); 5.62 (1H, ddd, J=4.4 Hz, 10.5 Hz, 17.3 Hz); 7.00–7.83 (4H, m). ^{13}C NMR (δ): 19.5; 20.3; 25.0; 26.3; 31.4; 34.9; 41.4; 46.6; 47.4; 56.7; 76.7; 87.3; 117.9; 122.0; 126.8; 127.3; 130.0; 131.9; 136.8; 142.3. IR (neat): 3020, 2900, 740 cm^{-1}. MS (*m*/*z*, %): 378 (M+1, 100), 380 (M+3, 82). Anal. Calcd for $C_{20}H_{28}BrNO$: C, 63.49; H, 7.46; N, 3.70. Found: C, 63.65; H, 7.29; N, 3.57.

3.4.2. *N*-(*o*-Bromobenzyl)-2α-(1′-propenyl)-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 4b. 78% yield. Oil. $[\alpha]_D^{25}$=−31.1 (c=1.1, $CHCl_3$). ^{1}H NMR (δ): 0.88–0.98 (2H, m); 0.94 (3H, d, J=6.5 Hz); 0.97 (3H, s); 1.02–1.12 (1H, m); 1.20 (3H, s); 1.32–1.50 (2H, m); 1.49 (3H, dd, J=0.7 Hz, 6.6 Hz); 1.52–1.70 (2H, m); 1.85–1.95 (1H, m); 3.53 (1H, dt, J=4.2 Hz, 10.6 Hz); 3.75 (1H, d, J=18.1 Hz); 3.85 (1H, d, J=18.1 Hz); 4.99 (1H, d, J=5.4 Hz); 5.15–5.25 (1H, m); 5.73–5.85 (1H, m); 6.99–7.82 (4H, m). ^{13}C NMR (δ): 17.6; 18.1; 22.2; 25.0; 26.5; 31.3; 34.9; 41.4; 47.5; 56.7; 75.4; 88.0; 122.1; 126.8; 127.2; 129.5; 130.2; 130.4; 131.7; 142.4. IR (neat): 3080, 2920, 750 cm^{-1}. MS (*m*/*z*, %): 392 (M+1, 100), 394 (M+3, 79). Anal. Calcd for $C_{21}H_{30}BrNO$: C, 64.28; H, 7.71; N, 3.57. Found: C, 64.39; H, 7.58; N, 3.72.

3.4.3. *N*-(*o*-Bromobenzyl)-2α-(2′-methyl-1′-propenyl)-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 4c. 80% yield. Oil. $[\alpha]_D^{25}=-22.1$ (c=2.1, $CHCl_3$). ^{1}H NMR (δ): 0.90–1.08 (2H, m); 0.94 (3H, d, *J*=6.5 Hz); 0.97 (3H, s); 1.08–1.22 (1H, m); 1.28 (3H, s); 1.47 (3H, s); 1.48–1.55 (2H, m); 1.60–1.80 (2H, m); 1.73 (3H, s); 1.91–2.02 (1H, m); 3.57 (1H, dt, *J*=4.1 Hz, 10.5 Hz); 3.79 (1H, d, *J*=18.1 Hz); 3.88 (1H, d, *J*=18.1 Hz); 5.00 (1H, d, *J*=6.6 Hz); 5.32 (1H, d, *J*=6.6 Hz); 6.98–7.74 (4H, m). ^{13}C NMR (δ): 18.9; 22.3; 25.0; 26.5; 31.4; 35.0; 41.5; 47.5; 56.9; 75.7; 84.5; 122.0; 123.8; 127.0; 130.2; 131.7; 136.8; 142.8. IR (neat): 3060, 2920, 750 cm^{-1}. MS (*m*/*z*, %): 406 (M+1, 100), 408 (M+3, 79). Anal. Calcd for $C_{22}H_{32}BrNO$: C, 65.02; H, 7.94; N, 3.45. Found: C, 65.14; H, 7.88; N, 3.37.

3.4.4. *N*-(*o*-Bromobenzyl)-2α-styryl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 4d. 81% yield. White solid (from ethanol) mp 86–87°C. $[\alpha]_D^{25}=-42.6$ (c=1.2, $CHCl_3$). ^{1}H NMR (δ): 0.92–1.08 (2H, m); 0.96 (3H, d, *J*=6.5 Hz); 1.03 (3H, s); 1.12–1.25 (1H, m); 1.29 (3H, s); 1.45–1.65 (2H, m); 1.66–1.80 (2H, m); 1.98–2.08 (1H, m); 3.62 (1H, dt, *J*=4.0 Hz, 10.6 Hz); 3.84 (1H, d, *J*=18.1 Hz); 3.92 (1H, d, *J*=18.1 Hz); 5.26 (1H, d, *J*=4.9 Hz); 5.88 (1H, dd, *J*=4.9 Hz, 16,0 Hz); 6.70 (1H, d, *J*=16.0 Hz); 6.98–7.88 (9H, m). ^{13}C NMR (δ): 19.1; 22.3; 25.1; 26.5; 31.4; 35.0; 41.4; 46.9; 47.6; 56.9; 75.8; 87.6; 122.0; 126.5; 126.9; 127.3; 127.4; 128.2; 128.5; 130.2; 131.9; 132.3; 136.6; 142.2. IR (neat): 3020, 2920, 750, 690 cm^{-1}. MS (*m*/*z*, %): 454 (M+1, 100), 456 (M+3, 90). Anal. Calcd for $C_{26}H_{32}BrNO$: C, 68.72; H, 7.10; N, 3.08. Found: C, 68.81; H, 7.18; N, 3.19.

