Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 2985–2990

TETRAHEDRON: *ASYMMETRY*

Regio- and diastereoselective tandem addition–carbocyclization promoted by sulfanyl radicals on chiral perhydro-1,3-benzoxazines

Rafael Pedrosa,* Celia Andrés,* Juan P. Duque-Soladana, Alicia Maestro and Javier Nieto

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid, Dr. Mergelina s/n, 47011 Valladolid, Spain

Received 6 May 2003; accepted 8 July 2003

Abstract—Radical addition–carbocyclization of 2-allyl-3-acyloyl-substituted perhydro-1,3-benzoxazines readily provides 3,4-disubstituted pyrrolidinone derivatives with total regioselectivity and good diastereoselectivity. The key step of the reaction is a tandem addition–5-*exo*-cyclization promoted by a sulfanyl radical.

1. Introduction

Diastereoselective free-radical addition to olefinic bonds is one of the most attractive ways to form carbon–carbon bonds.[1] Excellent diastereoselectivities have been described for intermolecular additions to α,β-unsaturated amides attached to different chiral auxiliaries[2] including chiral oxazolidinones.[3] Although the intramolecular version of this reaction has been less studied, it has been successfully used in the synthesis of lactams[4] and macrocyclic derivatives.[5] Recently, we have described the synthesis of enantiopure substituted pyrrolidines[6] and piperidines[7] by diastereoselective intramolecular addition of radicals generated from chiral 2,3-disubstituted perhydrobenzoxazines. Both enantiomers of the substituted heterocycles can be obtained from regioisomeric perhydrobenzoxazines which differ in the substituents at C-2 and the nitrogen atom.

The synthesis of 3,4-disubstituted pyrrolidines could also be achieved by addition–cyclization of a preformed heteroatom-centered radical to chiral perhydrobenzoxazines with two double bonds. The advantages of this approach are: (i) the starting compounds are inexpensive and easily obtained; (ii) the functionality of the final compounds can be changed by the choice of the radical that promotes the reaction, and (iii) it is possible to create two contiguous stereocenters in a single process.

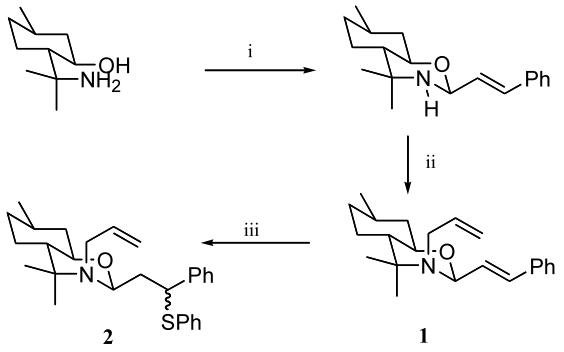
This strategy has been used previously in the preparation of cyclopentanes[8] and pyrrolidines,[9] and more recently, in the synthesis of substituted tetrahydrofurans,[10] γ-lactones,[11] lactams[12] or 2,3-disubstituted pyrrolidines.[13] Recently, we have studied this addition–cyclization process directed at the preparation of enantiopure stannanes and 3-methylstannyl-4-substituted pyrrolidines[14] starting from 3-acryloyl-2-vinyl perhydro-1,3-benzoxazines derived from (–)-8-amino menthol, and now we report the diastereoselective addition–cyclization reaction promoted by a sulfanyl radical.

First, we explored the reaction of *N*-allyl-2-cinnamyl perhydro-1,3-benzoxazine **1**, which was prepared in two steps by condensation of (–)-8-amino menthol with cinnamaldehyde followed by alkylation with allyl bromide and potassium carbonate in refluxing acetonitrile. The addition compound **2** was formed in 80%, as an equimolar mixture of epimers, when a 0.02 M solution of **1**, thiophenol (1.2 equiv.) and AIBN (0.2 equiv.) was refluxed in benzene for 4 h, and no cyclization products were detected (Scheme 1).

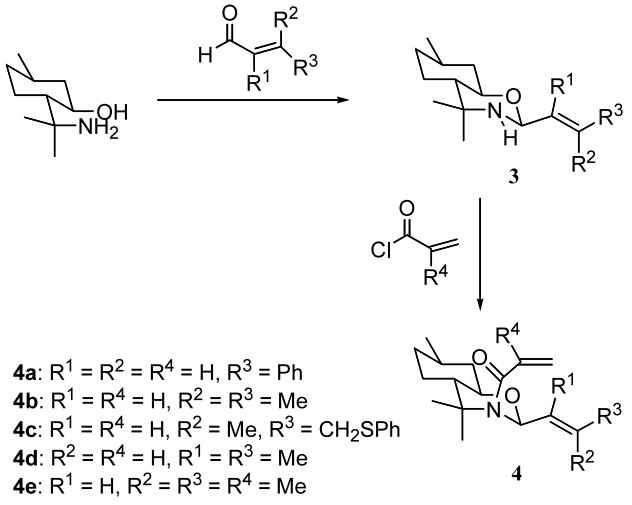
The failure of the cyclization step led us to consider changing the allyl group at the nitrogen atom to a better acceptor acryloyl substituent. In this way, perhydrobenzoxazines **4a**–**e** were prepared in excellent yields in two steps (Scheme 2). Condensation of (–)-8-amino menthol with the corresponding α,β-unsaturated aldehyde in benzene at 25°C yielded 2-vinyl substituted perhydrobenzoxazines **3a**–**e**, which were then acylated

* Corresponding authors. E-mail: pedrosa@qo.uva.es

0957-4166/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2003.06.003



Scheme 1. *Reagents and conditions*: (i) cinnamaldehyde, benzene, reflux, 6 h (86%); (ii) CH_2=$CHCH_2Br$, K_2CO_3, acetonitrile, reflux (80%); (iii) PhSH (1.2 equiv.), AIBN (0.2 equiv.), benzene, reflux, 4 h (80%).



