Pergamon

Tetrahedron 58 (2002) 1611–1616

TETRAHEDRON

Asymmetric induction in a new domino reaction of [3,3]-sigmatropic rearrangement of allylic thiocyanates and intramolecular heterocyclisation

Jozef Gonda,* Miroslava Martinková and Ján Imrich

Department of Organic Chemistry, P.J. Šafárik University, Moyzesova 11, 04167 Kosice, Slovakia

Received 17 September 2001; revised 30 November 2001; accepted 3 January 2002

Abstract—A new synthetic route to diastereomerically pure (4*S*,5*S*)-4-vinyltetrahydro-1*H*-2-imidazolethiones via a novel domino reaction of [3,3]-sigmatropic rearrangement of chiral thiocyanates followed by stereoselective intramolecular amine addition to arising isothiocyanates is reported.

1. Introduction

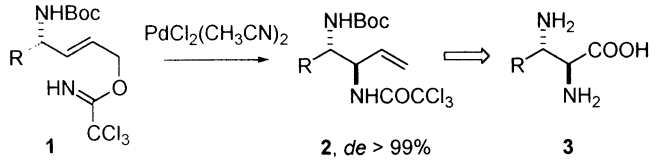
The usefulness of chiral 1,2-diamines as auxiliaries and controller groups in asymmetric dihydroxylation,[1] conjugate addition,[2] olefination,[3] allylation,[4] epoxidation,[5] or aldol condensation[6] is well documented. Although the 1,2-diamino unit is a constituent of natural products only an astonishingly small number of stereocontrolled syntheses have been developed for them.[7] In a previous paper, we have reported the excellent diastereoselectivity in 1,2-asymmetric induction[8] for the palladium(II) catalyzed aza-Claisen rearrangement of allylic trichloroacetimidates **1** leading to *anti*-1,2-diamines **2** and (2*S*,3*S*)-diaminobutanoic acids **3** (Scheme 1).

Due to the biological importance of the α,β-diamino acids, much effort has been directed toward their stereoselective synthesis. Specifically, synthetic approaches have been reported for preparing 2,3-diaminopropanoic[9] and diaminobutanoic[8,10] acids as well as other 2,3-diaminoalkanoic acids.[11]

2. Results and discussion

We wish to report now[12] a new and highly stereoselective preparation of (4*S*,5*S*)-4-vinyltetrahydro-1*H*-2-imidazolethiones, as useful precursors for (2*R*,3*S*)-diaminoalkanoic acids, by a novel domino reaction of [3,3]-sigmatropic rearrangement of chiral allylic thiocyanates followed by stereoselective intramolecular amine addition to arising isothiocyanates.

The starting thiocyanates **6a–e** were prepared by S_N2 displacement of the *O*-mesyl group in **5a–e**, derived from allylic alcohols **4a–e**,[13] by thiocyanate group (KSCN/CH_3CN) in 85–90% overall yields (Scheme 2). The thermal rearrangement of thiocyanate **6a** was carried out at 80°C in xylene under N_2 for 1 h with high yield of isothiocyanates **7a** and **8a** (92%), but without selectivity (*anti*-**7a**/*syn*-**8a**≈50:50). The prolonged heating of the reaction mixture (26 h) unexpectedly led to the formation of *tert*-butyl (4*S*,5*S*)-5-methyl-2-thioxo-4-vinyltetrahydro-1*H*-1-imidazolecarboxylate **9a** as a single reaction product in 89%

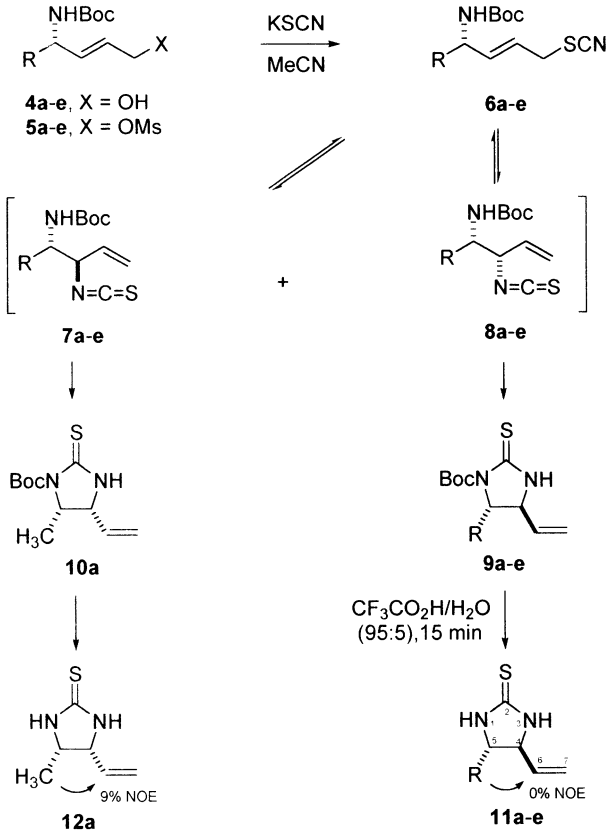


1 **2**, *de* > 99% **3**

Scheme 1.

Keywords: rearrangements; asymmetric induction; aminoacids.
* Corresponding author. Tel.: +421-95-62-28332; fax: +421-95-62-22124; e-mail: jgonda@kosice.upjs.sk

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00026-1



Scheme 2.

yield. To investigate the variability of this synthetic method, different allylic thiocyanates **6b–e** were examined. In all cases the heating of thiocyanates **6b–e** in xylene at 80°C for 3 h afforded the mixture of isothiocyanates **7b–e** and **8b–e** (50:50). Further heating at the same temperature for 26–44 h led to intramolecular addition of the amine to NCS group with stereoselective formation of imidazolidines **9b–e** (Table 1).

