Tetrahedron 65 (2009) 357–363

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

γ-Amino vinyl sulfoxides in asymmetric synthesis. Synthesis of optically pure α-substituted β-amino nitriles

Ricardo Alfaro [a], Francisco Yuste [a,*], Benjamín Ortiz [a], Rubén Sánchez-Obregón [a], José L. García Ruano [b,*]

[a] Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Cd. Universitaria, Coyoacán 04510, México D.F., Mexico
[b] Departamento de Química Orgánica (C-1), Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

ARTICLE INFO

Article history:
Received 16 September 2008
Received in revised form 13 October 2008
Accepted 15 October 2008
Available online 18 October 2008

ABSTRACT

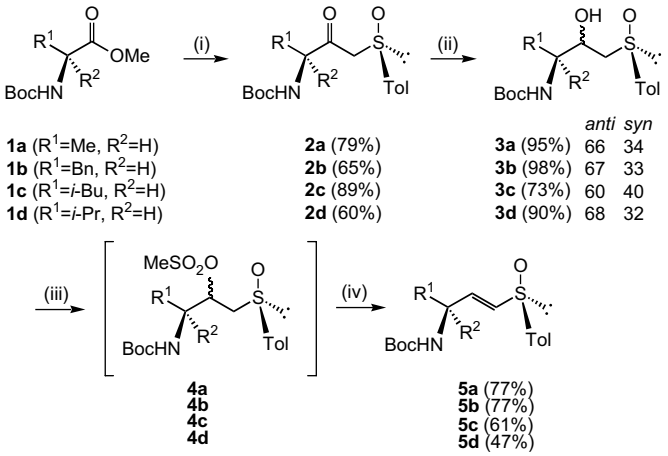
The synthesis of optically pure (*E*)- and (*Z*)-γ-amino vinyl sulfoxides derived from commercially available protected α-amino esters is reported. Hydrocyanation of the double bond with Et_2AlCN is completely stereoselective and provides enantiomerically pure α-substituted β-amino nitriles with complete control of the configuration at the α-carbon being exerted by the sulfinyl group.

1. Introduction

γ-Chiral vinyl sulfones are known to be useful chiral probes.[1] In particular, γ-oxygenated vinyl sulfones are versatile intermediates in asymmetric synthesis mainly because they undergo highly stereoselective conjugate addition of a large variety of nucleophiles.[2] γ-Chiral vinyl sulfoxides are also interesting chiral intermediates in which the sulfoxide moiety can transfer chiral information in subsequent asymmetric transformations. In this connection, several recent reports describe the preparation of optically pure γ-oxygenated α,β-unsaturated sulfoxides[3] and the use thereof as intermediates for stereocontrolled carbon–carbon bond formation reactions in the synthesis of optically active natural products and bioactive molecules.[4] In contrast, much less attention has been devoted to γ-nitrogenated vinyl sulfones and sulfoxides. To the best of our knowledge, there is only one report concerning the synthesis of chiral γ-amino vinyl sulfones,[5] which, however, does not mention the potential synthetic utility of these species. γ-Amino vinyl sulfoxides, which are potentially very interesting chiral synthons, do not as yet appear to have been described in the literature. In this article, we describe the synthesis of several examples of both double bond isomers of such compounds. The reactivity and synthetic utility of these compounds is illustrated by their reaction with Et_2AlCN, which has led to the generation of enantiomerically pure α-methylsulfinyl substituted β-amino nitriles.

2. Results and discussion

Given that vinyl sulfoxides can be prepared by sequential reduction and dehydration of β-keto sulfoxides, which in its turn can be easily obtained from esters, we envisioned the generation of (*E*)-γ-amino α,β-unsaturated sulfoxides via the synthetic sequence depicted in Scheme 1. As starting materials we have used the commercially available enantiopure amino esters **1**. The reaction thereof with (*R*)-(+)-methyl *p*-tolyl sulfoxide and LDA at −78 °C, afford the γ-amino-β-keto sulfoxides **2**.[6] The reduction of **2** with $NaBH_4$ produced mixtures of the β-hydroxy sulfoxide diastereoisomers **3**



1a (R^1=Me, R^2=H) **2a** (79%) **3a** (95%) anti 66 syn 34
1b (R^1=Bn, R^2=H) **2b** (65%) **3b** (98%) 67 33
1c (R^1=*i*-Bu, R^2=H) **2c** (89%) **3c** (73%) 60 40
1d (R^1=*i*-Pr, R^2=H) **2d** (60%) **3d** (90%) 68 32

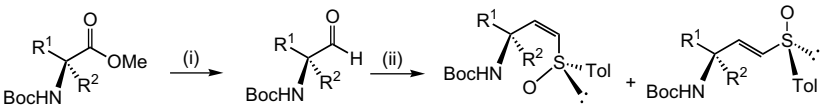
4a
4b
4c
4d

5a (77%)
5b (77%)
5c (61%)
5d (47%)

Scheme 1. *Reagents and conditions*: (i) (+)-(*R*)-*p*-TolSOMe, LDA, THF, −78 °C. (ii) $NaBH_4$, MeOH, −78 °C. (iii) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 25 °C. (iv) *t*-BuOK, DMSO, 25 °C.

* Corresponding authors. Tel.: +52 55 5622 4406; fax: +52 55 5616 2217 (F.Y.); tel.: +34 91 497 4701; fax: +34 91 497 3966 (J.L.G.R.).
E-mail addresses: yustef@servidor.unam.mx (F. Yuste), joseluis.garcia.ruano@uam.es (J.L. García Ruano).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.10.037



1a (R^1=Me, R^2=H)
1b (R^1=Bn, R^2=H)
1c (R^1=*i*-Bu, R^2=H)
1d (R^1=*i*-Pr, R^2=H)
ent-**1a** (R^1=H, R^2=Me)
ent-**1b** (R^1=H, R^2=Bn)

6a (93%)
6b (95%)
6c (98%)
6d (95%)
ent-**6a** (92%)
ent-**6b**

7a (46%)
7b (36%)
7c (51%)
7d (55%)
7e (45%)
7f (41%)

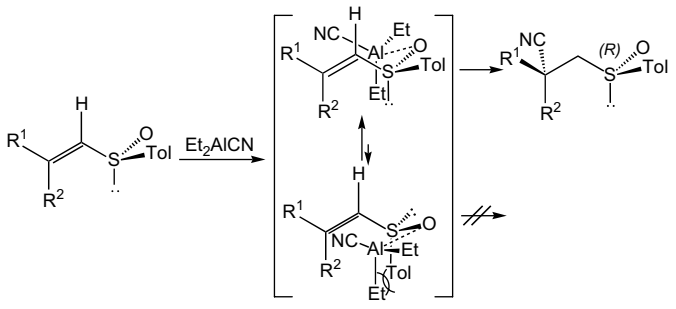
5a (25%)
5b (27%)
5c (17%)
5d (27%)
5e (15%)
5f (9%)

Scheme 2. *Reagents and conditions*: (i) DIBAH, CH_2Cl_2, −78 °C. (ii) (+)-(*S*)-*p*-TolSOCH$_2$PO(OMe)$_2$, *n*-BuLi, THF, −78 °C→ 25 °C.

(*anti*/*syn*≥68:32) in high yields. Treatment of the so produced mixtures of **3** with Et_3N (2 equiv) and MsCl (2 equiv) in CH_2Cl_2 at room temperature gave the mesylates **4**, which, without further purification, were subjected to the next reaction. The reaction of **4** with *t*-BuOK (1 equiv) in DMSO at room temperature gave the (*E*)-vinyl sulfoxides **5** exclusively in high yields. Since the stereochemistry of the double bond is not dependent on the configuration of the hydroxyl group of the precursor, neither the stereoselective reduction of the keto sulfoxides nor the isolation and separation of the epimeric mesylates derived there from is necessary.