3.5. Radical cyclizations. General method

To a refluxing solution of perhydrobenzoxazine (6.0 mmol) in dry degassed benzene (60 mL for 0.1 M and 300 mL for 0.02 M concentrations) under argon, was added for a 6–8 h period via syringe pump a solution of tributylin hydride (7.2 mmol) and AIBN (0.36 mmol) in the same solvent. The heating was continued until complete disappearance of the starting material by TLC (Tables 1 and 2) and the solvent was removed in vacuum. The resulting oil was re-dissolved in diethylether, and treated with 10% aqueous solution of KF for 4 h at room temperature. The mixture was filtered and the solid washed with ether. The aqueous layer was extracted with ether (3×50 mL) and the combined organic phases were washed with brine and dried over sodium sulfate. The solid was filtered off and the solvent removed under vacuum. The oily residue was purified by flash chromatography (silica gel, hexane/EtOAc: 10/1).

3.5.1. Compound 5a. 44% yield. Oil. $[\alpha]_D^{25}=-38.6$ (c=0.2, $CHCl_3$) ^{1}H NMR (δ): 0.80–1.15 (3H, m); 0.94 (3H, d, *J*=6.5 Hz); 1.16 (3H, s); 1.21 (3H, s); 1.32 (3H, d, *J*=6.5 Hz); 1.45–1.55 (2H, m); 1.60–1.75 (2H, m); 1.92–2.02 (1H, m); 2.83–2.96 (3H, m); 3.68 (1H, dt, *J*=4.2 Hz, 10.6 Hz); 5.41 (1H, s); 7.12–7.36 (4H, m). ^{13}C NMR (δ): 17.6; 19.4; 22.3; 25.2; 27.0; 31.4; 33.5; 35.0; 41.4; 45.4; 46.6; 55.4; 75.9; 84.3; 125.9; 126.8; 127.7; 128.0; 135.3; 140.5. IR (neat): 3020, 2920, 750 cm^{-1}. MSCI (*m*/*z*, %): 300 (M+1, 100). Anal. Calcd for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.68. Found: C, 80.36; H, 9.88; N, 4.57.

3.5.2. Compound 5b. 47% yield. Oil. $[\alpha]_D^{25}=-43.4$ (c=0.8, $CHCl_3$). ^{1}H NMR (δ): 0.90–1.05 (2H, m); 0.93 (3H, d, *J*=6.5 Hz); 0.99 (3H, t, *J*=10.4 Hz); 1.10 (3H, s); 1.10–1.22 (1H, m); 1.21 (3H, s); 1.42–1.51 (2H, m); 1.65–1.77 (2H, m); 1.78–1.90 (2H, m); 1.97–2.06 (1H, m); 2.61–2.64 (1H, m); 2.75 (1H, dd, *J*=4.3; 11.6 Hz); 3.06 (1H, dd, *J*=5.5; 11.6 Hz); 3.64 (1H, td, *J*=4.2, 10.6 Hz; 5.29 (1H, s); 7.14–7.39 (4H, m). ^{13}C NMR (δ): 12.4; 15.0; 22.3; 25.2; 26.7; 27.4; 31.4; 35.0; 40.5; 41.4; 42.4; 48.1; 55.5; 75.7; 85.0; 125.9; 127.4; 127.5; 127.6; 135.9; 139.9. IR (neat) cm^{-1}: 3085, 2950, 745. MSCI (*m*/*z*, %): 314 (M+1, 100). Anal. Calcd for $C_{21}H_{31}NO$: C, 80.46; H, 9.97; N, 4.47. Found: C, 80.58; H, 9.85; N, 4.59.

3.5.3. Compound 5c. 42% yield. Oil. $[\alpha]_D^{25}=-67.3$ (c=1.1, $CHCl_3$). ^{1}H NMR (δ): 0.80–1.10 (3H, m); 0.89 (3H, d, *J*=6,8 Hz); 0.93 (3H, d, *J*=6.5 Hz); 1.02 (3H, d, *J*=7.0 Hz); 1.12 (3H, s); 1.23 (3H, s); 1.40–1.55 (2H, m); 1.62–1.75 (2H, m); 1.96–2.04 (1H, m); 2.34–2.43 (1H, m); 2.53–2.63 (1H, m); 2.74 (1H, dd, *J*=4.4; 11.5 Hz); 3.16 (1H, dd, *J*=6.5; 11.5 Hz); 3.65 (1H, td, *J*=4.2; 10.6 Hz); 5.32 (1H, s); 7.17–7.38 (4H, m). ^{13}C NMR (δ): 16.2; 19.2; 21.5; 22.3; 25.1; 26.9; 30.1; 31.4; 34.9; 39.7; 41.4; 44.6; 47.4; 55.7; 76.1; 84.9; 125.9; 127.1; 127.7; 127.9; 136.0; 138.5. IR (neat) cm^{-1}: 3085, 2950, 740. MSCI (*m*/*z*, %): 328 (M+1, 100). Anal. Calcd for $C_{22}H_{33}NO$: C, 80.68; H, 10.16; N, 4.28. Found: C, 80.57; H, 10.24; N, 4.41.