In contrast with these results, treatment of *anti*-**7a** and *syn*-**8a** (crude mixture ~50:50, obtained by rearrangement of thiocyanate **6a**) with sodium hydride in THF at 0°C for 15 min afforded the mixture of diastereomers **10a** and **9a** in essentially the same ratio. We have found that the presence of catalytic amount of 2-hydroxypyridine (0.10 mol%) significantly reduces the reaction time (from 26–44 to 3 h) with the conservation of the high diastereoselectivity of the reaction.

Table 1. *tert*-Butyl (4*S*,5*S*)-5-alkyl-2-thioxo-4-vinyltetrahydro-1*H*-1-imidazolecarboxylates **9a–e** produced via Scheme 2

Entry	Educt	R	Product	Yield (%)[a]	Period (h)[a]	Ratio[b]
1	**6a**	Me	**9a**	89/89	26/3	98:2
2	**6b**	Et	**9b**	87/90	30/3	99:1
3	**6c**	*i*-Pr	**9c**	84/89	36/3	99.5:0.5
4	**6d**	Bn	**9d**	80/85	29/3	99.5:0.5
5	**6e**	*i*-Bu	**9e**	84/88	44/3	99.5:0.5

[a] Method A/Method B. Method A: all reaction were carried out at 80°C in xylene. Method B: all reaction were carried out at 80°C in xylene in the presence of 0.10 mol% 2-hydroxypyridine.
[b] Diastereoselectivities were determined by ^{1}H NMR analysis.

The reaction of imidazolidines **9a–e** and **10a** with TFA/H_2O afforded the corresponding cyclic thioureas **11a–e** and **12a** (Scheme 2). The reaction stereochemistry was determined by NOE difference experiments of cyclic thioureas **11a** and **12a**. Irradiation of the methyl protons in **12a** resulted in a 9% NOE on vinyl CH signal, indicating a *cis* relationship between these two substituents and thus 4*R*,5*S* configuration. Irradiation of the methyl protons in **11a** resulted in almost 0% NOE on vinyl CH, indicating a *trans* relationship between these substituents and thus the 4*S*,5*S*configuration of **11a**.

The observed stereochemistry of these reactions can be rationalized by transition states **A** and **B** of the heterocyclisation step in Fig. 1. Unfavorable interaction between the R group and vinyl group in the transition state **A** is in agreement with experimentally observed, very low yield of *cis*-isomer. Consequently, the preferred product is formed through transition state **B** in which the steric interactions between R and vinyl moiety is significantly reduced. The reversible rearrangement thiocyanate↔isothiocyanate[14] is a reason for complete conversion of diastereomers **7a–e** to **8a–e** via the corresponding thiocyanates **6a–e** and preferred formation of **9a–e**. 2-Hydroxypyridine probably works as proton transfer catalyst. This is indicative that the diastereoselectivity of the reaction may be explained by two-proton transfer[15] in the transition state **C** of the rate-determining step (Fig. 1).

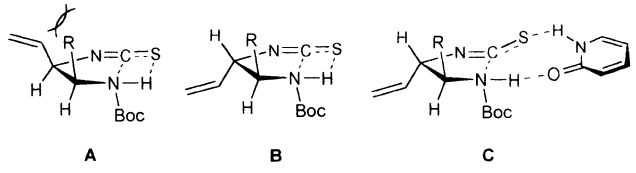


Figure 1. Proposed transition-state models of the heterocyclisation step.

3. Conclusion

In summary, we have developed a novel domino reaction of [3,3]-sigmatropic rearrangement of chiral allylic thiocyanates, followed by stereocontrolled intramolecular addition of amine to NCS group, leading to diastereomerically pure (4*S*,5*S*)-4-vinyltetrahydro-1*H*-2-imidazolethiones. Ab initio investigation of this reaction will be reported in due course.

4. Experimental

Melting points are uncorrected. The reagents and solvents: purchased from Fluka AG in the highest obtainable purity. $CHCl_3$ and $CDCl_3$ were passed throgh basic alumina (Woelm, act. 1) immediately before use. Optical rotations: Perkin–Elmer 241 MC. TLC: DC Alufolien Kieselgel 60 F254 (Merck), detection UV (254 nm) and/or $KMnO_4$ spray. Chromatography: silica gel 0.032–0.060 mesh (Merck). IR spectra (2–3%) in $CHCl_3$: Perkin–Elmer 599 IR spectrometer; absorptions in cm^{-1}. The elucidation of the structure

and stereochemical arrangement of compounds **9a–e**, **10a**, **11a–e** followed from NMR studies incorporating a suite of experiments. In addition to the 1D ^{1}H, NOE difference, 1D homonuclear selectively decoupled, ^{13}C broadband-decoupled, DEPT-90, and DEPT-135 spectra, 2D *H,H*-COSY, and CHSHF experiments were acquired on a JEOL Alpha 400 NMR spectrometer equipped with a 5 mm probe operating at 399.65 MHz for ^{1}H, and 100.00 MHz for ^{13}C. The spectra were recorded at 398.3 K in deuteriochloroform and both ^{1}H and ^{13}C spectra were referenced internally to tetramethylsilane (0 ppm for both).

4.1. General procedure for the synthesis of the mesylates 5a–e

To a solution of allylic alcohol **4a–e** (1 mmol) in dry CH_2Cl_2 (10 mL) were added Et_3N (1.5 mmol) and CH_3SO_2Cl (1.2 mmol) at 0°C. After being stirred under the same temperature for 1 h, the reaction mixture was concentrated under reduced pressure. The resulting residue was diluted with diethyl ether (15 mL) and solid was removed by filtration. The organic phase was concentrated under reduced pressure to afford the crude products, which were purified by flash chromatography over silica gel (20% ethyl acetate/hexane) to provide the mesylates **5a–e**. This material was used for the next reaction without further purification.