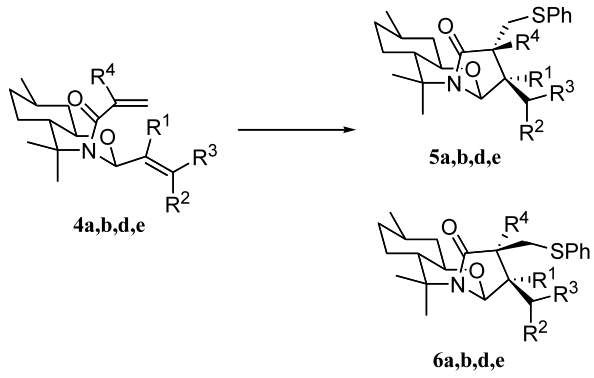
4a: $R^1 = R^2 = R^4 = H$, $R^3 = Ph$
4b: $R^1 = R^4 = H$, $R^2 = R^3 = Me$
4c: $R^1 = R^4 = H$, $R^2 = Me$, $R^3 = CH_2SPh$
4d: $R^2 = R^4 = H$, $R^1 = R^3 = Me$
4e: $R^1 = H$, $R^2 = R^3 = R^4 = Me$

Scheme 2.

by reaction with the corresponding acyl chloride in methylene chloride at 0°C in the presence of triethylamine. All these compounds were obtained as pure diastereomers except **4c**, which was prepared as a mixture of *Z* and *E* isomers.

The transformation of **4a**–**e** into the pyrrolidinone **5a**–**e** and **6a**–**e** was carried out by refluxing a 0.02 M solution of **4a**–**e**, thiophenol (1.1 equiv.) and AIBN (0.2 equiv.) in dry degassed benzene (Scheme 3). Under these conditions, compound **4a** was transformed into an inseparable mixture (61:25:7:7) of four diastereoisomers. In an attempt to improve the diastereoselection, the reaction was carried out under photochemical conditions by irradiation of the reaction mixture with a high-pressure mercury lamp at 25°C, but a very complex mixture of products was formed.

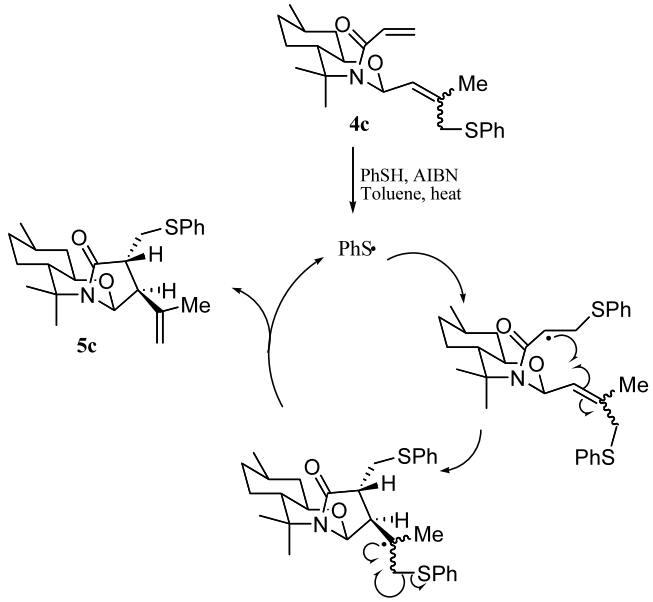
Much better results were obtained in the reaction of perhydro-1,3-benzoxazine **4b**. This compound was regioselectively transformed into a mixture (80:8:9:3) of four diastereomers when reacted under the described thermal conditions. Once isolated, the stereochemistry



Scheme 3. *Reagents and conditions*: PhSH, AIBN (20% mol), benzene, reflux.

of the major diastereoisomer was established as **5b** by NOE experiments. The cross signals showed a *cis* relationship between the hydrogen atoms at C-3 and C-5, and a *trans* disposition of the substituents at C-3 and C-4 of the pyrrolidinone ring. The photochemically induced reaction of **4b** also leads to a mixture (53:30:17) of three diastereoisomers, but with lower stereoselection than the thermally induced process.

The behavior of allylphenylsulphide derivative **4c** is noteworthy because only a single diastereomer **5c** (90%) was obtained on refluxing in toluene a solution (0.06 M) of **4c**, as a mixture of *Z* and *E* isomers, thiophenol (1 equiv.) and AIBN (0.2 equiv.). But more interestingly, **5c** was obtained in the same yield when the reaction of **4c** was carried out in refluxing toluene for 24 h with only 0.3 equiv. of thiophenol. This fact must be interpreted taking into account that the cyclization reaction is followed by elimination of a phenylsulfanyl radical which reinitiates the process and, in this way, the reaction can then be consider as a catalytic process