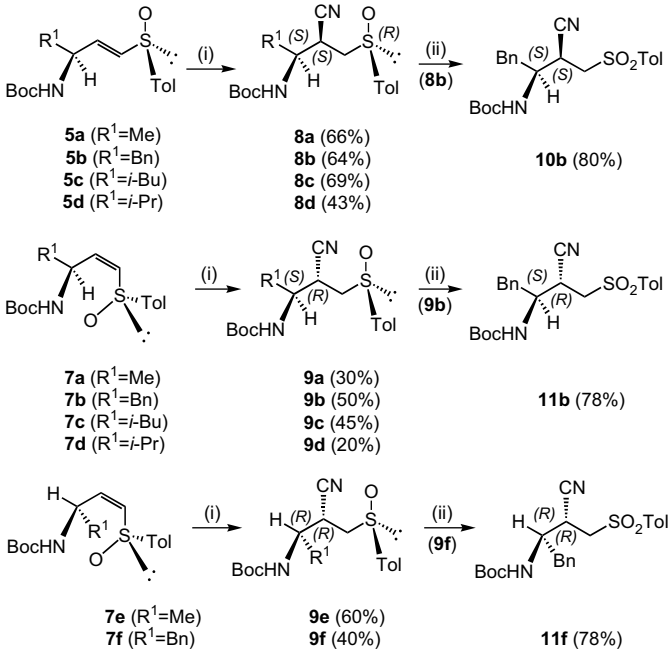
The (*Z*)-vinyl sulfoxides **7** were prepared by a Horner–Wittig reaction of the *N*-Boc protected α-amino aldehydes **6**, which were obtained by DIBAH reduction (−78 °C in CH_2Cl_2[7]) of the commercially available amino esters **1** (Scheme 2). Given the rather low configurational stability of **6**, these intermediates were prepared and used immediately as crude products. Thus, reaction of **6** with the lithio derivative of (+)-(*S*)-dimethylphosphorylmethyl *p*-tolyl sulfoxide[8] directly afforded mixtures of the (*E*) and (*Z*) double bond isomers **5** and **7**, usually in good combined yields. Chromatographic separation of these mixtures provided moderate yields of the desired, major (*Z*)-**7** isomers.

With the (*E*)- and (*Z*)-γ-amino vinyl sulfoxides in hand, exploration of the reactivity of these entities was undertaken. Hydrocyanation of double bonds is a highly interesting transformation, which permits the formal direct conversion of alkenes into carboxylic acid derivatives.[9] We have recently reported the highly stereoselective hydrocyanation of vinyl sulfoxides using Et_2AlCN.[10] In those reactions, the sulfinyl group functioned to control the intramolecular hydrocyanation stereoselectivity by virtue of its prior association with the reagent (Et_2AlCN) in a chair-like transition state (Scheme 3).[10b] The application of this reaction to compounds **5** and **7** was expected to provide β-amino nitriles containing two chiral centers, the synthetic usefulness of which as chiral synthons is obvious. The stereochemical outcome of the hydrocyanation of these vinyl sulfoxides is not necessarily predictable, however, because of the presence of an additional chiral center, i.e., the Boc-amine bearing carbon atom.



Scheme 3.

The reaction of the (*E*)-alkenyl sulfoxides **5a–d** with Et_2AlCN in THF at room temperature afforded the β-amino nitriles **8a–d** as the only diastereoisomers (Scheme 4). Hydrocyanation of the (*Z*) olefins **7a–d** under identical conditions gave the epimeric nitriles **9a–d** exclusively, with quite different NMR spectra. Both the reactivity of the (*E*) olefins and the hydrocyanation yields of them are slightly higher than that observed for the (*Z*) isomers. The (*E*) isomers required 2.5–3 h for completion whereas 5–6 h was necessary for the transformation of the (*Z*) isomers (Scheme 4). Similar trends were observed in our previously reported vinyl sulfoxide hydrocyanation reactions,[10b] which suggested a similar mechanism, based on the assumption that the sulfinyl group is the stereochemical controlling group. To confirm this assumption, we also studied the reaction of **7e** and **7f**, the epimers of **7a** and **7b** at the amine carbon, with Et_2AlCN. These reactions were also completely stereoselective, only one compound (**9e** or **9f**) being obtained in each case (Scheme 4).



5a (R^1=Me)
5b (R^1=Bn)
5c (R^1=*i*-Bu)
5d (R^1=*i*-Pr)

8a (66%)
8b (64%)
8c (69%)
8d (43%)

10b (80%)

7a (R^1=Me)
7b (R^1=Bn)
7c (R^1=*i*-Bu)
7d (R^1=*i*-Pr)

9a (30%)
9b (50%)
9c (45%)
9d (20%)

11b (78%)

7e (R^1=Me)
7f (R^1=Bn)

9e (60%)
9f (40%)

11f (78%)

Scheme 4. *Reagents and conditions*: (i) Et_2AlCN, THF, 0 °C→ 25 °C. (ii) MCPBA, CH_2Cl_2, 25 °C.

The absolute configuration of the β-cyano sulfoxide **8a**[11] was unequivocally assigned as (1*S*,2*S*,R_S) by an X-ray diffraction study (Fig. 1). The configuration of this nitrile at C-2 is *S*, predicted by the mechanism depicted in Scheme 3.

The configuration of nitriles **9b** and **9f** at C-2 was determined by chemical correlation with **8b**. The MCPBA oxidation to the sulfones **10b**, **11b**, and **11f** gave the results indicated in Scheme 4. The

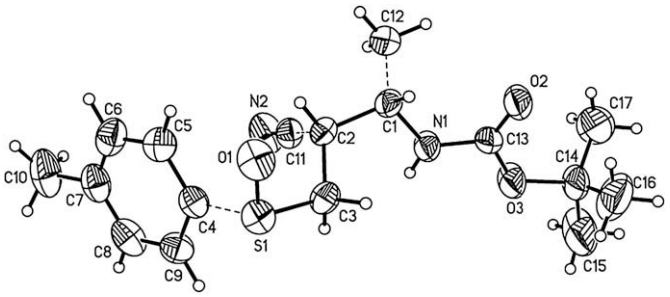


Figure 1. X-ray structure of compound **8a**.

configuration of **10b** is known (2*S*,3*S*) because it is derived from **8b**. Compound **11f** is the enantiomer of **10b** and therefore it must be assigned as (2*R*,3*R*). Finally, **11b** is a diastereoisomer of **11f** and therefore must be assigned as (2*S*,3*R*) since the starting amino esters have the opposite configuration. This shows that the configuration at C-2 induced in the hydrocyanation is the same starting from compounds with different configurations at the nitrogen bearing carbon (**7a**,**b** vs **7e**,**f**), which means that it is the sulfur, which completely controls the stereoselectivity of the reaction, regardless the configuration at the second chiral center. The mechanism indicated in Scheme 3 also explains the observation that the configuration of the center created in the hydrocyanation changes with the stereochemistry of the double bond. It confirms that **11f** is an enantiomer of **10b** (starting products differ in stereochemistry of the double bond and in the configuration at nitrogenated carbon) and diastereoisomer of **11b** (starting products differ only in the stereochemistry of the double bond).

In summary, we have reported the synthesis of the (*E*)-**5** and (*Z*)-**7** γ-amino vinyl sulfoxides of high optical purity from the readily available *N*-Boc protected amino esters **1**. Reaction of these compounds with Et_2AlCN affords the β-amino nitriles **8** and **9** with complete control of the configuration being exerted by the sulfinyl group.

3. Experimental

3.1. General methods

Melting points were determined in a Culatti melting point apparatus in open capillary tubes and are uncorrected. All moisture sensitive reactions were performed in flame-dried glassware equipped with rubber septa under a positive pressure of argon and monitored by TLC. Solvents were dried according to literature procedures. Flash chromatography was performed using silica gel 60 (230–400 mesh ASTM). Optical rotations were measured on a Perkin–Elmer 343 polarimeter at 20 °C (concentration in g/100 mL). The IR spectra were recorded on a Nicolet-5SX spectrophotometer. The ^1H and ^{13}C NMR spectra were obtained either on a Varian Unity 200 or Jeol Eclipse 300 NMR spectrometers at room temperature on deuterochloroform using TMS as internal standard. Mass spectra were measured on a Jeol JMS-SX 102A or JMS-AX 505HA mass spectrometers at 70 eV and 190 °C.

3.2. Preparation of β-keto sulfoxides 2

To a solution of (*R*)-(+)-methyl *p*-tolyl sulfoxide (2 equiv) in THF (2 mL/mmol) was added dropwise to a solution of LDA (2 equiv) in THF (2.5 mL/mmol) at −78 °C. The mixture was stirred at −78 °C for 2 h. Then, a solution of **1** (1 equiv) in THF (4 mL/mmol) was added and the resulting mixture was stirred at −25 °C for 12 h. The reaction mixture was decomposed with saturated ammonium chloride solution (2 mL/mmol) and extracted with CH_2Cl_2 (4×5 mL/mmol). The organic phase was washed with brine, dried, and evaporated.