4.1.1. (*E*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-2-pentenyl methanesulfonate (5a). 92%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, d, J=6.7 Hz, CH_3), 1.44 (9H, s, 3×CH_3), 3.01 (3H, s, CH_3SO_2), 4.30–4.35 (1H, m, H_4), 4.71 (2H, d, J=5.0 Hz, H_1); 5.76–5.82 (2H, m, H_2, H_3).

4.1.2. (*E*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-2-hexenyl methanesulfonate (5b). 95%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J=7.2 Hz, CH_3), 1.32–1.36 (2H, m, H_5), 1.48 (9H, s, 3×CH_3), 3.04 (3H, s, CH_3SO_2), 4.10–4.16 (1H, m, H_4), 4.74 (2H, d, J=5.1 Hz, H_1), 5.77–5.83 (2H, m, H_2, H_3).

4.1.3. (*E*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-5-methyl-2-hexenyl methanesulfonate (5c). 96%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (6H, d, J=6.7 Hz, 2×CH_3), 1.44 (9H, s, 3×CH_3), 1.76–1.80 (1H, m, H_5), 3.01 (3H, s, CH_3SO_2), 4.00–4.10 (1H, m, H_4), 4.73 (2H, d, J=4.7 Hz, H_1), 5.76–5.78 (2H, m, H_2, H_3).

4.1.4. (*E*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-5-phenyl-2-pentenyl methanesulfonate (5d). 91%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (9H, s, 3×CH_3), 2.94 (3H, s, CH_3SO_2) 2.94–2.96 (2H, m, H_5), 4.45–4.51 (1H, m, H_4), 4.67 (2H, d, J=5.1 Hz, H_1), 5.75–5.77 (2H, m, H_2, H_3), 7.22–7.26 (5H, m, Ph).

4.1.5. (*E*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-6-methyl-2-heptenyl methanesulfonate (5e). 95%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, d, J=6.6 Hz, CH_3), 0.95 (3H, d, J=6.6 Hz, CH_3), 1.28–1.32 (2H, m, H_5), 1.44 (9H, s, 3×CH_3), 1.47–1.53 (1H, m, H_6), 3.03 (3H, s, CH_3SO_2), 4.18–4.22 (1H, m, H_4), 4.71–4.75 (2H, m, H_1), 5.75–5.81 (2H, m, H_2, H_3).

4.2. General procedure for the synthesis of the thiocyanates 6a–e

To a solution of the mesylates **5a–e** (1 mmol) in CH_3CN (10 mL) was added KSCN (1.2 mmol). After being stirred for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure. The resulting residue was diluted with diethyl ether and solid was removed by filtration. The organic phase was concentrated under reduced pressure to afford the crude products, which were purified by silica gel chromatography (20% ethyl acetate/hexane) to provide the thiocyanates **6a–e**.

4.2.1. *tert*-Butyl *N*-[(1*S*,2*E*)-1-methyl-4-thiocyanato-2-pentenyl]carbamate (6a). 83%; colorless oil; $[\alpha]_D^{25}=-60.4$ (c 0.77 $CHCl_3$); IR ($CHCl_3$) 3443, 2150, 1685 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, d, J=6.5 Hz, CH_3), 1.45 (9H, s, 3×CH_3), 3.52–3.57 (2H, m, H_1), 4.34–4.42 (2H, m, NH, H_4), 5.70–5.76 (2H, m, H_2, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 28.1, 35.7, 56.9, 79.6, 111.75, 123.1, 137.7, 155.0. Anal. Calcd for $C_{11}H_{18}N_2O_2S$: C, 54.52; H, 7.49; N, 11.56; S, 13.23. Found: C, 54.63; H, 7.51; N, 11.45; S, 13.37.

4.2.2. *tert*-Butyl *N*-[(1*S*,2*E*)-1-ethyl-4-thiocyanato-2-hexenyl]carbamate (6b). 86%; colorless oil; $[\alpha]_D^{25}=-51.4$ (c 1.1 $CHCl_3$); IR ($CHCl_3$) 3440, 2152, 1686 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J=7.5 Hz); 1.45 (9H, s, 3×CH_3), 1.53–1.58 (2H, m, H_5), 3.53–3.59 (2H, m, H_1), 4.05 (1H, b s, NH), 4.52–4.58 (1H, m, H_4), 5.70–5.76 (2H, m, H_2, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 23.3, 28.4, 35.8, 55.9, 80.1, 111.8, 122.6, 138.6, 155.2. Anal. Calcd for $C_{12}H_{20}N_2O_2S$: C, 56.22; H, 7.86; N, 10.93; S, 12.51. Found: C, 56.31; H, 7.94; N, 10.73; S, 12.31.

4.2.3. *tert*-Butyl *N*-[(1*S*,2*E*)-1-isopropyl-4-thiocyanato-2-hexenyl]carbamate (6c). 85%; colorless oil; $[\alpha]_D^{25}=-60.4$ (c 0.81 $CHCl_3$); IR ($CHCl_3$) 3445, 2152, 1683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, d, J=6.8 Hz, CH_3), 0.95 (3H, d, J=6.8 Hz, CH_3), 1.46 (9H, s, 3×CH_3), 1.78–1.82 (1H, m, H_5), 3.56–3.60 (2H, m, H_1), 4.03 (1H, b s, NH), 4.55–4.61 (1H, m, H_4), 5.70–5.76 (2H, m, H_2, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 18.7, 28.4, 32.3, 36.0, 57.1, 79.6, 111.9, 123.7, 137.1, 155.4. Anal. Calcd for $C_{13}H_{22}N_2O_2S$: C, 57.75; H, 8.20; N, 10.36; S, 11.86. Found: C, 57.64; H, 8.24; N, 10.41; S, 11.73.