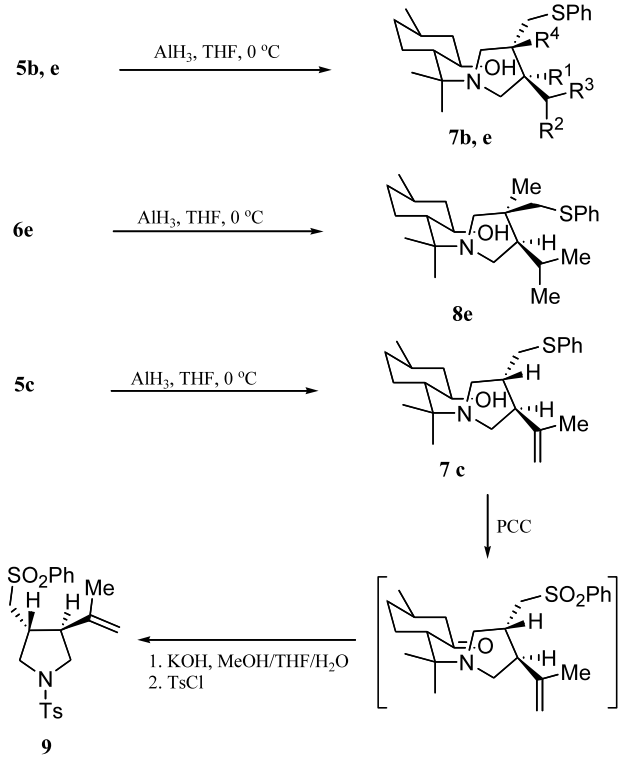
Scheme 4.

(Scheme 4). After isolation, the stereochemistry of **5c** was determined by NOE experiments, and is coincident with that described for **5b**.

The described results open the possibility to create quaternary stereocenters at C-3 or C-4 in the cyclized pyrrolidinone ring. To this end, we tested the cyclization of two different perhydrobenzoxazines **4d**, with a methyl group at C-α in the vinyl substituent at C-2 in the starting perhydrobenzoxazine ($R^1 = Me$) and **4e**, with a methyl substituent at C-α in the α,β-unsaturated amide group ($R^4 = Me$).

The reaction of **4d** with thiophenol (1 equiv.) and AIBN (0.2 equiv.) in boiling benzene for 1 h was totally regioselective, but not diastereoselective leading to an equimolar mixture of three diastereomeric pyrrolidinones. On the contrary, the reaction of **4e** was highly regio- and diastereoselective. Methacryloyl derivative **4e** gave a mixture of **5e** (70%) and **6e** (30%) by reaction with thiophenol in the same experimental conditions (Scheme 3).

Once isolated, diastereoisomers **5b**, **5c**, **5e**, and **6e** were transformed into the pyrrolidinyl menthols **7b**, **7c**, **7e**, and **8e**, respectively, by reductive ring opening with alane in THF at 0°C (Scheme 5). Compound **7c** was oxidized with excess PCC to the 8-pyrrolidinyl menthone derivative, which exert (+)-pulegone and enantiopure pyrrolidine derivative **9** by sequential treatment with a solution of KOH in THF/H_2O/MeOH, and tosyl chloride. The treatment of **7c** with PCC oxidized the sulfide group to the sulfone derivative.



Scheme 5.

In summary, the described protocol allowed the diastereoselective formation of 2,3-disubstituted pyrrolidine derivatives in good yields and total regioselectivity and moderate diastereoselectivity.

2. Experimental

All solvents were distilled prior to use. TLC was performed on silica gel 60 F254 plates. Flash chromatography was conducted using 240–300 mesh silica gel. All commercially available products were used without purification. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a sodium lamp. 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 TMS as internal standard ($\delta = 0$ for TMS). Mass spectra were obtained on a Hewlett-Packard 5988A spectrometer by chemical ionization. Infrared spectra were registered on a Philips PU9706 apparatus as neat films.

2.1. Synthesis of perhydro-1,3-benzoxazines 3a–e. General procedure

Compounds **3a**–**e** were prepared, as previously described for related compounds,[6c] by condensation of (−)-8-amino menthol with the corresponding α,β-unsaturated aldehyde in CH_2Cl_2 at rt. Compound **3a** has been previously described.[15]

2.2. 4,4,7α-Trimethyl-2α-prenyl-*trans*-octahydro-1,3-benzoxazine 3b

Yellow oil. $[\alpha]_D^{25} = -4.9$ (*c* 1.2, CH_2Cl_2). ^1H NMR, δ: 0.91 (d, 3H, $J = 6.5$ Hz); 0.94–1.08 (m, 3H); 1.09 (s, 3H); 1.13 (s, 3H); 1.41–1.55 (m, 1H); 1.65–1.74 (m, 3H); 1.71 (s, 3H); 1.73 (s, 3H); 1.91–1.96 (m, 1H); 3.47 (dt, 1H, $J_1 = 3.5$ Hz, $J_2 = 10.5$ Hz); 5.02 (d, 1H, $J = 7.4$ Hz); 5.12 (d, 1H, $J = 7.4$ Hz). ^{13}C NMR, δ: 18.6; 19.6; 22.2; 25.5; 25.6; 29.8; 31.3; 34.9; 41.6; 51.2; 51.3; 74.7; 79.6; 124.0; 137.3. IR (film): 3300, 1450, 1380, 830. CIMS, *m*/*z* (%): 238 (M+1, 100). Anal. calcd for $C_{15}H_{27}N$: C, 75.90%; H, 11.46%; N, 5.90%. Found: C, 75.76%; H, 11.61%; N, 5.76%.