3.2.1. (3*S*,*R*$_S$)-*N*-(tert-Butoxycarbonyl)-3-amino-1-(*p*-tolylsulfinyl)-2-butanone **2a**[6]

Obtained from 4.06 g (20 mmol) of **1a**. The crystalline crude product was purified by crystallization from CH_2Cl_2–hexane to give 4.31 g of **2a**. The mother liquors were purified by column chromatography eluting with hexane–EtOAc 35:65 to produce, additionally, 0.82 g of **2a** (79% yield). White crystals, mp 103–104 °C; $[\alpha]_D$ +183.9 (*c* 1, $CHCl_3$), de>97%; IR ($CHCl_3$) ν_{max}: 3437, 2984, 2931, 1706, 1496, 1370, and 1054 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.24 (d, 3H, *J* 7.2), 1.43 (s, 9H), 2.42 (s, 3H), 3.78 and 4.13 (AB system, 2H, *J* 13.8), 4.20 (m, 1H), 5.25 (m, 1H, interchangeable with D_2O), 7.34–7.57 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.1, 21.4, 28.3, 56.0, 65.5, 80.3, 124.1, 130.1, 140.2, 142.4, 155.0, 201.5; EIMS *m*/*z* 326 (2%, M^++1), 144 (100), 140 (74), 88 (36), 57 (98), 44 (84).

3.2.2. (3*S*,*R*$_S$)-*N*-(tert-Butoxycarbonyl)-3-amino-4-phenyl-1-(*p*-tolylsulfinyl)-2-butanone **2b**

Obtained from 12.0 g (43 mmol) of **1b**. The crystalline crude product was purified by crystallization from CH_2Cl_2–hexane to give 5.57 g of **2b**. The mother liquors were purified by column chromatography eluting with hexane–EtOAc 40:60 to produce, additionally, 5.63 g of **2b** (65% yield). White crystals, mp 134–135 °C; $[\alpha]_D$ +140.3 (*c* 1, $CHCl_3$), de>97%; IR (KBr) ν_{max}: 3384, 2972, 1720, 1691, 1602, 1513, 1165, and 1043 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.38 (s, 9H), 2.41 (s, 3H), 2.87 (dd, 1H, *J* 8.1 and 14.1), 3.07 (dd, 1H, *J* 5.7 and 14.1), 3.71 and 4.05 (AB system, 2H, *J* 14.1), 4.31 (dd, 1H, *J* 7.2 and 13.5), 5.18 (br d, 1H, interchangeable with D_2O), 7.05–7.16 (m, 2H), 7.20–7.34 (m, 5H), 7.45–755 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 28.2, 36.3, 61.4, 66.0, 80.2, 124.1, 126.9, 128.6, 129.3, 130.0, 136.2, 139.9, 142.2, 155.2, 200.8; EIMS *m*/*z* 402 (2%, M^++1), 220 (72), 164 (80), 139 (43), 120 (100), 91 (22), 57 (60). HMRS (EI): *m*/*z* calcd for $C_{22}H_{28}NO_4S$ [M+1]: 402.1739; found: 402.1749.

3.2.3. (3*S*,*R*$_S$)-*N*-(tert-Butoxycarbonyl)-3-amino-5-methyl-1-(*p*-tolylsulfinyl)-2-hexanone **2c**[12]

Obtained from 9.35 g (38 mmol) of **1c**. The crystalline crude product was purified by crystallization from CH_2Cl_2–hexane to give 8.45 g of **2c**. The mother liquors were purified by column chromatography eluting with hexane–EtOAc 40:60 to produce, additionally, 4.01 g of **2c** (89% yield). White crystals, mp 112 °C; $[\alpha]_D$ +140.0 (*c* 1, $CHCl_3$), de>97%; IR ($CHCl_3$) ν_{max}: 3439, 2962, 2933, 1707, 1598, 1495, 1369, and 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.89 (d, 3H, *J* 6.6), δ 0.90 (d, 3H, *J* 6.6), 1.20–1.35 (m, 1H), 1.43 (s, 9H), 1.60–1.75 (m, 2H), 2.42 (s, 3H), 3.75 and 4.19 (AB system, 2H, *J* 13.8), 4.10–4.26 (m, 1H), 5.15 (br d, 1H, interchangeable with D_2O), 7.33 and 7.58 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 23.1, 24.7, 28.3, 39.0, 58.7, 66.1, 80.2, 124.3, 130.1, 140.4, 142.3 155.6, 201.9; EIMS *m*/*z* 368 (3%, M^++1), 312 (10), 186 (65), 140 (38), 130 (98), 86 (100), 57 (63).

3.2.4. (3*S*,*R*$_S$)-*N*-(tert-Butoxycarbonyl)-3-amino-4-methyl-1-(*p*-tolylsulfinyl)-2-pentanone **2d**

Obtained from 13.04 g (56.45 mmol) of **1d**. The crystalline crude product was purified by crystallization from CH_2Cl_2–hexane to give 6.58 g of **2d**. The mother liquors were purified by column chromatography eluting with hexane–EtOAc 35:65 to produce, additionally, 4.72 g of **2d** (57% yield). White crystals, mp 113–114 °C; $[\alpha]_D$ +226 (*c* 1, $CHCl_3$), de>97%; IR (KBr) ν_{max}: 3272, 2975, 1702, 1594, 1521, 1363, 1275, 1163, and 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.74 (d, 3H, *J* 6.8), 0.95 (d, 3H, *J* 6.8), 1.44 (s, 9H), 2.18 (m, 1H), 2.42 (s, 3H), 3.74 and 4.18 (AB system, 2H, *J* 14.4), 4.16 (m, 1H), 5.36 (br d, 1H, interchangeable with D_2O), 7.33 and 7.59 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.8, 19.7, 21.4, 28.2, 29.2, 64.9, 66.7, 80.0, 124.2, 130.0, 140.2, 142.3 155.8, 201.4; EIMS *m*/*z* 354 (1%, M^++1), 172 (75), 116 (84), 72 (100), 57 (63). HMRS (EI): *m*/*z* calcd for $C_{18}H_{28}NO_4S$ [M+1]: 354.1739; found: 354.1726.

3.3. Preparation of β-hydroxy sulfoxides 3

$NaBH_4$ reduction. To a solution of $NaBH_4$ (1 equiv) in MeOH (5 mL/mmol) at −78 °C was added dropwise a solution of β-keto sulfoxide **2** (1 equiv) in MeOH (5 mL/mmol) at −78 °C. The reaction mixture was stirred for 1 h to completion and the excess of $NaBH_4$ was decomposed by addition of saturated ammonium chloride solution (5 mL/mmol). The solvents were removed under vacuum and the residue was treated with a 5% HCl solution (10 mL/mmol) and extracted with Et_2O (3×10 mL/mmol). The organic phase was washed with brine, dried, and evaporated.

3.3.1. (2S,3S,R_S) and (2R,3S,R_S)-N-(tert-Butoxycarbonyl)-3-amino-1-(p-tolylsulfinyl)-2-butanol ***3a***

Obtained from 1.0 g (3.07 mmol) of **2a**. The crude product was purified by column chromatography eluting with hexane–EtOAc 65:35 to give 0.95 g (95% yield) of **3a** as white crystals, mp 99–101 °C (CH_2Cl_2–hexane). IR (KBr) ν_{max}: 3362, 2977, 1692, 1510, 1170, and 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) data of the major isomer (2*S*,3*S*,R_S): δ 1.14 (d, 3H, *J* 6.8), 1.40 (s, 9H), 2.42 (s, 3H), 2.63 (dd, 1H, *J* 1.8 and 13.6), 3.07 (dd, 1H, *J* 10.0 and 13.6), 3.62 (br s, 1H), 4.07 (ddd, 1H, *J* 1.8, 4.4, and 10.2), 4.68 (br d, 1H, interchangeable with D_2O), 7.35 and 7.51 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.8, 21.4, 28.4, 50.4, 58.5, 69.6, 79.7, 124.1, 130.0, 139.5, 141.7, 155.4; EIMS *m*/*z* 327 (3%, M^+), 265 (15), 263 (17), 183 (53), 139 (100), 132 (75), 88 (34), 57 (94).