3.5.4. Compound 5d. 43% yield. Oil. $[\alpha]_D^{25}=-41.9$ (c=1.7, $CHCl_3$). ^{1}H NMR (δ): 0.83–1.05 (2H, m); 0.95 (3H, d, *J*=6.5 Hz); 0.99 (3H, s); 1.10 (3H, s); 1.10–1.21 (1H, m); 1.38–1.57 (2H, m); 1.64–1.73 (2H, m); 1.99–2.08 (1H, m); 2.55 (1H, dd, *J*=3.1, 11.9 Hz); 2.93 (1H, dd, *J*=3.1, 11.8 Hz); 3.03–3.10 (3H, m); 3.38 (1H, dt, *J*=4.1, 10.6 Hz); 5.21 (1H, s); 7.13–7.46 (9H, m). ^{13}C NMR (δ): 13.9; 22.2; 25.1; 26.6; 31.3; 34.8; 40.6; 41.2; 41.4; 42.6; 48.6; 55.7; 75.7; 85.1; 125.9; 126.2; 127.2; 127.4; 127.7; 128.2; 128.4; 129.0; 129.2; 136.0; 139.0; 141.2. IR (neat) cm^{-1}: 3020, 2910, 750, 700. MSCI (*m*/*z*, %): 376 (M+1, 100). Anal. Calcd for $C_{26}H_{33}NO$: C, 83.15; H, 8.86; N, 3.73. Found: C, 83.31; H, 9.01; N, 3.59.

3.5.5. Compound 7b. 26% yield. Oil. $[\alpha]_D^{25}=-49.8$ (c=0.9, $CHCl_3$). ^{1}H NMR (δ): 0.80–1.05 (3H, m); 0.83 (3H, d, *J*=6.5 Hz); 0.92 (3H, t, *J*=7.5 Hz); 1.18 (3H, s); 1.20 (3H, s); 1.32–1.48 (2H, m); 1.50–1.71 (2H, m); 1.73–1.83 (1H, m); 2.64–2.70 (1H, m); 3.47 (1H, td, *J*=4.0; 10.5 Hz); 3.88 (1H, d, *J*=14.9 Hz); 4.20 (1H, d, *J*=14.9 Hz); 4.76 (1H, d, *J*=2.3 Hz); 6.94–7.20 (4H, m). ^{13}C NMR (δ): 12.0; 20.6; 22.2; 25.1; 26.4; 29.6; 31.4; 35.0; 41.3; 43.6; 43.9; 45.3; 55.9; 76.7; 84.9; 125.3; 125.8; 126.0; 128.6; 133.9; 135.9. IR (neat) cm^{-1}: 3060, 2920, 750. MSCI (*m*/*z*, %): 314 (M+1, 100). Anal. Calcd for $C_{21}H_{31}NO$: C, 80.46; H, 9.97; N, 4.47. Found: C, 80.34; H, 10.12; N, 4.34.

3.5.6. Compound 7c. 70% yield. Oil. $[\alpha]_D^{25}=-82.6$ (c=0.6, $CHCl_3$). ^{1}H NMR (δ): 0.84 (3H, d, *J*=6.5 Hz); 0.88 (3H, d, *J*=6.9 Hz); 0.90–1.05 (3H, m); 0.94 (3H, d, *J*=7.0 Hz); 1.22 (6H, s); 1.42–1.52 (1H, m); 1.54–1.64 (2H, m); 1.65–1.76 (1H, m); 1.79–1.88 (1H, m); 1.89–2.03 (1H, m); 2.68 (1H, dd, *J*=2.2; 5.3 Hz); 3.52 (1H, dt, *J*=4.1; 10.5 Hz); 3.82 (1H, d, *J*=14.9 Hz); 4.01 (1H, d, *J*=14.9 Hz); 4.89 (1H, d, *J*=2.2 Hz); 6.98–7.82 (4H, m).

^{13}C NMR (δ): 19.6; 20.2; 21.0; 22.3; 25.1; 26.5; 31.5; 33.6; 35.1; 41.4; 43.8; 44.2; 49.7; 56.2; 76.6; 83.6; 125.4; 125.6; 125.9; 129.1; 134.9; 135.0. IR (neat) cm^{-1}: 3010, 2920, 745. MSCI (*m/z*, %): 328 (M+1, 100). Anal. Calcd for $C_{22}H_{33}NO$: C, 80.68; H, 10.16; N, 4.28. Found: C, 80.84; H, 9.98; N, 4.19.

3.5.7. Compound 7d. 50% yield. Oil. $[\alpha]_D^{25}=-123.2$ (c=0.8, $CHCl_3$). ^{1}H NMR (δ): 0.80–1.05 (3H, m); 0.83 (3H, d, *J*=6.5 Hz); 1.17 (3H, s); 1.27 (3H, s); 1.22–1.41 (1H, m); 1.52–1.78 (4H, m); 2.86 (2H, d, *J*=7.2 Hz); 3.09–3.14 (1H, m); 3.29 (1H, dt, *J*=4.0; 10.7 Hz); 3.94 (1H, d, *J*=15.0 Hz); 4.16 (1H, d, *J*=15.0 Hz); 4.72 (1H, d, *J*=1.3 Hz); 7.03–7.33 (9H, m). ^{13}C NMR (δ): 22.0; 22.3; 25.2; 26.6; 31.5; 35.2; 41.3; 42.9; 43.6; 44.0; 45.8; 56.2; 77.0; 83.5; 125.8; 126.0; 126.1; 126.3; 128.3; 128.9; 129.4; 133.7; 135.2; 140.5. IR (neat) cm^{-1}: 3010, 2920, 750, 730, 700. MSCI (*m/z*, %): 376 (M+1, 100). Anal. Calcd for $C_{26}H_{33}NO$: C, 83.15; H, 8.86; N, 3.73. Found: C, 83.28; H, 8.71; N, 3.85.