2.3. 2α-(2′-Butenyl)-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 3d

Colorless oil. $[\alpha]_D^{25} = -46.4$ (*c* 1.0, CH_2Cl_2). ^1H NMR, δ: 0.92 (d, 3H, $J = 6.3$ Hz); 1.10 (s, 3H); 1.12 (s, 3H); 1.61 (d, 3H, $J = 6.2$ Hz); 1.68 (d, 3H, $J = 1$ Hz); 3.47 (dt, 1H, $J_1 = 4.2$ Hz, $J_2 = 10.2$ Hz); 4.66 (s, 1H); 5.67 (dd, 1H, $J_1 = 1.0$ Hz, $J_2 = 6.2$ Hz). ^{13}C NMR, δ: 11.4, 12.8, 19.4, 22.1, 25.4, 29.8, 31.2, 34.8, 41.5, 51.1, 51.5, 74.7, 86.4, 121.9, 134.2. IR (film): 3200, 2900, 1650, 970, 750, 690. Anal. calcd for $C_{15}H_{27}NO$: C, 75.90%; H, 11.46%; N, 5.90%. Found: C, 76.02%; H, 11.63%; N, 5.99%.

2.4. Synthesis of *N*-allyl-2α-cinnamyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 1

A mixture of perhydrobenzoxazine **3a** (5.0 mmol), potassium carbonate (0.69 g, 7 mmol) and allyl bromide (7.5 mmol), in acetonitrile (8 mL) was refluxed with stirring for 24 h. The solid was separated by filtration, the solid was washed with hot EtOAc (25 mL), and the solvents were evaporated. Colorless oil. $[\alpha]_D^{25} = -46.4$ (*c* 1.0, CH_2Cl_2). ^1H NMR, δ: 0.86–1.06 (m, 2H); 0.93 (d, 3H, $J = 6.5$ Hz); 1.03–1.23 (m, 1H); 1.17 (s, 3H); 1.18 (s, 3H); 1.40–1.60 (m, 2H); 1.62–1.72 (m, 2H); 1.95–1.99 (m, 1H); 3.16, dd, 1H, $J_1 = 5.6$ Hz, $J_2 = 17.2$ Hz); 3.44 (dd, 1H, $J_1 = 5.3$ Hz, $J_2 = 17.2$ Hz); 3.54 (dt, 1H, $J_1 = 4.0$ Hz, $J_2 = 10.6$ Hz); 4.95 (dd, 1H, $J_1 = 1.6$ Hz, $J_2 = 10.1$ Hz); 5.07 (dd, 1H, $J_1 = 1.6$ Hz, $J_2 = 17.1$ Hz); 5.15 (d, 1H, $J = 4.9$ Hz); 5.81–5.93 (m, 1H); 6.16 (dd, 1H, $J_1 = 4.9$ Hz, $J_2 = 16.1$ Hz); 6.66 (d, 1H, $J = 16.1$ Hz); 7.18–7.37 (m, 5H). ^{13}C NMR, δ: 18.7, 22.2, 25.1, 26.8, 31.3, 35.0, 41.4, 46.5, 47.0, 56.8, 75.6, 87.5, 114.1, 126.5 (2C), 127.5, 128.4 (2C) 129.3, 131.9, 136.8, 140.5. IR (film): 2922, 1684, 1638, 972, 746, 690. Anal. calcd for $C_{22}H_{31}NO$: C, 81.18%; H, 9.60%; N, 4.30%. Found: C, 81.01%; H, 9.49%; N, 4.49%.

2.5. Synthesis of perhydrobenzoxazines 4a–e

To a solution of perhydrobenzoxazines **3a**–**e** (4.2 mmol) and triethylamine (4.8 mmol, 0.39 mL) in dry CH_2Cl_2 (30 mL) under argon, at 0°C was slowly added the corresponding acyl chloride (4.6 mmol). The mixture was stirred for additional 30 min at rt and then was diluted with hexane (75 mL). The solid was collected by filtration, and the solvents were evaporated under vacuum. The residue was chromatographed on silica gel using CH_2Cl_2 as eluent.

2.6. *N*-Acryloyl-2α-cinnamyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 4a

Colorless solid, mp 86–87°C. $[\alpha]_D^{25} = -32.6$ (*c* 1.1, $CHCl_3$). ^1H NMR, δ: 0.93 (d, 3H, $J = 6.5$ Hz); 1.56 (s, 3H); 1.68 (s, 3H); 3.72 (dt, 1H, $J_1 = 3.9$ Hz, $J_2 = 11.4$ Hz); 5.59 (dd, 1H, $J_1 = 2.2$ Hz, $J_2 = 10.2$ Hz); 5.91 (t, 1H, $J = 2.2$ Hz); 6.24 (dd, 1H, $J_1 = 2.2$ Hz, $J_2 = 16.8$ Hz); 6.38 (dd, 1H, $J_1 = 10.2$ Hz, $J_2 = 16.8$ Hz); 6.46 (dd, 1H, $J_1 = 2.6$ Hz, $J_2 = 16.2$ Hz); 6.57 dd, 1H, $J_1 = 1.9$ Hz, $J_2 = 16.2$ Hz); 7.27–7.40 (m, 5H). ^{13}C NMR, δ: 18.9, 21.9, 24.5, 25.2, 31.5, 34.3, 43.7, 46.1, 58.0, 73.5, 81.9, 126.7, 127.2, 128.2, 128.7, 130.8, 131.5, 132.0, 135.8, 166.5. IR (film): 3040, 2900, 2840, 1650, 1600, 980, 960, 750, 690. CIMS, *m*/*z* (%): 340 (M+1, 100); 236 (24); 208 (46); 186 (64). Anal. calcd for $C_{22}H_{29}NO_2$: C, 77.84%; H, 8.61%; N, 4.13%. Found: C, 77.69%; H, 8.78%; N, 3.99%.