3.3.2. (2S,3S,R_S) and (2R,3S,R_S)-N-(tert-Butoxycarbonyl)-3-amino-4-phenyl-1-(p-tolylsulfinyl)-2-butanol ***3b***

Obtained from 5.04 g (12.5 mmol) of **2b**. The crude product was purified by column chromatography eluting with hexane–EtOAc 65:35 to give 4.96 g (98% yield) of **3b** as white crystals, mp 115–117 °C (CH_2Cl_2–hexane). IR (KBr) ν_{max}: 3355, 2978, 1696, 1520, 1170, 1040, and 1021 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) data of the major isomer (2*S*,3*S*,R_S): δ 1.35 (s, 9H), 2.41 (s, 3H), 2.59 (dd, 1H, *J* 1.6 and 13.5), 2.81–3.07 (m, 2H), 3.16 (dd, 1H, *J* 10.2 and 13.5), 3.58–3.62 (m, 1H), 4.11–4.17 (m, 1H), 4.51 (br d, 1H, interchangeable with D_2O), 7.14–7.55 (m, 9H); EIMS *m*/*z* 403 (4%, M^+), 312 (15), 208 (76), 164 (49), 139 (46), 120 (100), 72 (37), 57 (68).

3.3.3. (2S,3S,R_S) and (2R,3S,R_S)-N-(tert-Butoxycarbonyl)-3-amino-5-methyl-1-(p-tolylsulfinyl)-2-hexanol ***3c***

Obtained from 0.8 g (2.17 mmol) of **2c**. The crude product was purified by column chromatography eluting with hexane–EtOAc 65:35 to give 0.58 g (73% yield) of **3c** as white crystals, mp 79–80 °C (CH_2Cl_2–hexane). IR (KBr) ν_{max}: 3361, 2955, 1690, 1525, 1174, and 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) data of the major isomer (2*S*,3*S*,R_S): δ 0.87 (d, 3H, *J* 6.4), 0.91 (d, 3H, *J* 6.4), 1.20–1.35 (m, 2H), 1.40 (s, 9H), 1.45–1.70 (m, 1H), 2.43 (s, 3H), 2.67 (dd, 1H, *J* 1.8 and 13.6), 3.03 (dd, 1H, *J* 10.2 and 13.4), 3.60 (m, 1H), 4.04 (m, 1H), 4.44 (br d, 1H, interchangeable with D_2O), 7.34 and 7.52 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.4, 23.6, 24.6, 28.3, 39.2, 53.2, 59.0, 70.1, 79.8, 124.0, 130.1, 139.7, 141.6, 156.3; EIMS *m*/*z* 369 (1%, M^+), 296 (8), 278 (9), 186 (27), 183 (30), 174 (42), 139 (66), 130 (70), 86 (100), 57 (89).

3.3.4. (2S,3S,R_S) and (2R,3S,R_S)-N-(tert-Butoxycarbonyl)-3-amino-4-methyl-1-(p-tolylsulfinyl)-2-pentanol ***3d***

Obtained from 0.32 g (0.92 mmol) of **2d**. The crude product was purified by column chromatography eluting with hexane–EtOAc 65:35 to give 0.29 g (90% yield) of **3d** as white crystals, mp 173–175 °C (CH_2Cl_2–hexane). IR (KBr) ν_{max}: 3317, 2956, 1681, 1532, 1170, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) data of the major isomer (2*S*,3*S*,R_S): δ 0.88 (d, 3H, *J* 6.4), 0.91 (d, 3H, *J* 6.5), 1.40 (s, 9H), 1.84 (m, 1H), 2.42 (s, 3H), 2.66 (dd, 1H, *J* 1.8 and 13.8), 3.02 (t, 1H, *J* 9.6), 3.12 (dd, 1H, *J* 10.5 and 13.8), 4.38 (m, 1H), 4.85 (d, 1H, interchangeable with D_2O), 5.00 (br, 1H, interchangeable with D_2O), 7.30 and 7.51 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.3, 19.7, 21.4, 28.3, 30.2, 59.6, 60.3, 65.6, 79.1, 124.0, 130.0, 139.0, 141.6, 156.4; EIMS *m*/*z* 355 (3%, M^+), 282 (14), 183 (46), 160 (69), 139 (75), 116 (82), 72 (100), 57 (83).

3.4. Preparation of mesylates 4

To a solution of β-hydroxy sulfoxide **3** (1 equiv) in dry CH_2Cl_2 (10 mL/mmol) at 0 °C was added dropwise triethylamine (2 equiv). The mixture was kept for 30 min and then was added dropwise methanesulfonyl chloride (2 equiv). The reaction mixture was stirred for 1 h and then was decomposed by the addition of saturated ammonium chloride solution (5 mL/mmol). The organic phase was separated, washed with brine, dried, and evaporated.

3.5. Preparation of (*E*)-vinyl sulfoxides 5

To a solution of mesylate **4** (1 equiv) in DMSO (10 mL/mmol) was added dropwise a solution of potassium *tert*-BuOK (1 equiv) in DMSO (10 mL/mmol) at 25 °C and the resulting mixture was stirred for 30 min. Then, the reaction was decomposed with saturated ammonium chloride solution and extracted with toluene. The organic phase was separated, washed with brine, dried, and evaporated.

3.5.1. (E,3S,R_S)-tert-Butyl-1-(p-tolylsulfinyl)but-1-en-3-ylcarbamate ***5a***

Obtained from 0.28 g (0.85 mmol) of **3a**. The crude product was purified by column chromatography eluting with hexane–EtOAc 60:40 to give 0.20 g (77% yield) of **5a** as white crystals, mp 106–107 °C (CH_2Cl_2–hexane). $[\alpha]_D$ +117 (*c* 1, $CHCl_3$); IR (KBr) ν_{max}: 3389, 2979, 1706, 1520, 1247, 1166, and 1033 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.28 (d, 3H, *J* 6.6), 1.39 (s, 9H), 2.40 (s, 3H), 4.50 (b, 2H), 6.30 (dd, 1H, *J* 1.2 and 15.0), 6.54 (dd, 1H, *J* 4.6 and 15.0), 7.30 and 7.50 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.4, 21.4, 28.3, 47.1, 79.8, 125.0, 130.1, 134.3, 140.0, 140.5, 141.7, 154.7; EIMS *m*/*z* 310 (1%, M^++1), 292 (11), 236 (100), 192 (30), 57 (35). HMRS (EI): *m*/*z* calcd for $C_{16}H_{24}NO_3S$ [M+1]: 310.1477; found: 310.1470.

3.5.2. (E,3S,R_S)-tert-Butyl-4-phenyl-1-(p-tolylsulfinyl)but-1-en-3-ylcarbamate ***5b***

Obtained from 0.104 g (0.25 mmol) of **3b**. The crude product was purified by column chromatography eluting with hexane–EtOAc 65:35 to give 0.076 g (77% yield) of **5b** as white crystals, mp 103–105 °C (CH_2Cl_2–hexane). $[\alpha]_D$ +116.6 (*c* 1, $CHCl_3$); IR (KBr) ν_{max}: 3371, 2976, 1690, 1514, 1251, 1172, and 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.36 (s, 9H), 2.40 (s, 3H), 2.90 (dd, 2H, *J* 2.8 and 6.2), 4.56 (br, 2H), 6.21 (dd, 1H, *J* 1.4 and 15.0), 6.53 (dd, 1H, *J* 9.6 and 15.0), 7.11–7.45 (m, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.4, 28.2, 40.9, 52.4, 80.0, 125.1, 126.9, 128.6, 129.5, 130.0, 135.4, 136.2, 137.3, 140.3, 141.8, 154.8; EIMS *m*/*z* 368 (15%, M^+−17), 312 (54), 190 (61), 146 (52), 91 (33), 57 (100).

3.5.3. (E,3S,R_S)-tert-Butyl-5-methyl-1-(p-tolylsulfinyl)hex-1-en-3-ylcarbamate ***5c***

Obtained from 0.5 g (1.35 mmol) of **3c**. The crude product was purified by column chromatography eluting with hexane–EtOAc 65:35 to give 0.29 g (61% yield) of **5c** as white crystals, mp 87–88 °C (CH_2Cl_2–hexane). $[\alpha]_D$ +115.7 (*c* 1, $CHCl_3$); IR (KBr) ν_{max}: 3386, 3018, 2959, 1688, 1510, 1174, and 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.93 (d, 6H, *J* 6.8), 1.23–1.45 (m, 2H), 1.38 (s, 9H), 1.60–1.77 (m, 1H), 2.40 (s, 3H), 4.42 (br, 2H), 6.31 (d, 1H, *J* 15.0), 6.50 (dd, 1H, *J* 4.8 and 15.0), 7.29 and 7.50 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 22.2, 22.6, 24.7, 28.2, 43.8, 49.8, 79.7, 125.1, 130.1, 134.5, 139.6,

140.5, 141.7, 155.0; EIMS *m/z* 334 (7%, M^+-17), 278 (100), 234 (30), 190 (19), 57 (51).