4.2.4. *tert*-Butyl *N*-[(1*S*,2*E*)-1-benzyl-4-thiocyanato-2-pentenyl]carbamate (6d). 87%; white solid: mp 58–60°C; $[\alpha]_D^{25}=-40.2$ (c 0.91 $CHCl_3$); IR ($CHCl_3$) 3446, 2151, 1684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (9H, s, 3×CH_3), 2.84–2.88 (2H, m, H_5), 3.50–5.54 (2H, m, H_1), 4.09 (1H, b s, NH), 4.57–4.64 (1H, m, H_4), 5.70–5.76 (2H, m, H_2, H_3), 7.17–7.21 (2H, m, Ph), 7.27–7.33 (3H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 35.7, 41.5, 52.6, 79.8, 111.8, 122.8, 126.7, 128.4, 129.5, 136.8, 137.7, 155.1. Anal. Calcd for $C_{14}H_{24}N_2O_2S$: C, 59.12; H, 8.51; N, 9.85; S, 11.27. Found: C, 59.18; H, 8.62; N, 9.79; S, 11.33.

4.2.5. *tert*-Butyl *N*-[(1*S*,2*E*)-1-isobutyl-4-thiocyanato-2-heptenyl]carbamate (6e). 82%; colorless oil;

$[\alpha]_D^{25}=-82.4$ (*c* 0.80 $CHCl_3$); IR ($CHCl_3$) 3445, 2151, 1683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, d, J=6.6 Hz, CH_3), 0.94 (3H, d, J=6.6 Hz, CH_3), 1.46 (9H, s, 3×CH_3), 1.54–1.58 (3H, m, H_5, H_6), 3.53–3.59 (2H, m, H_1), 4.00 (1H, b s, NH), 4.50–4.52 (1H, m, H_4), 5.71–5.75 (2H, m, H_2, H_3); ^{13}C NMR (100 Hz, $CDCl_3$) δ 22.2, 22.7, 24.7, 28.4, 35.8, 44.4, 51.0, 79.6, 111.8, 122.2, 139.2, 155.2. Anal. Calcd for $C_{17}H_{22}N_2O_2S$: C, 64.12; H, 6.96; N, 8.80; S, 10.07. Found: C, 64.23; H, 6.87; N, 8.83; S, 10.12.

4.3. General procedure for the synthesis of the (4*S*,5*S*)-4-vinyltetrahydro-1*H*-2-imidazolethiones 9a–e

A solution of thiocyanates **6a**–**e** (1 mmol) and 2-hydroxypyridine (0.1 mmol, Method B) in dry xylene (5 mL) was heated at 80°C for 3 h (26–44 h, without 2-hydroxypyridine, Method A). The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (20% ethyl acetate/hexane) to provide the title compounds **9a**–**e**.

4.3.1. *tert*-Butyl (4*S*,5*S*)-5-methyl-2-thioxo-4-vinyltetrahydro-1*H*-1-imidazolecarboxylate (9a). 89%; colorless oil; $[\alpha]_D^{25}=-20.3$ (*c* 1.2 $CHCl_3$); IR ($CHCl_3$) 3445, 1688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (d, 3H, J=6.5 Hz, CH_3CH), 1.64 (9H, s, 3×CH_3), 3.89 (1H, ddt, $J_{6,4}$=7.1 Hz, $J_{5,4}$=6.3 Hz, $J_{7,4}$=0.8 Hz, H_4), 4.26 (1H, dq, $J_{Me,5}$=6.5 Hz, $J_{5,4}$=6.3 Hz, H_5), 5.33 (1H, dd, $J_{7,6}$=10.3 Hz, $J_{7,4}$=0.8 Hz, H_{7cis}), 5.39 (1H, dd, $J_{7,6}$=17.0 Hz, $J_{7,4}$=0.8 Hz, H_{7trans}), 5.89 (1H, ddd, $J_{7trans,6}$=17.0 Hz, $J_{7cis,6}$=10.3 Hz, $J_{6,4}$=7.1 Hz, H_6), 7.60 (1H, b s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 28.1, 61.6, 62.8, 83.5, 118.4, 135.0, 150.0, 180.0. Anal. Calcd for $C_{11}H_{18}N_2O_2S$: C, 54.52; H, 7.49; N, 11.56; S, 13.23. Found: C, 54.43; H, 7.52; N, 11.54; S, 13.26.

4.3.2. *tert*-Butyl (4*S*,5*S*)-5-ethyl-2-thioxo-4-vinyltetrahydro-1*H*-1-imidazolecarboxylate (9b). 90%; colorless oil; $[\alpha]_D^{25}=-31.4$ (*c* 0.71 $CHCl_3$); IR ($CHCl_3$) 3446, 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, J=7.5 Hz, CH_3CH$_2$), 1.45–1.49 (1H, m, H_8), 1.56 (3H, s, 3×CH_3), 1.80–1.84 (1H, m, H_8), 3.90 (1H, dd, $J_{6,4}$=7.0 Hz, $J_{5,4}$=6.8 Hz, H_4), 4.06 (1H, ddd, $J_{8,5}$=7.9 Hz, $J_{5,8}$=7.2 Hz, $J_{5,4}$=6.8 Hz, H_5), 5.24 (1H, d, $J_{7cis,6}$=10.2 Hz, H_{7cis}), 5.29 (1H, d, $J_{7trans,6}$=17.0 Hz, H_{7trans}), 5.83 (1H, ddd, $J_{7trans,6}$=17.0 Hz, $J_{7cis,6}$=10.2 Hz, $J_{6,4}$=7.0 Hz, H_6), 6.91 (1H, b s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.6, 27.3, 28.1, 60.1, 66.7, 83.5, 117.9, 135.9, 150.1, 180.3. Anal. Calcd for $C_{12}H_{20}N_2O_2S$: C, 56.22; H, 7.86; N, 10.93; S, 12.51. Found: C, 56.32; H, 7.96; N, 10.84; S, 12.41.