3.5.8. Compound 8a. 70% yield. Oil. $[\alpha]_D^{25}=-67.2$ (c=0.5, $CHCl_3$). ^{1}H NMR (δ): 0.81–1.10 (3H, m); 0.92 (3H, d, *J*=6.5 Hz); 1.11 (3H, s); 1.22 (3H, s); 1.25–1.37 (1H, m); 1.38–1.46 (1H, m); 1.61–1.72 (2H, m); 1.78–1.95 (2H, m); 1.98–2.12 (1H, m); 2.81 (1H, dd, *J*=10.5, 14.9 Hz); 2.99 (1H, dd, *J*=10.5, 13.9 Hz); 3.50 (1H, td, *J*=4.2, 10.6 Hz); 3.54 (1H, d, *J*=15.0 Hz); 4.04 (1H, d, *J*=15.0 Hz); 4.67 (1H, broad s); 7.05–7.10 (4H, m). ^{13}C NMR (δ): 22.3; 25.1; 27.2; 27.3; 28.9; 31.3; 33.4; 34.9; 41.5; 46.3; 48.1; 56.6; 75.0; 86.6; 125.6; 126.3; 127.9; 129.1; 140.3; 141.5. IR (neat) cm^{-1}: 3060, 2920, 750. MSCI (*m/z*, %): 300 (M+1, 100). Anal. Calcd for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.68. Found: C, 80.34; H, 9.64; N, 4.79.

3.5.9. Compound 8b. 26% yield. Oil. $[\alpha]_D^{25}=-12.6$ (c=0.8, $CHCl_3$). ^{1}H NMR (δ): 0.83–1.03 (3H, m); 0.91 (3H, d, *J*=6.5 Hz); 1.04 (3H, s); 1.25–1.40 (2H, m); 1.30 (3H, s); 1.38 (3H, d, *J*=7.0 Hz); 1.58–1.77 (3H, m); 1.83–1.94 (1H, m); 1.95–2.06 (1H, m); 3.13–3.24 (1H, m); 3.40–3.51 (2H, m); 3.83–3.87 (1H, m); 4.45–4.47 (1H, m); 7.04–7.25 (4H, m). ^{13}C NMR (δ): 20.1; 21.9; 24.9; 26.5; 30.8; 34.4; 41.1; 47.1; 49.1; 56.7; 74.0; 87.8; 125.6; 126.7; 128.5; 139.2; 145.0. IR (neat) cm^{-1}: 3060, 2920, 750. MSCI (*m/z*, %): 314 (M+1, 100). Anal. Calcd for $C_{21}H_{31}NO$: C, 80.46; H, 9.97; N, 4.47. Found: C, 80.54; H, 9.86; N, 4.36.

3.6. Synthesis of 4-substituted-1,2,3,4-tetrahydroisoquinolines. General method

3.6.1. Reductive cleavage. To a suspension of $LiAlH_4$ (0.19 g, 5 mmol) and $AlCl_3$ (0.23 g, 1.7 mmol) in anhydrous THF (15 mL) was dropped a solution of the corresponding cyclized product **5a–d**, **7b–d** or **8b** (1 mmol) in the same solvent (7 mL) at 0°C under argon, and the solution was stirred for 20–30 min. The reaction mixture was hydrolyzed by addition of water, the solids were separated by filtration, and the solids were washed with EtOAc (2×15 mL). The solution was dried over anhydrous $MgSO_4$, the solvents were eliminated in vacuo and the amino menthol derivatives were used in the next step without further purification.

3.6.2. Oxidation–elimination. The corresponding amino menthol (0.05 mmol) derivative was dissolved in CH_2Cl_2 (7 mL) and added to a mixture of PCC (0.2 mmol), NaOAc (0.05 mmol) and 3 Å molecular sieves, and stirred at rt for 2 h. The reaction mixture was cooled to 0°C and treated for 15 min. with 2 M NaOH solution (2 mL). The organic layer was decanted, and the aqueous phase extracted with $CHCl_3$. The organics were washed with brine, dried over anhydrous Na_2SO_4, and the solvents removed. The residue was redissolved in THF (1 mL), MeOH (0.3 mL) and 2.5 M KOH solution (0.3 mL), and the mixture was stirred overnight. The volatiles were eliminated, and the residue was acidified with 1 N solution of HCl and extracted with Et_2O. The aqueous phase was made alkaline by addition of 2 M NaOH solution and extracted with $CHCl_3$. The organic phase was washed, dried and concentrated, and the residue was purified by flash chromatography (silica gel, $CHCl_3$/EtOH). In this way were prepared the following compounds.

3.6.3. (*R*)-4-Methyl-1,2,3,4-tetrahydroisoquinoline 10a. Reductive ring opening of compound **5a** yielded quantitatively **9a**, which was transformed, without isolation, into **10a**. 68% from **5a**. Oil. $[\alpha]_D^{25}=+47.2$ (c=0.5, $CHCl_3$). ^{1}H NMR (δ): 1.29 (3H, d, *J*=6.7 Hz); 2.51 (1H, broad s); 2.81 (1H, dd, *J*=6.1, 12.3 Hz); 2.89 (1H, m); 3.22 (1H, dd, *J*=4.6, 12.3 Hz); 4.01 (2H, s); 6.99–7.26 (4H, m). ^{13}C NMR (δ): 20.5; 31.9; 48.6; 51.0; 125.7; 125.9; 126.2; 128.1; 135.4; 140.0. IR (neat) cm^{-1}: 3280, 3060, 2920, 750. MSCI (*m/z*, %): 148 (M+1, 100). This compound was converted into the known N-methyl derivative by reaction with dimethyl pyrocarbonate and subsequent reduction with lithium aluminum hydride.[21]