3.5.4. (E,3S,R_S)-tert-Butyl-4-methyl-1-(p-tolylsulfinyl)pent-1-en-3-ylcarbamate ***5d***

Obtained from 0.5 g (1.40 mmol) of **3d**. The crude product was purified by column chromatography eluting with hexane–EtOAc 65:35 to give 0.22 g (47% yield) of **5d** as an oil. $[\alpha]_D$ +85.0 (*c* 1, $CHCl_3$); IR (KBr) ν_{max}: 3302, 2967, 1705, 1520, 1170, and 1043 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.92 (d, 3H, *J* 7.0), 0.95 (d, 3H, *J* 6.8), 1.38 (s, 9H), 1.80–1.97 (m, 1H), 2.40 (s, 3H), 4.18 (m, 1H), 4.58 (br d, 1H, interchangeable with D_2O), 6.31 (dd, 1H, *J* 1.2 and 15.0), 6.51 (dd, 1H, *J* 5.2 and 15.0), 7.29 and 7.50 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.0, 18.8, 21.3, 28.2, 32.3, 56.7, 79.7, 125.1, 130.1, 135.6, 137.8, 140.6, 141.8, 155.3; EIMS *m/z* 338 (5%, M^++1), 320 (15), 282 (32), 264 (100), 220 (30), 190 (44), 57 (77). HMRS (EI): *m/z* calcd for $C_{18}H_{28}NO_3S$ [M+1]: 338.1790; found: 338.1785.

3.6. Preparation of *N*-Boc protected amino aldehydes 6

To a cooled (−78 °C) solution of the amino ester **1** (1 equiv) in CH_2Cl_2 (2 mL/mmol) under argon atmosphere a solution of DIBAH in hexanes (2.1 equiv) was added dropwise over 20 min. The reaction mixture was stirred at −78 °C for 1.5 h and then quenched with water. It was then allowed to come to 25 °C and the resulting white precipitate was removed by filtration over Celite. The organic phase was separated, washed with brine, dried, and concentrated under reduced pressure yielded the aldehydes **6**, which were used immediately as crude products.

3.6.1. (S)-N-(tert-Butoxycarbonyl)-2-aminopropanal ***6a***

White crystals (93% yield), mp 76–77 °C; $[\alpha]_D$ −30.1 (*c* 1, MeOH) [lit[13] $[\alpha]_D$ −25.0 (*c* 1, MeOH)]; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33 (d, 3H, *J* 7.2), 1.45 (s, 9H), 4.23 (q, 1H, *J* 6.9), 5.10 (br s, 1H, interchangeable with D_2O), 9.56 (s, 1H).

3.6.2. (S)-N-(tert-Butoxycarbonyl)-2-amino-3-phenylpropanal ***6b***

White crystals (95% yield), mp 104–105 °C; $[\alpha]_D$ −37.9 (*c* 1, MeOH) [lit[13] $[\alpha]_D$ −35.7 (*c* 1, MeOH)]; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.43 (s, 9H), 3.11 (d, 2H, *J* 6.6), 4.42 (m, 1H), 5.02 (br s, 1H, interchangeable with D_2O), 7.14–7.36 (m, 9H), 9.63 (s, 1H).

3.6.3. (S)-N-(tert-Butoxycarbonyl)-2-amino-4-methylpentanal ***6c***

Oil (98% yield); $[\alpha]_D$ −45.5 (*c* 1, MeOH) [lit[13] $[\alpha]_D$ −30.0 (*c* 1, MeOH)]; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.96 (d, 6H, *J* 6.6), 1.45 (s, 9H), 1.30–1.80 (m, 3H), 4.25 (m, 1H), 4.90 (br, 1H, interchangeable with D_2O), 9.60 (s, 1H).

3.6.4. (S)-N-(tert-Butoxycarbonyl)-2-amino-3-methylbutanal ***6d***

Oil (95% yield); $[\alpha]_D$ −11.5 (*c* 1, MeOH) [lit[13] $[\alpha]_D$ −11.0 (*c* 1, MeOH)]; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.95 (d, 3H, *J* 6.8), 1.03 (d, 3H, *J* 6.8), 1.45 (s, 9H), 2.27 (m, 1H), 4.25 (m, 1H), 5.08 (br, 1H, interchangeable with D_2O), 9.65 (s, 1H).

*3.6.5. (R)-N-(tert-Butoxycarbonyl)-2-aminopropanal ent-***6a**

White crystals (92% yield), mp 76–77 °C; $[\alpha]_D$ +30.3 (*c* 1, MeOH) [lit[14] $[\alpha]_D$ +28.53 (*c* 2.45, MeOH)]; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.33 (d, 3H, *J* 7.2), 1.45 (s, 9H), 4.23 (q, 1H, *J* 6.9), 5.10 (br s, 1H, interchangeable with D_2O), 9.56 (s, 1H).

3.7. Preparation of (*Z*)-vinyl sulfoxides 7

To a solution of (+)-(*S*)-dimethylphosphorylmethyl *p*-tolyl sulfoxide[8] (1.1 equiv) in THF (10 mL/mmol) was added dropwise a solution of *n*-BuLi in hexanes (1.2 equiv) at −78 °C. The mixture was stirred at −78 °C for 30 min. Then, a solution of **6** (1 equiv) in THF (5 mL/mmol) was added. After 5 min, the reaction mixture was warmed to 25 °C and stirred for 3 h. The reaction mixture was decomposed with saturated ammonium chloride solution and extracted with CH_2Cl_2 (50 mL/mmol). The organic phase was washed with brine, dried, and evaporated.

3.7.1. (Z,3S,R_S)-tert-Butyl-1-(p-tolylsulfinyl)but-1-en-3-ylcarbamate ***7a***

Obtained from 0.45 g (2.60 mmol) of **6a**. The crude product was purified by chromatography eluting with hexane–EtOAc 65:35 to give 0.20 g (25%) of **5a** and 0.37 g (46%) of **7a**. Isomer **7a**, white crystals (CH_2Cl_2–hexane), mp 123–124 °C. $[\alpha]_D$ −180.3 (*c* 1, $CHCl_3$); IR (KBr) ν_{max}: 3266, 2976, 1705, 1534, 1251, 1166, and 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.37 (d, 3H, *J* 6.9), 1.45 (s, 9H), 2.39 (s, 3H), 4.61 (br, 1H, interchangeable with D_2O), 5.07 (dd, 1H, *J* 6.9 and 9.3), 5.92 (t, 1H, *J* 9.3), 6.14 (dd, 1H, *J* 0.9 and 9.6), 7.28 and 7.68 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.3 (2C), 28.4, 45.1, 79.9, 124.6, 129.8, 136.6, 141.0 (2C), 141.7, 154.6.

3.7.2. (Z,3S,R_S)-tert-Butyl-4-phenyl-1-(p-tolylsulfinyl)but-1-en-3-ylcarbamate ***7b***

Obtained from 0.62 g (2.49 mmol) of **6b**. The crude product was purified by chromatography eluting with hexane–EtOAc 70:30 to give 0.258 g (27%) of **5b** and 0.345 g (36%) of **7b**. Isomer **7b**: white semisolid; $[\alpha]_D$ −164.0 (*c* 1, $CHCl_3$); IR (film) ν_{max}: 3353, 2977, 1697, 1530, 1252, 1166, and 1014 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.42 (s, 9H), 2.39 (s, 3H), 3.01 (m, 2H), 4.65 (br, 1H, interchangeable with D_2O), 5.25 (m, 1H), 5.96 (t, 1H, *J* 9.6), 6.17 (d, 1H, *J* 9.6), 7.22–7.38 (m, 7H), 7.63 (br d, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 28.3, 41.1, 49.9, 80.0, 124.5, 127.1, 128.7, 129.5, 129.9, 135.9, 137.5, 139.4, 140.8, 141.1, 154.7.