4.3.3. *tert*-Butyl (4*S*,5*S*)-5-isopropyl-2-thioxo-4-vinyltetrahydro-1*H*-1-imidazolecarboxylate (9c). 89%; colorless oil; $[\alpha]_D^{25}=-41.5$ (*c* 0.97 $CHCl_3$); IR ($CHCl_3$) 3444, 1689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, J=6.9 Hz, CH_3CH), 0.98 (3H, d, J=6.9 Hz, CH_3CH), 1.55 (9H, s, 3×CH_3), 2.35 (1H, dseptet, $J_{8,Me}$=6.9 Hz, $J_{8,Me}$=6.9 Hz, $J_{8,5}$=7.2 Hz, H_8), 3.97 (1H, dd, $J_{6,4}$=6.7 Hz, $J_{5,4}$=6.6 Hz, H_4), 4.08 (1H, dd, $J_{8,5}$=7.2 Hz, $J_{4,5}$=6.6 Hz, H_5), 5.22 (1H, d, $J_{6,7cis}$=10.0 Hz, H_{7cis}), 5.28 (1H, d, $J_{7trans,6}$=17.0 Hz, H_{7trans}), 5.82 (1H, ddd, $J_{7trans,6}$=17.0 Hz, $J_{7cis,6}$=10.0 Hz, $J_{6,4}$=6.7 Hz, H_6), 7.33 (1H, b s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 17.8, 28.1, 30.1, 55.8, 70.2, 83.5, 117.4, 136.4, 150.2, 180.4. Anal. Calcd for $C_{13}H_{22}N_2O_2S$: C, 57.75; H, 8.20; N, 10.36; S, 11.86. Found: C, 57.79; H, 8.13; N, 10.42; S, 11.79.

4.3.4. *tert*-Butyl (4*S*,5*S*)-5-benzyl-2-thioxo-4-vinyltetrahydro-1*H*-1-imidazolecarboxylate (9d). 85%; colorless oil; $[\alpha]_D^{25}=-55.6$ (*c* 0.77 $CHCl_3$); IR ($CHCl_3$) 3443, 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.60 (9H, s, 3×CH_3), 2.80 (1H, dd, $J_{8,8}$=13.3 Hz, $J_{8,5}$=10.1 Hz, H_8), 3.33 (1H, dd, $J_{8,8}$=13.3 Hz, $J_{8,5}$=3.4 Hz, H_8), 3.94 (1H, dd, $J_{5,4}$=7.0 Hz, $J_{6,4}$=6.5 Hz, H_4), 4.35 (1H, ddd, $J_{5,4}$=7.0 Hz, $J_{8,5}$=3.4 Hz, $J_{8,5}$=10.1 Hz, H_5), 4.99 (1H, d, $J_{7trans,6}$=17 Hz, H_{7trans}), 5.05 (1H, d, $J_{7cis,6}$=10.3 Hz, H_{7cis}), 5.55 (1H, ddd, $J_{7trans,6}$=17.1 Hz, $J_{7cis,6}$=10.3 Hz, $J_{6,4}$=6.5 Hz, H_6), 7.18–7.22 (2H, m, Ph), 7.29–7.33 (3H, m, Ph), 7.53 (1H, b s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 38.9, 58.6, 66.7, 83.8, 117.5, 127.2, 128.9, 129.4, 135.4, 135.6, 150.0, 180.0. Anal. Calcd for $C_{17}H_{22}N_2O_2S$: C, 64.12; H, 6.96; N 8.80; S, 10.07. Found: C, 64.15; H, 6.92; N 8.84; S, 10.11.

4.3.5. *tert*-Butyl (4*S*,5*S*)-5-isobutyl-2-thioxo-4-vinyltetrahydro-1*H*-1-imidazolecarboxylate (9e). 88%; white solid: mp 75–77°C; $[\alpha]_D^{25}=-63.2$ (*c* 0.80 $CHCl_3$); IR ($CHCl_3$) 3446, 1689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, d, J=6.6 Hz, CH_3), 0.98 (3H, d, J=6.6 Hz, CH_3), 1.55 (9H, s, 3×CH_3), 1.65–1.69 (3H, m, H_8, H_9), 3.90–3.94 (1H, m, H_5), 4.14–4.16 (1H, m, H_4), 5.24 (1H, dd, $J_{7cis,6}$=10.3 Hz, $J_{7cis,4}$=0.7 Hz, H_{7cis}), 5.30 (1H, dd, $J_{7trans,6}$=17.0 Hz, $J_{7trans,4}$=0.7 Hz, H_{7trans}), 5.84 (1H, ddd, $J_{7trans,6}$=17.0 Hz, $J_{7cis,6}$=10.1 Hz, $J_{6,4}$=7.5 Hz, H_6), 7.45 (1H, b s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 23.8, 24.5, 28.2, 42.2, 60.8, 64.4, 83.7, 117.9, 135.7, 149.9, 179.7. Anal. Calcd for $C_{14}H_{24}N_2O_2S$: C, 59.12; H, 8.51; N, 9.85; S, 11.27. Found: C, 59.21; H, 8.54; N, 9.83; S, 11.34.