3.6.4. (4*R*)-2,4-Dimethyl-1,2,3,4-tetrahydroisoquinoline Me-10a. Oil. $[\alpha]_D^{25}=+34.9$ (c=0.4, $CHCl_3$); lit.[14] $[\alpha]_D^{25}=+35.5$ (c=1.1, $CHCl_3$). ^{1}H NMR (δ): 1.31 (3H, d, *J*=7.0 Hz); 2.32 (1H, dd, *J*=7.0, 11.3 Hz); 2.43 (3H, s); 2.79 (1H, dd, *J*=5.3; 11.3 Hz); 3.07 (1H, m); 3.55 (1H, d, *J*=15.0 Hz); 3.57 (1H, d, *J*=15.0 Hz); 7.00–7.24 (4H, m). ^{13}C NMR (δ): 20.6; 32.9; 46.2; 58.6; 60.8; 125.5; 125.9; 126.2; 127.4; 135.4; 140.0. IR (neat) cm^{-1}: 3020, 2920, 750. MSCI (*m/z*, %): 162 (M+1, 100). Anal. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69. Found: C, 82.09; H, 9.21; N, 8.82.

3.6.5. (*R*)-4-Ethyl-1,2,3,4-tetrahydroisoquinoline 10b. Reductive ring opening of compounds **5b** or **7b** yielded quantitatively **9b**. Oil. $[\alpha]_D^{25}=+7.4$ (c=0.5, EtOAc). ^{1}H NMR (δ): 0.85–1.20 (6H, m); 0.91 (3H, d, *J*=6.5 Hz); 0.98 (3H, s); 1.35–1.55 (1H, m); 1.60–2.00 (6H, m); 2.30–2.70 (2H, m); 3.25–3.45 (1H, m); 3.55–3.75 (1H, m); 3.60 (1H, td, *J*=4.0; 10.3 Hz); 3.90–4.10 (1H, m); 7.01–7.15 (4H, m); 7,80 (1H, broad s). ^{13}C NMR (δ): 12.5; 17.2; 20.8; 21.8; 25.6; 28.0; 30.6; 34.9; 40.6; 44.6; 46.5; 47.8; 48.3; 60.2; 72.2; 125.3; 125.7; 126.5; 128.2; 133.9; 138.6. IR (neat) cm^{-1}: 3200, 2900, 740. MSCI (*m/z*, %): 316 (M+1, 100). Oxidation–elimination process leads to **10b** (72% from **5b**, 70% from **7b**). Oil. $[\alpha]_D^{25}=+6.7$ (c=1.1, $CHCl_3$). ^{1}H NMR (δ)1.01 (3H, t, *J*=7.4 Hz); 1.60–1.85 (2H, m); 2.58–2.66 (1H, m); 2.76 (1H, broad s); 3.02 (1H, dd, *J*=4.8; 12.9 Hz); 3.15 (1H, dd, *J*=4.9, 12.9 Hz); 3.99 (2H, s); 7.07–7.21 (4H, m). ^{13}C NMR (δ): 11.8; 28.0;

38.5; 47.0; 48.4; 125.7; 126.0; 126.1; 128.7; 135.5; 139.1. IR (neat) cm^{-1}: 3300, 3060, 2920, 750. MSCI (*m/z*, %): 162 (M+1, 100). Anal. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69. Found: C, 82.13; H, 9.52; N, 8.54.

3.6.6. (*R*)-4-Isopropyl-1,2,3,4-tetrahydroisoquinoline 10c. Reductive ring opening of compounds **5c** or **7c** yielded quantitatively **9c**. Oil. $[\alpha]_D^{25}=+5.4$ (c=0.6, EtOAc). ^1H NMR (δ): 0.50–1.55 (20H, m); 1.25 (3H, s); 1.55–2.00 (4H, m); 2.10–2.60 (1H, m); 2.95–3.70 (4H, m); 3.90–4.15 (1H, m); 6.90–7.20 (4H, m). ^{13}C NMR (δ): 16.4; 18.2; 21.1; 22.1; 25.9; 29.6; 30.9; 35.1; 44.5; 46.7; 60.7; 72.4; 125.5; 126.2; 126.7; 137.3. IR (neat) cm^{-1}: 3200, 2940, 750. MSCI (*m/z*, %): 330 (M+1, 100). Oxidation–elimination process lead to **10c**. (66% from **5c**, 72% from **7c**). Oil. $[\alpha]_D^{25}=+27.6$ (c=0.3, $CHCl_3$). ^1H NMR (δ): 0.83 (3H, d, *J*=6.8 Hz); 1.04 (3H, d, *J*=6.9 Hz); 2.17–2.28 (1H, m); 2.65 (1H, q, *J*=5.7 Hz); 2.90 (1H, broad s); 3.07 (1H, dd, *J*=6.2, 13.2 Hz); 3.14 (1H, dd, *J*=5.7, 13.2 Hz); 3.98 (2H, s); 6.99–7.26 (4H, m). ^{13}C NMR (δ): 18.2; 21.1; 31.1; 42.5; 44.2; 48.3; 125.6; 125.9; 126.0; 128.6; 136.1; 137.9. IR (neat) cm^{-1}: 3380, 2900, 740. MSCI (*m/z*, %): 176 (M+1, 100). Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.12; H, 9.56; N, 8.12.