3.7.3. (Z,3S,R_S)-tert-Butyl-5-methyl-1-(p-tolylsulfinyl)hex-1-en-3-ylcarbamate ***7c***

Obtained from 0.20 g (0.93 mmol) of **6c**. The crude product was purified by chromatography eluting with hexane–EtOAc 65:35 to give 0.056 g (17%) of **5c** and 0.166 g (51%) of **7c**. Isomer **7c**: oil; $[\alpha]_D$ −183.2 (*c* 1, $CHCl_3$); IR (film) ν_{max}: 3286, 2959, 1705, 1522, 1170, and 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.99 (d, 3H, *J* 6.6), 1.03 (d, 3H, *J* 6.6), 1.46 (s, 9H), 1.40–1.58 (m, 2H), 1.65–1.80 (m, 1H), 2.40 (s, 3H), 4.55 (br, 1H, interchangeable with D_2O), 5.02 (m, 1H), 5.83 (t, 1H, *J* 9.6), 6.17 (d, 1H, *J* 9.6), 7.29 and 7.71 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 22.5, 22.6, 24.6, 28.4, 44.1, 47.7, 80.0, 124.6, 129.8, 137.3 (2C), 140.4, 140.9, 154.7.

3.7.4. (Z,3S,R_S)-tert-Butyl-4-methyl-1-(p-tolylsulfinyl)pent-1-en-3-ylcarbamate ***7d***

Obtained from 1.0 g (4.97 mmol) of **6d**. The crude product was purified by chromatography eluting with hexane–EtOAc 70:30 to give 0.452 g (27%) of **5d** and 0.922 g (55%) of **7d**. Isomer **7d**: white crystals (CH_2Cl_2–hexane), mp 83–84 °C; $[\alpha]_D$ −208.5 (*c* 1, $CHCl_3$); IR (film) ν_{max}: 3258, 2970, 1702, 1533, 1174, and 1011 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.03 (d, 3H, *J* 6.9), 1.06 (d, 3H, *J* 6.9), 1.47 (s, 9H), 1.82 (m, 1H), 2.39 (s, 3H), 4.64 (br, 1H, interchangeable with D_2O), 4.75 (m, 1H), 5.87 (t, 1H, *J* 9.6), 6.23 (d, 1H, *J* 9.9), 7.28 and 7.69 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.6, 18.9, 21.4, 28.4, 32.6, 54.7, 79.8, 124.6, 129.8, 138.5 (2C), 141.0, 141.1, 155.0.

3.7.5. (Z,3R,R_S)-tert-Butyl-1-(p-tolylsulfinyl)but-1-en-3-ylcarbamate ***7e***

Obtained from 0.47 g (2.71 mmol) of *ent*-**6a**. The crude product was purified by chromatography eluting with hexane–EtOAc 65:35 to give 0.057 g (15%) of **5e** and 0.378 g (45%) of **7e**. Isomer **7e**: white crystals (CH_2Cl_2–hexane), mp 79–80 °C; $[\alpha]_D$ −262.2 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.29 (d, 3H, *J* 6.9), 1.47 (s, 9H), 2.40 (s, 3H), 4.77 (br, 1H, interchangeable with D_2O), 4.87 (m, 1H), 5.99 (m, 1H),

6.18 (dd, 1H, *J* 0.9 and 9.6), 7.31 and 7.53 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.3, 21.4, 28.4, 45.8, 80.2, 124.3, 130.1, 136.9, 140.9, 141.4, 141.5, 154.8.

3.7.6. (Z,3R,R_S)-tert-Butyl-4-phenyl-1-(p-tolylsulfinyl)but-1-en-3-ylcarbamate ***7f***

Obtained from 0.45 g (1.80 mmol) of *ent*-**6b** (Aldrich). The crude product was purified by chromatography eluting with hexane–EtOAc 70:30 to give 0.062 g (9%) of **5f** and 0.285 g (41%) of **7f**. Isomer **7f**: white crystals (CH_2Cl_2–hexane), mp 146 °C; $[\alpha]_D$ −222.6 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.48 (s, 9H), 2.37 (s, 3H), 2.85 (dd, 1H, *J* 8.1 and 13.2), 3.10 (dd, 1H, *J* 6.0 and 13.5), 4.81 (br, 1H, interchangeable with D_2O), 5.05 (m, 1H), 6.05 (t, 1H, *J* 9.3), 6.18 (dd, 1H, *J* 0.9 and 9.6), 7.05–7.35 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.3, 28.4, 41.6, 51.2, 80.3, 124.2, 127.0, 128.8, 129.6, 130.0, 136.6, 138.0, 138.9, 140.7, 141.2, 154.7.

3.8. Preparation of β-cyano sulfoxides 8

To a solution of vinyl sulfoxide (1 equiv) in THF (10 mL/mmol) was added dropwise a solution 1 M of Et_2AlCN in toluene (3 equiv) at 0 °C. The mixture was stirred at 25 °C for 2.5–3 h. The reaction mixture was decomposed with 30 mL of saturated Rochelle's salt and extracted with AcOEt (2×40 mL). The organic phase was washed with brine, dried, and evaporated.

3.8.1. (2S,3S,R_S)-(tert-Butyl)-2-cyano-1-(p-tolylsulfinyl)butan-3-ylcarbamate ***8a***

Obtained from 0.211 g (0.68 mmol) of **5a**. The crystalline crude product was purified by crystallization from CH_2Cl_2–hexane to give 0.154 g (66% yield) of **8a** as white crystals, mp 102 °C. IR (KBr) ν_{max}: 3238, 2978, 2241, 1702, 1530, 1250, and 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.39 (d, 3H, *J* 6.8), 1.46 (s, 9H), 2.42 (s, 3H), 2.95 (dd, 1H, *J* 4.8 and 13.2), 3.15 (dd, 1H, *J* 8.8 and 13.2), 3.28 (m, 1H), 4.32 (m, 1H), 4.71 (br d, 1H, interchangeable with D_2O), 7.34 and 7.58 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.8, 21.4, 28.3, 33.5, 46.1, 56.8, 80.5, 117.8, 124.0, 130.2, 139.0, 142.1, 155.5; EIMS *m*/*z* 337 (1%, M^++1), 263 (12), 141 (100), 140 (36), 57 (65). HMRS (EI): *m*/*z* calcd for $C_{17}H_{25}N_2O_3S$ [M+1]: 337.1586; found: 337.1579.

3.8.2. (2S,3S,R_S)-(tert-Butyl)-2-cyano-4-phenyl-1-(p-tolylsulfinyl)butan-3-ylcarbamate ***8b***

Obtained from 2.69 g (5.6 mmol) of **5b**. The crystalline crude product was purified by crystallization from CH_2Cl_2–hexane to give 0.713 g (35% yield) of **8b** as white crystals, mp 123–125 °C. IR (film) ν_{max}: 3272, 2977, 2243, 1706, 1526, 1499, 1251, 1167, and 1043 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.38 (s, 9H), 2.41 (s, 3H), 2.86–3.00 (m, 3H), 3.07–3.27 (m, 2H), 4.42 (m, 1H), 4.78 (br d, 1H, interchangeable with D_2O), 7.20–7.50 (m, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.4, 28.1, 31.3, 40.0, 51.6, 56.7, 80.5, 117.8, 123.9, 127.3, 128.9, 129.0, 130.1, 135.7, 142.1, 143.4, 155.7; EIMS *m*/*z* 412 (M^+ not observed), 217 (65), 140 (25), 91 (97), 57 (100).

3.8.3. (2S,3S,R_S)-(tert-Butyl)-2-cyano-5-methyl-1-(p-tolylsulfinyl)hexan-3-ylcarbamate ***8c***

Obtained from 0.151 g (0.43 mmol) of **5c**. The crystalline crude product was purified by crystallization from CH_2Cl_2–hexane to give 0.091 g (56% yield) of **8c** as white crystals, mp 110–112 °C. $[\alpha]_D$ +48.6 (*c* 1, $CHCl_3$); IR (film) ν_{max}: 3348, 2960, 2927, 2225, 1707, 1514, 1250 and 1167 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.96 (d, 3H, *J* 6.4), 0.97 (d, 3H, *J* 6.4), 1.44 (s, 9H), 1.25–1.80 (m, 3H), 2.42 (s, 3H), 2.96 (dd, 1H, *J* 4.4 and 13.0), 3.17 (dd, 1H, *J* 9.0 and 13.0), 3.28 (m, 1H), 4.25 (m, 1H), 4.68 (br d, 1H, interchangeable with D_2O), 7.34 and 7.59 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 21.7, 22.7, 24.9, 28.2, 32.6, 42.6, 48.5, 57.0, 80.4, 117.9, 123.9, 130.1, 139.0, 142.1, 155.9; EIMS *m*/*z* 379 (10%, M^++1), 323 (40), 305 (20), 279 (40), 183 (100), 140 (55), 91 (30), 86 (50), 57 (95).