4.4. Preparation of a mixture of diastereomers of imidazolidines 9a and 10a

A solution of thiocyanate **6a** (0.20 g, 0.83 mmol) in xylene (5 mL) was heated at 80°C for 1 h under a nitrogen atmosphere. The organic phase was concentrated under reduced pressure to afford the crude products, which were purified by flash chromatography over silica gel (20% ethyl acetate/hexane) to provide the isothiocyanates **7a/8a** (50:50). This material was used for the next reaction without further purification. To NaH (0.032 g, 0.74 mmol) in THF (6 mL) at 0°C was added mixture of isothiocyanates **7a/8a** (0.18 g, 0.74 mmol). The reaction mixture was stirred at 0°C for 15 min and concentrated under reduced pressure. Purification of the residue by flash chromatography (20% ethyl acetate/hexane) afforded the title compounds **9a** and **10a** (50:50, 0.16 g, 88.9% combined yield).

4.4.1. *tert*-Butyl (4*S*,5*R*)-5-methyl-2-thioxo-4-vinyltetrahydro-1*H*-1-imidazolecarboxylate (10a). Colorless oil; $[\alpha]_D^{25}=+34.0$ (*c* 0.86 $CHCl_3$); IR ($CHCl_3$) 3445, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, d, J=6.8 Hz, CH_3), 1.62 (9H, s, 3×CH_3), 4.03 (1H, dd, $J_{5,4}$=7.2 Hz, $J_{5,Me}$=6.8 Hz, H_5), 4.40 (1H, dddd, $J_{6,4}$=7.9 Hz, $J_{5,4}$=7.2 Hz, $J_{7trans,4}$=1.1 Hz, $J_{7cis,4}$=0.8 Hz, H_4), 5.32 (1H, ddd, $J_{7cis,6}$=10.3 Hz, $J_{7trans,7cis}$=1.1 Hz, $J_{7cis,4}$=0.8 Hz, H_{7cis}), 5.33 (1H, ddd, $J_{7trans,6}$=17.1 Hz, $J_{7trans,7cis}$=

1.1 Hz, $J_{7cis,4}$=1.0 Hz, H_{7trans}), 5.73 (1H, ddd, $J_{7trans,6}$=17.1 Hz, $J_{7cis,6}$=10.6 Hz, $J_{6,4}$=7.9 Hz, H_6), 5.92 (1H, b s, NH), 6.05 (1H, b s, NH); ^{13}C NMR (100 Hz, $CDCl_3$) δ 9.6, 27.3, 28.1, 56.1, 63.0, 119.5, 132.8, 152.0, 183.5. Anal. Calcd for $C_{11}H_{18}N_2O_2S$: C, 54.52; H, 7.49; N, 11.56; S, 13.23. Found: C, 54.46; H, 7.50; N, 11.53; S, 13.28.

4.5. General procedure for the synthesis of 11a–e and 12a

The imidazolidines **9a**–**e** and **10a** (1 mmol) were dissolved in the mixture of CF_3COOH and H_2O (95:5, 5 mL). The reaction mixture was stirred at room temperature for 15 min and then concentrated under reduced pressure. The resulting residue was diluted with diethyl ether and washed with saturated aq. sodium hydrogen carbonate and brine. After being dried, evaporation of the solvent gave the crude products, which were purified by silica gel chromatography with a mixture ethyl acetate–cyclohexane (20% ethyl acetate/hexane) to provide the products **11a**–**e** and **12a.**

4.5.1. (4*S*,5*S*)-4-Vinyl-5-methyltetrahydro-1*H*-2-imidazolethione (11a). 96%; white solid: mp 115–117°C; $[\alpha]_D^{25}$=−110.0 (*c* 0.63 $CHCl_3$); IR ($CHCl_3$) 3452, 3441, 1680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, d, *J*=6.6 Hz, CH_3), 4.19 (1H, dq, $J_{5,4}$=7.1 Hz, $J_{5,Me}$=6.6 Hz, H_5), 4.46 (1H, dddd, $J_{6,4}$=7.7 Hz, $J_{5,4}$=7.1 Hz, $J_{7trans,4}$=1.0 Hz, $J_{7cis,4}$=0.9 Hz, H_4), 5.32 (1H, ddd, $J_{7cis,6}$=10.3 Hz, $J_{7trans,7cis}$=1.1 Hz, $J_{7cis,4}$=0.9 Hz, H_{7cis}), 5.34 (1H, ddd, $J_{7trans,6}$=17.1 Hz, $J_{7trans,7cis}$=1.1 Hz, $J_{7cis,4}$=1.0 Hz, H_{7trans}), 5.82 (1H, ddd, $J_{7trans,6}$=17.1 Hz, $J_{7cis,6}$=10.3 Hz, $J_{6,4}$=7.7 Hz, H_6), 6.03 (1H, b s, NH), 6.19 (1H, b s, NH); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.0, 56.1, 63.1, 119.7, 132.1, 183.6. Anal. Calcd for $C_6H_{10}N_2S$: C, 50.67; H, 7.09; N, 19.70; S, 22.54. Found: C, 50.72; H, 7.11; N, 19.75; S, 22.46.

4.5.2. (4*S*,5*S*)-4-Vinyl-5-ethyltetrahydro-1*H*-2-imidazolethione (11b). 98%; white solid: mp 147–149°C; $[\alpha]_D^{25}$=−106.7 (*c* 0.71 $CHCl_3$); IR ($CHCl_3$) 3450, 3440, 1679 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J*=7.5 Hz, CH_3), 2.36–2.40 (2H, m, H_8), 3.61 (1H, ddd, $J_{5,4}$=7.3 Hz, $J_{8,5}$=6.8 Hz, $J_{8,5}$=5.9 Hz, H_5), 4.08 (1H, dddd, $J_{6,4}$=7.6 Hz, $J_{5,4}$=7.4 Hz, $J_{7trans,4}$=1.1 Hz, $J_{7c,4}$=0.8 Hz, H_4), 5.23 (1H, ddd, $J_{7cis,6}$=10.1 Hz, $J_{7cis,7trans}$=0.9 Hz, $J_{7cis,4}$=0.8 Hz, H_{7cis}), 5.30 (1H, ddd, $J_{7trans,6}$=17.1 Hz, $J_{7trans,4}$=1.1 Hz, $J_{7,7}$=0.9 Hz, H_{7trans}), 5.84 (1H, ddd, $J_{7trans,6}$=17.1 Hz, $J_{7cis,6}$=10.1 Hz, $J_{6,4}$=7.6 Hz, H_6), 6.14 (1H, b s, NH), 6.30 (1H, b s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.8, 27.2, 65.1, 65.6, 118.5, 135.7, 183.0. Anal.Calcd for $C_7H_{12}N_2S$: C, 53.81; H, 7.74; N, 17.93; S, 20.52. Found: C, 53.83; H, 7.84; N, 17.80; S, 20.56.