3.6.7. (*R*)-4-Benzyl-1,2,3,4-tetrahydroisoquinoline 10d. Reductive ring opening of compounds **5d** or **7d** yielded quantitatively **9d**. Oil. $[\alpha]_D^{25}=+4.7$ (c=0.9, EtOAc). ^1H NMR (δ): 0.80–1.10 (9H, m); 1.10–1.80 (9H, m); 1.90–2.40 (2H, m); 2.90–3.40 (3H, m); 3.50–3.80 (1H, m); 3.90–4.20 (1H, m); 7.00–7.60 (9H, m); 7.95 (1H, broad s). ^{13}C NMR (δ): 17.4; 21.2; 22.3; 25.8; 30.8; 35.1; 40.8; 41.4; 44.4; 45.6; 46.1; 48.2; 60.8; 72.6; 125.8; 126.0; 126.2; 126.8; 128.1; 128.6; 129.1; 129.6; 134.6; 137.6; 141.0. IR (neat) cm^{-1}: 3200, 2900, 740. MSCI (*m/z*, %): 392 (M+1, 100). Oxidation–elimination process leads to **10d**. (66% from **5d**, 70% from **7d**). Oil $[\alpha]_D^{25}=-32.9$ (c=1.3, $CHCl_3$). ^1H NMR (δ): 1.85 (1H, broad s); 2.86 (1H, dd, *J*=9.3, 12.7 Hz); 2.94–3.00 (3H, m); 3.07 (1H, dd, *J*=4.0, 12.7 Hz); 3.92 (2H, s); 6.99–7.32 (9H, m). ^{13}C NMR (δ): 39.1; 42.1; 46.9; 48.7; 126.0; 126.1; 128.4; 129.0; 129.2; 135.9; 138.5; 140.4. IR (neat) cm^{-1}: 3300, 3060, 3010, 2900, 1590, 750, 690. MSCI (*m/z*, %): 224 (M+1, 100). Anal. Calcd for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 86.23; H, 7.84; N, 6.09.

3.6.8. (*R*)-5-Methyl-[1H]-2,3,4,5-tetrahydro-2-benzazepine 11b. Reductive ring opening of compounds **8b** yielded quantitatively the corresponding aminomenthol derivative as an oil. $[\alpha]_D^{25}=-25.2$ (c=0.6, EtOAc). ^1H NMR (δ): 0.83–1.05 (3H, m); 0.92 (3H, d, *J*=6.5 Hz); 1.00 (3H, s); 1.06–1.46 (4H, m); 1.35 (3H, d, *J*=7.1 Hz); 1.50–1.85 (6H, m); 2.70–2.85 (1H, m); 3.05–3.15 (1H, m); 3.20–3.70 (3H, m); 3.95–4.05 (1H, m); 7.10–7.20 (4H, m); 7.64 (1H, broad s). ^{13}C NMR (δ): 17.9; 20.5; 21.6; 22.1; 25.9; 30.9; 35.2; 36.1; 37.4; 45.0; 48.0; 50.0; 53.8; 61.7; 72.2; 124.8; 126.0; 127.3; 129.6; 138.4. IR (neat) cm^{-1}: 3200, 3040, 2920, 740. MSCI (*m/z*, %): 316 (M+1, 100). Oxidation–elimination process of this intermediate leads to **11b** (71% from **8b**). Oil. $[\alpha]_D^{25}=+16.8$ (c=0.6, $CHCl_3$). ^1H NMR (δ): 1.30 (3H, d, *J*=7.1 Hz); 1.43–1.60 (1H, m); 1.74–1.82 (1H, m); 2.30 (1H, broad s); 3.08–3.26 (2H, m); 3.31 (1H, ddd, *J*=3.3; 5.8; 13.9 Hz); 3.95 (1H, d, *J*=14.7 Hz); 4.00 (1H, d, *J*=14.7 Hz); 7.10–7.26 (4H, m). ^{13}C NMR (δ): 20.1; 37.5; 37.8; 50.5; 54.0; 125.9; 127.3; 128.9; 140.9; 146.0. IR (neat) cm^{-1}: 3260, 2920, 750. MSCI (*m/z*, %): 162 (M+1, 100). Anal. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69. Found: C, 81.80; H, 9.26; N, 8.53.

3.7. Synthesis of 1,4-disubstituted-1,2,3,4-tetrahydroisoquinolines

Cyclized compounds **5a**, **5d**, **7c**, and **7d** were reacted with methylmagnesium iodide as previously described[18] yielding aminomenthol derivatives, which were transformed into the isoquinoline derivatives by elimination of the chiral appendage as described above.

3.7.1. (1*S*, 4*R*)-*N*-Tosyl-1,4-dimethyl-1,2,3,4-tetrahydroisoquinoline 13a. Reaction of **5a** with methylmagnesium iodide gave compound **12a**, which was transformed by oxidation–elimination, and treatment with tosyl chloride into **13a** (57% from **5a**). $[\alpha]_D^{25}=+45.2$ (c=1.7, $CHCl_3$). ^1H NMR (δ): 1.21 (3H, d, *J*=6.8 Hz); 1.45 (3H, d, *J*=6.8 Hz); 2.34 (3H, s); 2.81 (1H, m); 3.04 (1H, dd, *J*=11.2, 13.8 Hz); 3.86 (1H, dd, *J*=6.1, 13.8 Hz); 5.15 (1H, q, *J*=6.8 Hz); 7.01–7.78 (8H, m). ^{13}C NMR (δ): 17.8; 21.4; 22.9; 30.8; 45.1; 52.3; 115.0; 126.1; 126.6; 126.7; 126.9; 127.1; 129.5; 137.4; 137.7; 137.9; 143.0. IR (neat) cm^{-1}: 3020, 2940, 1650, 1460, 740. MSCI (*m/z*, %): 316 (M+1, 100). Anal. Calcd for $C_{18}H_{21}NO_2S$: C, 68.54; H, 6.71; N, 4.44. Found: C, 68.70; H, 6.82; N, 4.56.