2.7. *N*-Acryloyl-2α-prenyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 4b

Colorless oil. $[\alpha]_D^{25} = +37.7$ (*c* 1.0, CH_2Cl_2). ^1H NMR, δ: 0.92 (d, 2H, $J = 6.5$ Hz); 1.49 (s, 3H); 1.62 (s, 3H); 1.73 (s, 3H); 1.76 (s, 3H); 3.60 (dt, 1H, $J_1 = 3.7$ Hz, $J_2 = 11.4$ Hz); 5.41 (m, 1H); 5.54 (dd, 1H, $J_1 = 2.0$ Hz, $J_2 = 10.4$ Hz); 5.74 (d, 1H, $J = 5.3$ Hz); 6.13 (dd, 1H, $J_1 = 2.2$ Hz, $J_2 = 16.8$ Hz); 6.27 (dd, 1H, $J_1 = 10.4$ Hz, $J_2 = 16.8$ Hz). ^{13}C NMR, δ: 18.5, 18.7, 21.9, 24.6, 25.2, 25.5, 31.5, 34.5, 43.0, 46.7, 57.7, 73.0, 79.6, 126.0, 127.1, 131.2, 137.2, 137.8, 165.9. IR (film): 2910, 1645, 1610, 1450, 1360, 980, 960, 810. Anal. calcd for $C_{18}H_{29}NO_2$: C, 74.18%; H, 10.03%; N, 4.81%. Found: C, 74.31%; H, 10.14%; N, 4.97%.

2.8. *N*-Acryloyl-2α-(2′-butenyl)-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 4d

Colorless oil. $[\alpha]_D^{25} = +36.4$ (*c* 1.0, CH_2Cl_2). ^1H NMR, δ: 0.76 (d, 3H, $J = 6.2$ Hz); 1.36 (s, 3H); 1.46 (s, 3H); 1.52 (d, 3H, $J = 6.9$ Hz); 1.55 (s, 3H); 3.48 (dt, 1H, $J_1 = 3.7$ Hz, $J_2 = 11.5$ Hz); 5.21 (z, 1H); 5.36 (dd, 1H, $J_1 = 3.3$ Hz, $J_2 = 9.0$ Hz); 5.51 (d, 1H, $J = 6.6$ Hz); 5.92–6.02 (m, 2H). ^{13}C NMR, δ: 13.2, 13.4, 18.8, 21.7, 23.5, 24.9, 31.4, 34.3, 42.7, 45.1, 57.5, 73.9, 85.7, 122.1, 126.6, 130.9, 137.3, 166.6. IR (film): 3040, 2900, 2830, 1650, 1600, 970, 750, 690. Anal. calcd for $C_{18}H_{29}NO_2$: C, 74.18%; H, 10.03%; N, 4.81%. Found: C, 74.26%; H, 9.92%; N, 4.91%.

2.9. *N*-Methacryloyl-2α-prenyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 4e

Colorless oil. $[\alpha]_D^{25} = +53.1$ (*c* 1.1, CH_2Cl_2). ^1H NMR, δ: 0.84–1.18 (m, 2H); 0.92 (d, 3H, $J = 6.5$ Hz); 1.35–1.60 (m, 2H); 1.48 (s, 3H); 1.62 (s, 3H); 1.65 (s, 3H); 1.69–1.87 (m, 2H); 1.73 (s, 3H); 1.89–2.02 (m, 2H); 1.90 (s, 3H); 3.62 (dt, 1H, $J_1 = 4.0$ Hz, $J_2 = 11.3$ Hz); 4.98 (s, 1H); 5.05 (s, 1H); 5.40 (d, 1H, $J = 5.6$ Hz); 5.72 (d, 1H, $J = 5.6$ Hz). ^{13}C NMR, δ: 18.3; 18.5; 20.0; 21.9; 25.1; 25.4; 25.6; 31.5; 34.6; 43.1; 47.2; 57.9; 73.4; 80.4; 114.9; 127.4; 136.3; 142.6; 172.2. IR (film): 2910, 1645, 1610, 1450, 1360, 940, 840, 810. CIMS, *m*/*z* (%): 306 (M+1, 100). Anal. calcd for $C_{19}H_{31}NO_2$: C, 74.71%; H, 10.23%; N, 4.59%. Found: C, 74.59%; H, 10.40%; N, 4.66%.

2.10. Cyclization of acrylamides 4a–e. General procedure

A 0.02 M of the corresponding amide **4a**–**e** thiophenol (1.1 equiv.) and AIBN (0.2 equiv.) in benzene was refluxed, while stirring, under an argon atmosphere until the starting compound have disappeared (TLC). When the reaction was finished, the solvent was removed under vacuum, and the residue was chromatographed on silica gel using EtOAc/hexanes or dichloromethane as eluents.