4.5.3. (4*S*,5*S*)-4-Vinyl-5-isopropyltetrahydro-1*H*-2-imidazolethione (11c). 94%; white solid: mp 127–130°C; $[\alpha]_D^{25}$=−100.3 (*c* 0.68 $CHCl_3$); IR ($CHCl_3$) 3439, 3451, 1678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, $J_{Me,8}$=6.6 Hz, CH_3), 1.00 (3H, d, $J_{Me,8}$=6.6 Hz, CH_3), 1.84 (1H, dseptet, $J_{8,5}$=9.3 Hz, $J_{8,Me}$=6.6 Hz, H_8), 3.69 (1H, dd, $J_{8,5}$=9.3 Hz, $J_{5,4}$=8.4 Hz, H_5), 4.35 (1H, dd, $J_{5,4}$=8.4 Hz, $J_{6,4}$=8.3 Hz, H_4), 5.30 (1H, d, $J_{7cis,6}$=10.1 Hz, H_{7cis}), 5.32 (1H, d, $J_{7trans,6}$=17.1 Hz, H_{7trans}), 5.92 (1H, ddd, $J_{7trans,6}$=17.1 Hz, $J_{7cis,6}$=10.1 Hz, $J_{6,4}$=8.3 Hz, H_6), 6.33 (1H, b s. NH), 6.49 (1H, b s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 19.6, 27.8, 62.8, 67.4, 119.8, 131.9, 184.2. Anal. Calcd for $C_8H_{14}N_2S$: C, 56.43; H, 8.29; N, 16.45; S, 18.83. Found: C, 56.47; H, 8.30; N, 16.51; S, 18.78.

4.5.4. (4*S*,5*S*)-4-Vinyl-5-benzyltetrahydro-1*H*-2-imidazolethione (11d). 94%; white solid: mp 126–128°C; $[\alpha]_D^{25}$=−60.3 (*c* 0.84 $CHCl_3$); IR ($CHCl_3$) 3442, 3451, 1678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (1H, dd, $J_{8,8}$=13.5 Hz, $J_{8,5}$=8.9 Hz, H_8), 2.95 (1H, dd, $J_{8,8}$=13.5 Hz, $J_{8,5}$=5.1 Hz, H_8), 3.89 (1H, dddd, $J_{8,5}$=8.9 Hz, $J_{5,4}$=7.2 Hz, $J_{8,5}$=5.1 Hz, $J_{7trans,5}$=1.0 Hz, H_5), 4.18 (1H, ddd, $J_{6,4}$=7.4 Hz, $J_{5,4}$=7.2 Hz, $J_{7,4}$=0.9 Hz, H_4), 5.21 (1H, ddd, $J_{7,6}$=10.1 Hz, $J_{7,4}$=0.9 Hz, $J_{7,7}$=0.9 Hz, H_{7cis}), 5.25 (1H, ddd, $J_{7trans,6}$=17.3 Hz, $J_{7,5}$=1.0 Hz, $J_{7,7}$=0.9 Hz, H_{7trans}), 5.78 (1H, ddd, $J_{7trans,6}$=17.3 Hz, $J_{7cis,6}$=10.1 Hz, $J_{6,4}$=7.4 Hz, H_6), 6.18 (1H, b s, NH), 6.35 (1H, b s, NH), 7.16–7.20 (2H, m, Ph), 7.28–7.32 (3H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.3, 64.9, 65.4, 118.8, 127.3, 129.0, 129.1, 135.1, 136.0, 183.1. Anal. Calcd for $C_{12}H_{14}N_2S$: C, 66.02; H, 6.46; N, 12.83; S, 14.69. Found: C, 66.08; H, 6.40; N, 12.85; S, 14.74.

4.5.5. (4*S*,5*S*)-4-Vinyl-5-isobutyltetrahydro-1*H*-2-imidazolethione (11e). 93%; white solid: mp 128–131°C; $[\alpha]_D^{25}$=−90.3 (*c* 0.93 $CHCl_3$); IR ($CHCl_3$) 3452, 3439, 1680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, *J*=6.3 Hz, CH_3), 0.94 (3H, d, *J*=6.3 Hz, CH_3), 1.48–1.52 (3H, m, H_8, H_9), 3.77–3.79 (1H, m, H_5), 4.09 (1H, dd, $J_{6,4}$=7.2 Hz, $J_{5,4}$=6.8 Hz, H_4), 5.27 (1H, dd, $J_{7cis,6}$=10.1 Hz, $J_{7,7}$=0.7 Hz, H_{7cis}), 5.32 (1H, dd, $J_{7trans,6}$=17.0 Hz, $J_{7,7}$=0.7 Hz, H_{7trans}), 5.81 (1H, ddd, $J_{7trans,6}$=17.0 Hz, $J_{7cis,6}$=10.1 Hz, $J_{6,4}$=7.2 Hz, H_6), 6.24 (1H, b s, NH), 6.48 (1H, b s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 25.0, 43.4, 62.2, 66.6, 119.1, 135.2, 182.5. Anal. Calcd for $C_9H_{16}N_2S$: C, 58.65; H, 8.75; N, 15.20; S, 17.40. Found: C, 58.59; H, 8.78; N, 15.14; S, 17.44.