3.7.2. (1*S*, 4*R*)-*N*-Tosyl-4-benzyl-1-methyl-1,2,3,4-tetrahydroisoquinoline 13d. Reaction of **5d** with methylmagnesium iodide gave compound **12d**. Oil. $[\alpha]_D^{25}=-25.8$ (c=1.4, EtOAc). ^1H NMR (δ): 0.80–1.10 (3H, m); 0.82 (3H, s); 0.90 (3H, d, *J*=6.5 Hz); 1.22 (3H, s); 1.35–1.50 (1H, m); 1.36 (3H, d, *J*=6.7 Hz); 1.50–1.60 (1H, m); 1.60–1.75 (2H, m); 1.85–1.95 (1H, m); 2.83 (1H, dd, *J*=7.6; 13.2 Hz); 3.10–3.30 (4H, m); 3.62 (1H, td, *J*=4.0; 10.3 Hz); 4.30–4.40 (1H, m); 7.02–7.35 (9H, m); 8.25 (1H, broad s). ^{13}C NMR (δ): 21.3; 22.1; 23.3; 26.0; 31.0; 35.0; 38.5; 42.1; 43.3; 44.4; 47.0; 51.9; 62.8; 72.5; 126.2; 126.3; 126.7; 128.1; 128.3; 129.3; 137.5; 139.6; 140.6. IR (neat) cm^{-1}: 3200, 2920, 760, 710. MSCI (*m/z*, %): 392 (M+1, 100). **12d** was transformed by oxidation–elimination, and treatment with tosyl chloride into **13d** (59% from **5d**). Oil. $[\alpha]_D^{25}=+19.1$ (c=0.5, $CHCl_3$). ^1H NMR (δ): 1.52 (3H, d, *J*=6.7 Hz); 2.37 (3H, s); 2.67 (1H, dd, *J*=9.7, 13.8 Hz); 2.96 (1H, m); 3.20 (1H, dd, *J*=9.5, 13.6 Hz); 3.26 (1H, dd, *J*=4.5, 13.8 Hz); 3.49 (1H, dd, *J*=5.7, 13.8 Hz); 5.04 (1H, q, *J*=6.8 Hz); 7.05–7.57 (13H, m). ^{13}C NMR (δ): 22.2; 25.1; 37.5; 39.5; 43.5; 52.6; 126.3; 126.5; 126.6; 126.8; 127.1; 128.5; 128.8; 129.4; 136.2; 137.0; 137.9; 138.8; 143.0. IR (neat) cm^{-1}: 3040, 2920, 1640, 1460, 750, 710. MSCI (*m/z*, %): 392 (M+1, 100). Anal. Calcd for $C_{24}H_{25}NO_2S$: C, 73.62; H, 6.44; N, 3.58. Found: C, 73.51; H, 6.37; N, 3.69.

3.7.3. (3*S*, 4*R*)-*N*-Tosyl-4-isopropyl-3-methyl-1,2,3,4-tetrahydroisoquinoline 16c. Reaction of **7c** with methylmagnesium iodide gave compound **14c**. Oil. $[\alpha]_D^{25}=-18.6$ (c=0.9, $CHCl_3$). ^1H NMR (δ): 0.69 (3H, d, *J*=6.6 Hz); 0.80–1.15 (3H, m); 0.92 (3H, d, *J*=6.5 Hz); 0.96 (3H, d, *J*=6.4 Hz); 1.11 (3H, s); 1.15 (3H, d, *J*=6.3 Hz); 1.38–1.55