Lactam **5b**. Yellow oil. $[\alpha]_D^{25} = -41.2$ (*c* 1.2, CH_2Cl_2). ^1H NMR, δ: 0.87 (d, 3H, $J = 6.7$ Hz); 0.89 (d, 3H, $J = 6.6$ Hz); 0.93 (d, 3H, $J = 6.6$ Hz); 1.17 (s, 3H); 1.67 (s, 3H); 1.79–1.86 (m, 1H); 1.93–1.99 (m, 2H); 2.31–2.37 (m, 1H); 3.15 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 13.0$ Hz); 3.40 (dt, 1H, $J_1 = 4.2$ Hz, $J_2 = 10.9$ Hz); 3.42 (dd, 1H, $J_1 = 4.3$ Hz, $J_2 = 13.0$ Hz); 4.65 (d, 1H, $J = 4.4$ Hz); 7.11–7.33 (m, 5H). ^{13}C NMR, δ: 19.2, 19.3, 20.0, 22.0, 24.0, 25.3, 29.7, 31.2, 34.4, 36.2, 41.4, 44.7, 47.8, 49.8, 52.3, 57.4, 76.3, 87.0, 125.9, 128.8, 129.2, 136.2, 172.7. IR (film):

3050, 2970, 2870, 1710, 1590, 1450, 740, 690. Anal. calcd for $C_{24}H_{35}NO_2S$: C, 71.78%; H, 8.78%; N, 3.49%. Found: C, 71.65%; H, 8.90%; N, 3.60%.

Lactam **5c**. Yellow oil. $[\alpha]_D^{25}=-45.5$ (c 1.0, CH_2Cl_2). ^{1}H NMR, δ: 0.95 (d, 3H, $J=6.5$ Hz); 1.19 (s, 3H); 1.72 (s, 3H); 1.74 (s, 3H); 2.55–2.61 (m, 1H); 2.66 (dt, 1H, $J_1=6.2$ Hz, $J_2=9.5$ Hz); 3.15 (dd, 1H, $J_1=4.3$ Hz, $J_2=11.1$ Hz); 4.66 (d, 1H, $J=6.2$ Hz); 4.85 (d, 1H, $J=1.2$ Hz); 4.92 (d, 1H, $J=1.2$ Hz). ^{13}C NMR, δ: 18.5, 20.9, 22.0, 23.9, 25.5, 31.1, 34.3, 34.4, 40.9, 45.0, 49.5, 50.7, 57.2, 76.2, 87.1, 113.8, 125.8, 128.8, 129.1, 136.4, 141.7, 171.8. IR (film): 3060, 2920, 2840, 1670, 1570, 1450, 730, 680. CIMS, m/z (%): 400 (M+1, 100); 401 (M+2, 39; 246 (11). Anal. calcd for $C_{24}H_{33}NO_2S$: C, 72.14%; H, 8.32%; N, 3.51%. Found: C, 72.26%; H, 8.45%; N, 3.60%.

Lactam **5e**. Yellow solid. $[\alpha]_D^{25}=-17.7$ (c 1.0, CH_2Cl_2). ^{1}H NMR, δ: 0.92 (d, 3H, $J=6.6$ Hz); 0.95 (d, 3H, $J=6.5$ Hz); 1.00 (d, 3H, $J=6.7$ Hz); 1.14 (s, 3H); 1.66 (s, 3H); 1.90–2.00 (m, 1H); 2.11 (dd, 1H, $J_1=6.9$ Hz, $J_2=9.0$ Hz); 2.98 (d, 1H, $J=12.6$ Hz); 3.35 (dt, 1H, $J_1=4.2$ Hz, $J_2=10.6$ Hz); 3.44 (d, 1H, $J=12.6$ Hz); 4.58 (d, 1H, $J=6.8$ Hz); 7.12–7.44 (m, 5H). ^{13}C NMR, δ: 18.3, 19.6, 21.2, 22.0, 22.3, 23.9, 25.6, 27.4, 31.2, 34.4, 41.1, 42.5, 48.0, 48.8, 49.3, 56.8, 76.0, 87.0, 126.0, 128.6, 130.4, 137.0, 174.9. IR (film): 3060, 2940, 2860, 1690, 1590, 1450, 750, 695. CIMS, m/z (%): 416 (M+1, 100); 417 (M+2, 27); 348 (39). Anal. calcd for $C_{25}H_{37}NO_2S$: C, 72.24%; H, 8.97%; N, 3.37%. Found: C, 72.12%; H, 9.08%; N, 3.46%.

Lactam **6e**. Yellow oil. $[\alpha]_D^{25}=-51.1$ (c 1.3, CH_2Cl_2). ^{1}H NMR, δ: 0.94 (d, 3H, $J=6.5$ Hz); 0.95 (d, 3H, $J=6.5$ Hz); 1.23 (s, 3H); 1.33 (s, 3H); 1.71 (s, 3H); 1.92–1.96 (m, 1H); 2.06 (dd, 1H, $J_1=6.5$ Hz, $J_2=10.7$ Hz); 3.10 (d, 1H, $J=12.8$ Hz); 3.23 (d, 1H, $J=12.8$ Hz); 3.38 (dt, 1H, $J_1=4.2$ Hz, $J_2=12.7$ Hz); 4.93 (d, 1H, $J=7.1$ Hz); 7.25–7.41 (m, 5H). ^{13}C NMR, δ: 18.9, 21.6, 22.0, 23.3, 24.0, 25.7, 27.2, 27.5, 31.2, 34.5, 40.5, 41.2, 48.2, 49.6, 54.5, 57.6, 76.0, 87.6, 126.0, 128.8, 129.1, 137.0, 175.4. IR (film): 3060, 2940, 2860, 1690, 1590, 1450, 750, 695. CIMS, m/z (%): 416 (M+1, 100); 417 (M+2, 27); 348 (39). Anal. calcd for $C_{25}H_{37}NO_2S$: C, 72.24%; H, 8.97%; N, 3.37%. Found: C, 72.38%; H, 8.86%; N, 3.36%.