3.8.4. (2S,3S,R_S)-(tert-Butyl)-2-cyano-4-methyl-1-(p-tolylsulfinyl)pentan-3-ylcarbamate ***8d***

Obtained from 0.595 g (1.7 mmol) of **5d**. The crystalline crude product was purified by crystallization from CH_2Cl_2–hexane to give 0.247 g (40% yield) of **8d** as white crystals, mp 107–108 °C. $[\alpha]_D$ +71.0 (*c* 1, $CHCl_3$); IR (film) ν_{max}: 3282, 2972, 2243, 1705, 1525, 1168, and 1042 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.05 (d, 3H, *J* 6.6), 1.07 (d, 3H, *J* 6.6), 1.46 (s, 9H), 1.85 (m, 1H), 2.42 (s, 3H), 2.96 (dd, 1H, *J* 4.5 and 13.5), 3.12 (dd, 1H, *J* 9.0 and 13.5), 3.51 (ddd, 1H, *J* 2.7, 4.8, and 9.0), 3.82 (dt, 1H, *J* 2.4 and 10.2), 4.68 (br d, 1H, interchangeable with D_2O), 7.34 and 7.57 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.3, 19.8, 21.4, 28.2, 29.8, 32.0, 56.3, 57.4, 80.4, 117.9, 123.9, 130.1, 139.2, 142.1, 156.1; EIMS *m*/*z* 365 (2%, M^++1), 309 (15), 169 (75), 139 (50), 81 (45), 57 (100). HMRS (EI): *m*/*z* calcd for $C_{19}H_{29}N_2O_3S$ [M+1]: 365.1899; found: 365.1897.

3.9. Preparation of β-cyano sulfoxides 9

The procedure described for the preparation of β-cyano sulfoxides **8** was followed (reaction time 5–6 h).

3.9.1. (2R,3S,R_S)-(tert-Butyl)-2-cyano-1-(p-tolylsulfinyl)butan-3-ylcarbamate ***9a***

Obtained from 0.20 g (0.64 mmol) of **7a**. The crude product was purified by column chromatography eluting with hexane–EtOAc 65:35, to give 0.065 g (30% yield) of **9a** as an oil. $[\alpha]_D$ +127.0 (*c* 1, $CHCl_3$); IR (film) ν_{max}: 3304, 2979, 2243, 1706, 1523, 1250, and 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.33 (d, 3H, *J* 6.8), 1.42 (s, 9H), 2.43 (s, 3H), 2.90 (m, 2H), 3.48 (dd, 1H, *J* 6.9 and 14.1), 3.93 (m, 1H), 4.80 (br d, 1H, interchangeable with D_2O), 7.36 and 7.57 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.5, 21.4, 28.2, 33.9, 47.5, 57.4, 80.4, 118.1, 124.0, 130.3, 139.8, 142.5, 154.7.

3.9.2. (2R,3S,R_S)-(tert-Butyl)-2-cyano-4-phenyl-1-(p-tolylsulfinyl)butan-3-ylcarbamate ***9b***

Obtained from 0.10 g (0.25 mmol) of **7b**. The crude product was purified by column chromatography eluting with hexane–EtOAc 70:30 to give 0.053 g (50% yield) of **9b** as white crystals (CH_2Cl_2–hexane), mp 115–116 °C. $[\alpha]_D$ +158.7 (*c* 1, $CHCl_3$); IR (KBr) ν_{max}: 3379, 2981, 2245, 1701, 1511, 1246, 1169, and 1049 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 9H), 2.42 (s, 3H), 2.86–2.98 (m, 3H), 3.13 (dd, 1H, *J* 4.2 and 14.7), 3.35 (dd, 1H, *J* 7.5 and 14.7), 4.14 (m, 1H), 4.50 (br d, 1H, interchangeable with D_2O), 7.17–7.36 (m, 7H), 7.50–7.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 28.1, 32.3, 38.0, 52.2, 57.3, 80.5, 118.4, 124.0, 127.3, 128.9, 129.3, 130.3, 135.3, 139.8, 142.4, 154.9.

3.9.3. (2R,3S,R_S)-(tert-Butyl)-2-cyano-5-methyl-1-(p-tolylsulfinyl)hexan-3-ylcarbamate ***9c***

Obtained from 0.05 g (0.14 mmol) of **7c**. The crude product was purified by column chromatography eluting with hexane–AcOEt 75:25 to give 0.024 g (45% yield) of **9c** as an oil. $[\alpha]_D$ +83.8 (*c* 1, $CHCl_3$); IR (film) ν_{max}: 3293, 2967, 2930, 2243, 1706, 1525, 1247, and 1168 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (d, 3H, *J* 6.3), 0.95 (d, 3H, *J* 6.6), 1.41 (s, 9H), 1.40–1.52 (m, 2H), 1.70 (m, 1H), 2.43 (s, 3H), 2.91 (d, 2H, *J* 7.5), 3.33 (dd, 1H, *J* 7.5 and 14.1), 3.80–3.94 (m, 1H), 4.57 (br d, 1H, interchangeable with D_2O), 7.36 and 7.57 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.1, 21.5, 23.5, 24.7, 28.2, 33.7, 40.7, 49.9, 57.3, 80.4, 118.4, 124.0, 130.3, 139.8, 142.5, 155.1.

3.9.4. (2R,3S,R_S)-(tert-Butyl)-2-cyano-4-methyl-1-(p-tolylsulfinyl)pentan-3-ylcarbamate ***9d***

Obtained from 0.16 g (0.47 mmol) of **7d**. The crude product was purified by column chromatography eluting with hexane–EtOAc

70:30 to give 0.034 g (20% yield) of **9d** as an oil. $[\alpha]_D$ +181.6 (*c* 1, $CHCl_3$); IR (film) ν_{max}: 3308, 2970, 2243, 1708, 1526, 1247, and 1169 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.93 (d, 3H, *J* 6.9), 0.98 (d, 3H, *J* 6.6), 1.38 (s, 9H), 1.80 (m, 1H), 2.43 (s, 3H), 2.96 (m, 2H), 3.20 (m, 1H), 3.84 (dt, 1H, *J* 3.6 and 10.2), 4.58 (br d, 1H, interchangeable with D_2O), 7.34 and 7.54 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.2, 20.0, 21.4, 28.1, 29.9, 31.0, 55.6, 57.9, 80.3, 118.4, 123.9, 130.3, 139.8, 142.4, 155.8.

3.9.5. (2R,3R,R_S)-(tert-Butyl)-2-cyano-1-(p-tolylsulfinyl)butan-3-ylcarbamate ***9e***

Obtained from 0.05 g (0.16 mmol) of **7e**. The crude product was purified by column chromatography eluting with hexane–EtOAc 65:35 to give 0.032 g (60% yield) of **9e** as an oil. $[\alpha]_D$ +161.8 (*c* 1, $CHCl_3$); IR (film) ν_{max}: 3259, 2979, 2243, 1706, 1525, 1250, and 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.35 (d, 3H, *J* 6.9), 1.38 (s, 9H), 2.43 (s, 3H), 2.90–3.10 (m, 2H), 3.30 (m, 1H), 3.96 (m, 1H), 4.78 (br d, 1H, interchangeable with D_2O), 7.35 and 7.54 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.8, 21.4, 28.1, 34.7, 47.8, 57.4, 80.4, 117.9, 123.9, 130.3, 139.4, 142.3, 155.1.

3.9.6. (2R,3R,R_S)-(tert-Butyl)-2-cyano-4-phenyl-1-(p-tolylsulfinyl)butan-3-ylcarbamate ***9f***

Obtained from 0.05 g (0.12 mmol) of **7f**. The crude product was purified by column chromatography eluting with hexane–EtOAc 65:35 to give 0.021 g (40% yield) of **9b** as white crystals (CH_2Cl_2–hexane), mp 112 °C. $[\alpha]_D$ +142.0 (*c* 1, $CHCl_3$); IR (KBr) ν_{max}: 3386, 2979, 2249, 1702, 1495, 1369, 1256, 1117, and 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.34 (s, 9H), 2.41 (s, 3H), 2.82–3.06 (m, 2H), 3.16 (m, 1H), 4.01 (m, 1H), 4.72 (br d, 1H, interchangeable with D_2O), 7.13–7.35 (m, 7H), 7.41–7.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 28.1, 31.9, 40.5, 53.4, 57.1, 80.6, 117.9, 123.9, 127.3, 129.0 (2C), 130.3, 135.6, 139.3, 142.2, 155.3.