(1H, m); 1.55–1.75 (2H, m); 1.80–1.97 (3H, m); 2.05 (1H, d, J=10.5 Hz); 3.55–3.71 (2H, m); 3.78 (1H, d, J=13.2 Hz); 4.00 (1H, d, J=13.2 Hz); 7.00–7.14 (4H, m); 7.73 (1H, broad s). ^{13}C NMR (δ): 21.3; 21.9; 22.1; 26.5; 28.7; 31.1; 35.3; 44.3; 44.5; 46.9; 48.2; 57.1; 61.2; 72.7; 125.9; 126.1; 127.0; 130.2; 134.9; 137.8. IR (neat) cm^{-1}: 3200, 2940, 750. MSCI (*m*/*z*, %): 344 (M+1, 100). Oxidation of **14c** with PCC as described above gave directly (3*S*, 4*R*)-4-isopropyl-3-methyl-3,4-dihydroisoquinoline **15c** (76% from **7c**). Oil. $[\alpha]_D^{25}$=−479.3 (c=0.7, $CHCl_3$). ^{1}H NMR (δ): 0.78 (3H, d, J=6.8 Hz); 0.91 (3H, d, J=6.8 Hz); 1.01 (3H, d, J=6.8 Hz); 1.73 (1H, oct. J=6.8 Hz); 2.30 (1H, d, J=6.8 Hz); 4.31 (1H, q, J=6.8 Hz); 7.10–7.39 (4H, m); 8.23 (1H, s). ^{13}C NMR (δ): 19.6; 20.3; 20.6; 32.8; 47.8; 54.0; 126.7; 126.9; 127.3; 130.1; 130.5; 137.0; 157.9. IR (neat) cm^{-1}: 2940, 1630. MSCI (*m*/*z*, %): 188 (M+1, 100). Reduction of **15c** with $NaBH_4$ as previously described[22] leads to **16c** (92%). White solid (from hexanes); mp 97–98°C. $[\alpha]_D^{25}$=−9.1 (c=0.5, $CHCl_3$). ^{1}H NMR (δ): 0.75 (3H, d, J=6.7 Hz); 0.81 (3H, d, J=6.8 Hz); 1.04 (3H, d, J=6.6 Hz); 1.68–1.80 (1H, m); 2.18 (1H, d, J=8.3 Hz); 2.41 (3H, s); 4.08 (1H, d, J=15.4 Hz); 4.55 (1H, q, J=6.7 Hz); 4.62 (1H, d, J=15.4 Hz); 7.04–7.16 (4H, m); 7.31 (2H, d, J=8.1 Hz); 7.78 (2H, d, J=8.1 Hz). ^{13}C NMR (δ): 17.0; 20.8; 21.4; 21.5; 31.9; 42.9; 49.2; 53.1; 126.0; 126.2; 127.3; 129.6; 130.7; 131.3; 135.2; 136.6; 143.2. IR (neat) cm^{-1}: 3040, 2920, 1650, 1450, 750. MSCI (*m*/*z*, %): 344 (M+1, 100). Anal. Calcd for $C_{20}H_{25}NO_2S$: C, 69.93; H, 7.34; N, 4.08. Found: C, 70.06; H, 7.45; N, 4.19.

3.7.4. (3*S*, 4*R*)-*N*-Tosyl-4-benzyl-3-methyl-1,2,3,4-tetrahydroisoquinoline 16d. Reaction of **7d** with methylmagnesium iodide gave compound **14d**. Oil. $[\alpha]_D^{25}$=−25.7 (c=1.1, $CHCl_3$). ^{1}H NMR (δ): 0.78–1.18 (3H, m); 0.95 (3H, d, J=6.5 Hz); 1.05 (3H, d, J=6.4 Hz); 1.07 (3H, s); 1.33 (3H, s); 1.35–1.54 (1H, m); 1.62–1.78 (3H, m); 1.92–2.01 (1H, m); 2.86–2.91 (1H, m); 2.98 (1H, dd, J=6.2; 14.2 Hz); 3.28 (1H, dd, J=8.8; 14.2 Hz); 3.51 (1H, q, J=14.8 Hz); 3.63 (1H, td, J=4.0; 10.4 Hz); 3.96 (1H, d, J=14.8 Hz); 4.05 (1H, d, J=14.8 Hz); 6.90–7.35 (9H, m); 7.40 (1H, broad s). ^{13}C NMR (δ): 21.9; 22.2; 23.4; 26.4; 31.0; 35.3; 41.6; 43.0; 44.6; 47.0; 49.2; 49.4; 61.1; 73.0; 125.6; 125.9; 126.1; 126.7; 128.2; 128.5; 129.2; 134.8; 137.1; 141.0. IR (neat) cm^{-1}: 3200, 2920, 750, 700. MSCI (*m*/*z*, %): 392 (M+1, 100). Oxidation of **14d** with PCC as described above gave directly (3*S*, 4*R*)-4-benzyl-3-methyl-3,4-dihydroisoquinoline **15d** (75% from **7d**). Oil. $[\alpha]_D^{25}$=−512.3 (c=0.5, $CHCl_3$). ^{1}H NMR (δ): 0.97 (3H, d, J=6.9 Hz); 2.65–2.82 (3H, m); 4.16 (1H, q, J=6.9 Hz); 6.81–7.31 (9H, m); 8.34 (1H, s). ^{13}C NMR (δ): 18.7; 41.7; 43.8; 55.1; 126.1; 126.6; 127.2; 128.2; 129.1; 129.3; 130.9; 138.0; 139.4; 158.0. IR (neat) cm^{-1}: 3040, 2940, 1630, 770, 740, 710. MSCI (*m*/*z*, %): 236 (M+1, 100). Reduction of **15d** with $NaBH_4$ as previously described[22] leads to **16d** (94%). White solid (from hexanes); mp 107–108°C. $[\alpha]_D^{25}$=−89.7 (c=0.5, $CHCl_3$). ^{1}H NMR (δ): 0.71 (3H, d, J=6.8 Hz); 2.42 (3H, s); 2.76–2.81 (2H, m); 3.01 (1H, dd, J=10.5; 14.7 Hz); 4.09 (1H, d, J=15.5 Hz); 4.29 (1H, q, J=6.8 Hz); 4.77 (1H, d, J=15.5 Hz); 6.95–7.80 (13H, m). ^{13}C NMR (δ): 15.5; 21.5; 42.5; 43.0; 48.6; 49.7; 125.9; 126.2; 126.4; 126.7; 127.4; 128.3; 129.6; 129.7; 130.4; 130.5; 135.7; 136.5; 140.1; 143.4. IR (neat) cm^{-1}: 3040, 2920, 1640, 1460, 760, 700. MSCI (*m*/*z*, %): 392 (M+1, 100). Anal. Calcd for $C_{24}H_{25}NO_2S$: C, 73.62; H, 6.44; N, 3.58. Found: C, 73.76; H, 6.56; N, 3.49.

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