2.11. Reductive cleavage of lactams 5b,c,e and 6e. General procedure

To a mixture of $LiAlH_4$ (0.5 g, 13.1 mmol) and $AlCl_3$ (713 mg, 5.34 mmol) in anhydrous THF (30 mL) at 0°C was slowly added to a solution of the corresponding lactams (2.7.mmol) in the same solvent. The solution was stirred for 10 min at that temperature and then carefully quenched with water (40 mL) and extracted with chloroform (3×50 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum to give pure pyrrolidinyl menthols.

2.12. (3′*R*,4′*R*)-8-(3′-Phenylsulfinylmethyl-4′-isopropenylpyrrolidinyl) menthol 7c

Yellow oil. $[\alpha]_D^{25}=+19.3$ (c 1.2, CH_2Cl_2). ^{1}H NMR, δ: 0.89 (s, 3H); 1.11 (s, 3H); 1.63 (s, 3H); 1.85–1.91 (m, 1H); 2.38 (q, 1H); 2.64–2.72 (m, 2H); 2.94–2.98 (m, 2H); 3.07–3.11 (m, 2H); 3.58 (dt, 1H, $J_1=3.86$ Hz, $J_2=10.3$ Hz); 4.71 (d, 1H, $J=1.2$ Hz); 4.76 (d, 1H, $J=1.2$ Hz); 7.10–7.30 (m, 5H). ^{13}C NMR, δ: 21.6, 22.1, 25.5, 30.9, 34.9, 44.2, 48.3, 51.4, 59.4, 72.8, 112.4, 126.0, 128.8, 129.2. IR (film): 3100, 2940, 1650, 1600, 1500, 1450, 750. CIMS, m/z (%): 388 (M+1, 100); 389 (M+2, 26); 386 (19); 274 (32). Anal. calcd for $C_{24}H_{37}NOS$: C, 74.37%; H, 9.62%; N, 3.61%. Found: C, 74.40%; H, 9.79%; N, 3.77%.

2.13. (3′*R*,4′*R*)-8-(3′-Methyl-3′-phenylsulfinylmethyl-4′-isopropylpyrrolidinyl) menthol 7e

Yellow oil. $[\alpha]_D^{25}=-16.6$ (c 1.6, CH_2Cl_2). ^{1}H NMR, δ: 0.89 (d, 3H, $J=6.6$ Hz); 0.91 (d, 3H, $J=6.5$ Hz); 0.96 (d, 3H, $J=6.0$ Hz); 1.10 (s, 3H); 1.12 (s, 3H); 1.54 (s, 3H); 1.58–1.68 (m, 1H); 1.90–1.94 (m, 1H); 2.64–2.97 (m, 4H); 3.02 (d, 1H, $J=12.1$ Hz); 3.21 (d, 1H, $J=12.1$ Hz); 3.61 (dt, 1H, $J_1=3.9$ Hz, $J_2=10.3$ Hz); 7.14–7.33 (m, 5H); 8.79 (broad s, 1H). ^{13}C NMR, δ: 16.7, 21.6, 22.1, 25.5, 30.9, 34.9, 44.2, 48.3, 51.4, 59.4, 72.8, 112.4, 126.0, 128.8, 129.2. IR (film): 3040, 2960, 2820, 1680, 1580, 1450, 730, 680. CIMS, m/z (%): 404 (M+1, 100); 405 (M+2, 27). Anal. calcd for $C_{25}H_{41}NOS$: C, 74.39%; H, 10.24%; N, 3.47%. Found: C, 74.52%; H, 10.35%; N, 3.36%.

2.14. (3′*S*,4′*R*)-8-(3′-Methyl-3′-phenylsulfinylmethyl-4′-isopropylpyrrolidinyl) menthol 8e

Yellow oil. $[\alpha]_D^{25}=+10.2$ (c 0.9, CH_2Cl_2). ^{1}H NMR, δ: 0.93 (d, 3H, $J=6.5$ Hz); 0.97 (d, 3H, $J=6.4$ Hz); 1.05 (d, 3H, $J=6.4$ Hz); 1.17 (s, 3H); 1.28 (s, 3H); 1.89–1.95 (m, 1H); 2.57–2.79 (m, 2H); 3.03–3.10 (m, 4H); 3.66 (dt, 1H, $J_1=4.2$ Hz, $J_2=12.7$ Hz); 7.19–7.45 (m, 5H); 8.40 (broad s, 1H). ^{13}C NMR, δ: 19.1, 21.2, 22.1, 22.8, 25.4, 29.6, 30.9, 35.0, 43.6, 44.1, 45.1, 48.6, 50.5, 52.2, 58.9, 72.8, 125.9, 128.8, 129.3, 137.7. IR (film): 3110, 2940, 1640, 1600, 1500, 1450, 740. calcd for $C_{25}H_{41}NOS$: C, 74.39%; H, 10.24%; N, 3.47%. Found: C, 74.28%; H, 10.34%; N, 3.59%.