3.10. Preparation of β-cyano sulfones

To a solution of β-cyano sulfoxide **8b**, **9b** or **9f** (1 equiv) in dry CH_2Cl_2 (10 mL/mmol) was added MCPBA (1.5 equiv) at 25 °C and the mixture was stirred for 1 h. The reaction was decomposed with $NaHSO_3$ solution and then washed with saturated sodium bicarbonate solution. The organic phase was separated, washed with brine, dried, and evaporated.

3.10.1. (2S,3S)-(tert-Butyl)-2-cyano-4-phenyl-1-(p-tolylsulfonyl)butan-3-ylcarbamate ***10b***

From 0.042 g (0.10 mmol) of **8b**, 0.035 g (80% yield) of **10b** was obtained. Mp 143 °C (CH_2Cl_2–hexane); $[\alpha]_D$ −21.0 (*c* 1, $CHCl_3$); IR (film) ν_{max}: 3364, 2975, 2933, 2247, 1705, 1600, 1519, 1293, 1167, and 1145 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.37 (s, 9H), 2.45 (s, 3H), 2.84 (dd, 1H, *J* 8.4 and 15.8), 2.97 (dd, 1H, *J* 7.5 and 14.1), 3.09 (m, 1H), 3.40 (m, 2H), 4.70 (m, 1H), 4.74 (br d, 1H, interchangeable with D_2O), 7.16–7.34 (m, 7H), 7.66–7.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.7, 28.1, 31.7, 40.0, 53.2, 55.3, 80.7, 117.2, 127.3, 128.2, 128.9, 129.0, 130.2, 134.9, 135.6, 145.6, 155.3; EIMS *m*/*z* 429 (3%, M^++1), 373 (20), 237 (25), 155 (50), 81 (75), 57 (100).

3.10.2. (2R,3S)-(tert-Butyl)-2-cyano-4-phenyl-1-(p-tolylsulfonyl)butan-3-ylcarbamate ***11b***

From 0.021 g (0.05 mmol) of **9b**, 0.017 g (78% yield) of **11b** was obtained. Mp 130–1 °C (CH_2Cl_2–hexane); $[\alpha]_D$ −5.5 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.34 (s, 9H), 2.47 (s, 3H), 2.85 (dd, 1H, *J* 9.3 and 13.8), 3.09 (dd, 1H, *J* 4.2 and 13.8), 3.30–3.40 (m, 3H), 4.11 (m, 1H), 4.60 (br d, 1H, interchangeable with D_2O), 7.16–7.42 (m, 7H), 7.79–7.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.7, 28.2, 31.8, 37.5, 52.3, 54.8, 80.6, 117.7, 127.3, 128.4, 128.9, 129.2, 130.2, 135.1, 135.3, 145.8, 154.9; EIMS *m*/*z* 429 (3%, M^++1), 373 (20), 237 (25), 155 (50), 81 (75), 57 (100).

3.10.3. (2R,3R)-(tert-Butyl)-2-cyano-4-phenyl-1-(p-tolylsulfonyl)butan-3-ylcarbamate ***11f***

From 0.021 g (0.05 mmol) of **9f**, 0.017 g (78% yield) of **11f** was obtained. Mp 156 °C (CH_2Cl_2–hexane); $[\alpha]_D$ +23.8 (*c* 1, $CHCl_3$). The spectroscopic data were identical to those of **10b**.

Acknowledgements

We thank M. I. Chávez, E. García-Ríos, S. Hernández, E. Huerta, R. Patiño, M. A. Peña, J. Pérez, B. Quiroz, H. Ríos, L. Velasco, and M. N. Zavala for their technical assistance and to Consejo Nacional de Ciencia y Tecnología (CONACYT-México) for a predoctoral fellowship to R.A. We also thank Dr. J. M. Muchowski for their critical reviewing of the manuscript.

References and notes

1. (a) Suizer-Mosse, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123; (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701; (c) Meadows, D. C.; Gervay-Hague, J. *Med. Res. Rev.* **2006**, *26*, 793; (d) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon: Oxford, 1993; (e) Fuchs, P. L.; Braish, T. F. *Chem. Rev.* **1986**, *86*, 903.
2. (a) Mauleon, P.; Alonso, I.; Rodríguez Rivero, M.; Carretero, J. C. *J. Org. Chem.* **2007**, *72*, 9924; (b) Llamas, T.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3329; (c) Mauleon, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961; (d) Mauleon, P.; Carretero, J. C. *Org. Lett.* **2004**, *6*, 3195; (e) Garrido, J. L.; Alonso, I.; Carretero, J. C. *J. Org. Chem.* **1998**, *63*, 9406; (f) Carretero, J. C.; Gómez Arrayás, R. *J. Org. Chem.* **1998**, *63*, 2993; (g) Adrio, J.; Carretero, J. C. *Tetrahedron* **1998**, *54*, 1601; (h) Alonso, I.; Carretero, J. C.; Garrido, J. L.; Magro, V.; Pedregal, C. *J. Org. Chem.* **1997**, *62*, 5682; (i) Jackson, R. F. W.; Standen, S. P.; Clegg, W. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 149 and references cited therein.
3. (a) Guerrero de la Rosa, V.; Ordóñez, M.; Llera, J. M. *Tetrahedron: Asymmetry* **2001**, *12*, 1089; (b) Guerrero de la Rosa, V.; Ordóñez, M.; Llera, J. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2991; (c) Fernández de la Pradilla, R.; Buergo, M. V.; Manzano, P.; Montero, C.; Priego, J.; Viso, A.; Cano, F. H.; Martínez-Alcázar, M. P. *J. Org. Chem.* **2003**, *68*, 4797; (d) Marino, J. P.; Anna, L. J.; Fernández de la Pradilla, R.; Martínez, M. V.; Montero, C.; Viso, A. *J. Org. Chem.* **2000**, *65*, 6462; (e) Westwell, A. D.; Thornton-Pett, M.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 847.
4. For reviews on synthetic applications of sulfoxides, see: (a) García Ruano, J. L.; Alemán, J.; Cid, M. B.; Fernandez-Ibañez, M. A.; Maestro, M. C.; Martín, M. R.; Martín-Castro, A. M. In *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2008; Chapter 3, pp 55–161; (b) Pellissier, H. *Tetrahedron* **2006**, *62*, 5559; (c) Hanquet, G.; Colobert, F.; Lanners, S.; Solladié, G. *ARKIVOC* **2003**, *vii*, 328; (d) García Ruano, J. L.; Cid de la Plata, B. *Top. Curr. Chem.* **1999**, *204*, 1; (e) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717 and references cited therein.
5. Sengupta, S.; Sen Sarma, D.; Mondal, S. *Tetrahedron: Asymmetry* **1998**, *9*, 2311.
6. Yuste, F.; Ortiz, B.; Carrasco, A.; Peralta, M.; Quintero, L.; Sánchez-Obregón, R.; Walls, F.; García Ruano, J. L. *Tetrahedron: Asymmetry* **2000**, *11*, 3079.
7. Fujii, T.; Ohba, M.; Kawamura, H.; Nakashio, Y.; Honda, K.; Matsubara, S. *Chem. Pharm. Bull.* **1994**, *42*, 1045.
8. Mikolajczyk, M.; Midura, W.; Grzejszczak, S.; Zatorski, A.; Chefczynska, A. *J. Org. Chem.* **1978**, *43*, 473.
9. Effenberger, F.; Ziegler, T. In *Methods of Organic Chemistry (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21b.
10. (a) García Ruano, J. L.; Cifuentes, M.; Martin Castro, A.; Rodríguez, J. H. *Org. Lett.* **2002**, *4*, 55; (b) García Ruano, J. L.; Cifuentes García, M.; Nieves, M.; Laso, A.; Castro, M.; Rodríguez Ramos, J. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 2507.
11. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 703226 (**8a**). 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).
12. Ortiz, B.; Hernández, A.; Quintero, L.; Sánchez-Obregón, R.; Yuste, F.; García Ruano, J. L. *Rev. Soc. Quím. Méx.* **2001**, *45*, 163; *Chem. Abstr.* **2002**, *137*, 311168.
13. Falorni, M.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *J. Org. Chem.* **1999**, *64*, 8962.
14. Chakravarty, P. K.; Greenlee, W. J.; Parsons, W. H.; Patchett, A. A.; Combs, P.; Roth, A.; Busch, R. D.; Mellin, T. N. *J. Med. Chem.* **1989**, *32*, 1886.