2.15. Elimination of the menthol appendage. Synthesis of tosylate of (3*R*,4*R*)-3-methylsulfonyl phenyl-4-isopropyl pyrrolidine 9

The elimination of the chiral appendage was carried out as previously described.[6c] In this case the sulfide group was also oxidized to sulfone, and the pyrrolidine derivative was isolated as tosylate. Yellow oil. $[\alpha]_D^{25}=+21.4$ (c 1.2, CH_2Cl_2). ^{1}H NMR, δ: 0.66 (d, 3H, $J=6.7$ Hz); 0.77 (d, 3H, $J=6.7$ Hz); 1.48 (m, 1H, $J=6.7$ Hz); 1.65 (m, 1H, $J=7.5$ Hz); 2.24–2.29 (m, 1H); 2.43 (s, 3H); 2.77 (dd, 1H, $J_1=9.0$ Hz, $J_2=9.0$ Hz); 2.95 (dd, 1H, $J_1=10.4$ Hz, $J_2=14.1$ Hz); 3.10 (dd, 1H, $J_1=7.6$ Hz; $J_2=10.4$ Hz); 3.12 (dd, 1H, $J_1=7.6$ Hz, $J_2=10.4$ Hz); 3.30 (dd, 1H, $J_1=9.0$ Hz, $J_2=9.0$ Hz); 3.46 (dd,

1H, $J_1 = 7.6$ Hz, $J_2 = 10.4$ Hz); 7.27–7.87 (m, 9H). ^{13}C NMR, δ: 18.3; 20.9; 21.5; 29.1; 35.5; 49.1; 50.0; 53.0; 59.5; 127.7; 127.8; 129.4; 129.7; 132.4; 134.0; 138.9; 143.6. CIMS, m/z (%): 422 (M+1, 100); 423 (23). Anal. calcd: $C_{21}H_{25}NO_4S_2$: C, 60.12%; H, 6.01%; N, 3.34%. Found: C, 60.01%; H, 5.89%; N, 3.47%.

Acknowledgements

We thank the financial support provided by the Spanish Ministerio de Ciencia y Tecnología (Project BQU2002-1046) and Junta de Castilla y León (Project VA042/03).

References

1. See for instance: (a) Curran, D. P.; Porter, N. A.; Giese, B. In *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996; (b) *Radicals in Organic Synthesis*, Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2.
2. (a) Porter, N. A.; Scott, D. M.; Lacher, B.; Giese, B.; Zeitz, H.-G.; Lindner, H. J. *J. Am. Chem. Soc.* **1989**, *111*, 8311; (b) Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738; (c) Porter, N. A.; Swann, E.; Nally, J.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 6740; (d) Giese, B.; Zehnder, M.; Roth, M.; Zeitz, H. G. *J. Am. Chem. Soc.* **1990**, *112*, 6741; (e) Porter, N. A.; Rosenstein, I. J.; Breyer, R. A.; Bruhnke, J. D.; Wu, W.-X.; McPhail, A. T. *J. Am. Chem. Soc.* **1992**, *114*, 7664; (f) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779; (g) Tararov, V. I.; Kuznetzov, N. Y.; Bakhmutov, V. I.; Ikonnikov, N. S.; Bubnov, Y. N.; Khrustalev, V. N.; Saveleva, T. F.; Belokon, Y. N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3101.
3. (a) Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029; (b) Sibi, M. P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 9200; (c) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800.
4. Colombo, L.; Di Giacomo, M.; Scolastico, C.; Manzoni, L.; Belvisi, L.; Molteni, V. *Tetrahedron Lett.* **1995**, *36*, 625.
5. (a) Porter, N. A.; Lacher, B.; Chang, V. H.-T.; Magnin, D. R. *J. Am. Chem. Soc.* **1989**, *111*, 8309; (b) Blake, A. J.; Hollingworth, G. J.; Pattenden, G. *Synlett* **1996**, 643.
6. (a) Pedrosa, R.; Andrés, C.; Duque-Soladana, J. P.; Mendiguchía, P. *Eur. J. Org. Chem.* **2000**, 3727; (b) Andrés, C.; Duque-Soladana, J. P.; Pedrosa, R. *J. Org. Chem.* **1999**, *64*, 4282; (c) Andrés, C.; Duque-Soladana, J. P.; Pedrosa, R. *J. Org. Chem.* **1999**, *64*, 4273; (d) Andrés, C.; Duque-Soladana, J. P.; Iglesias, J. M.; Pedrosa, R. *Tetrahedron Lett.* **1996**, *37*, 9085.
7. (a) Pedrosa, R.; Andrés, C.; Duque-Soladana, J. P.; Rosón, C. *Tetrahedron: Asymmetry* **2000**, *11*, 2809; (b) Andrés, C.; Duque-Soladana, J. P.; Iglesias, J. M.; Pedrosa, R. *Tetrahedron Lett.* **1999**, *40*, 2421.
8. Kuehne, M. E.; Damon, R. E. *J. Org. Chem.* **1977**, *42*, 1825.
9. Padwa, A.; Nimmersgern, H.; Wong, G. S. K. *J. Org. Chem.* **1985**, *50*, 5620.
10. Bertrand, M. P.; De Riggi, I.; Lesueur, C.; Gastaldi, S.; Nouguir, R.; Jaime, C.; Virgili, A. *J. Org. Chem.* **1995**, *60*, 6040.
11. Miyata, O.; Nishiguchi, A.; Nimomiya, I.; Naito, T. *Tetrahedron Lett.* **1996**, *37*, 229.
12. De Riggi, I.; Gastaldi, S.; Surzur, J. M.; Bertrand, M. P. *J. Org. Chem.* **1992**, *57*, 6118.
13. (a) Bertrand, M. P.; Gastaldi, S.; Nouguier, R. *Tetrahedron Lett.* **1996**, *37*, 1229; (b) Miyata, O.; Muroya, K.; Koide, J.; Naito, T. *Synlett* **1998**, 271.
14. Andrés, C.; Duque-Soladana, J. P.; Pedrosa, R. *Chem. Commun.* **1999**, 31.
15. Pedrosa, R.; Andrés, C.; Iglesias, J.; Pérez-Encabo, A. *J. Am. Chem. Soc.* **2001**, *123*, 1817.