4.5.6. (4*S*,5*R*)-4-Vinyl-5-methyltetrahydro-1*H*-2-imidazolethione (12a). 96%; white solid: mp 212–213°C; $[\alpha]_D^{25}$=+64.0 (*c* 0.86 $CHCl_3$); IR ($CHCl_3$) 3440, 3451, 1683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (3H, d, *J*=6.7 Hz, CH_3), 4.03 (1H, dq, $J_{5,4}$=7.0 Hz, $J_{5,Me}$=6.7 Hz, H_5), 4.40 (1H, dddd, $J_{6,4}$=7.9 Hz, $J_{5,4}$=7.0 Hz, $J_{7trans,4}$=1.0 Hz, $J_{7cis,4}$=0.8 Hz, H_4), 5.32 (1H, ddd, $J_{7cis,6}$=10.3 Hz, $J_{7trans,4}$=1.1 Hz, $J_{7cis,4}$=0.8 Hz, H_{7cis}), 5.30 (1H, ddd, $J_{7trans,6}$=17.1 Hz, $J_{7trans,4}$=1.1 Hz, $J_{7cis,4}$=1.0 Hz, H_{7trans}), 5.78 (1H, ddd, $J_{7trans,6}$=17.1 Hz, $J_{7cis,6}$=10.3 Hz, $J_{6,4}$=7.9 Hz, H_6), 5.98 (1H, b s, NH), 6.11 (1H, b s, NH); ^{13}C NMR (100 Hz, $CDCl_3$) δ 15.9, 56.1, 63.0, 119.3, 132.3, 183.0. Anal. Calcd for $C_6H_{10}N_2S$: C, 50.67; H, 7.09; N, 19.70; S, 22.54. Found: C, 50.72; H, 7.11; N, 19.75; S, 22.46.

Acknowledgements

A possibility to realize selected NMR experiments during the visit of J. I. to the Department of Chemistry, University of Turku, Finland (a Professor Kalevi Pihlaja's Group) is

gratefully acknowledged. The present work was supported by Grant Agency (No. 1/6080/99) from the Ministry of Education, Slovak republic.

References

1. Oishi, T.; Hirama, M. *J. Org. Chem.* **1989**, *54*, 5834–5835. Tokles, M.; Snider, J. K. *Tetrahedron Lett.* **1986**, *27*, 3951–3954. Corey, E. J.; DaSilva Jardine, P.; Virgil, S.; Yuen, P.-W.; Connel, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243–9244.
2. Alexakis, A.; Serdrani, R.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 4411–4414.
3. Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754–5756.
4. Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495–5496.
5. Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801–2803.
6. Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976–4977.
7. Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Chem. Pharm. Bull.* **1988**, *57*, 6653–6658. Nantz, M. H.; Lee, D. A.; Bender, D. M.; Roohi, A. H. *J. Org. Chem.* **1992**, *57*, 6653–6657. Dieter, R. K.; Deo, N.; Lagu, B.; Dieter, J. W. *J. Org. Chem.* **1992**, *57*, 1663–1671. Phammatter, E.; Seebach, D. *Liebigs Ann. Chem.* **1991**, 1323–1336. Yoda, H.; Shirai, T.; Kawasaki, T.; Katagiri, T.; Takabe, K.; Kimata, K.; Hosoya, K. *Chem. Lett.* **1991**, 793–794. Dunn, P. J.; Hänner, R.; Rappoport, H. *J. Org. Chem.* **1990**, *55*, 5017–5025. Shigematsu, N.; Setoi, H.; Uchida, I.; Shibata, T.; Terano, H.; Hashimoto, M. *Tetrahedron Lett.* **1988**, *29*, 5147–5150. Mangeney, P.; Tejero, T.; Alexakis, A.; Grosjean, F.; Normant, J. *Synthesis* **1988**, 255–257. Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 3152–3154. Arrowsmith, R. J.; Carter, K.; Dann, J. G.; Davies, D. E.; Harris, C. J.; Morton, J. A.; Lister, P.; Robinson, J. A.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1986**, 755–757. Natsugari, H.; Whittle, R. R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 7867–7872.
8. Gonda, J.; Helland, A.-Ch.; Ernst, B.; Belluš, D. *Synthesis* **1993**, 729–733.
9. See inter alia: Jones, R. C.; Crockett, A. K.; Rees, D. C.; Gilbert, I. H. *Tetrahedron: Asymmetry* **1994**, *5*, 1661–1664. Solomon, M. E.; Lynch, C. L.; Rich, D. H. *Tetrahedron Lett.* **1995**, *36*, 4955–4988. Cardillo, G.; Orena, M.; Penna, M.; Sandri, S.; Tomasini, C. *Tetrahedron* **1991**, *47*, 2263–2272. Hartwig, W.; Mittendorf, J. *Synthesis* **1991**, 939–941.
10. Nakamura, Y.; Hirai, M.; Tamotsu, K.; Yonezawa, Y.; Shin, C. *Bull. Chem. Soc. Jpn* **1995**, *68*, 1369–1377 and references cited therein.
11. Dunn, P. J.; Haner, R.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5017–5025 and references cited therein. Palomo, C.; Aizpurua, J. M.; Cabre, F.; Cuevas, C.; Munt, S.; Odriozola, J. M. *Tetrahedron Lett.* **1994**, *35*, 2725–2728. Rossi, F. M.; Powers, E. T.; Yoon, R.; Rosenberg, L.; Meinwald, J. *Tetrahedron* **1996**, *52*, 10279–10286. Lin, Y.-R.; Xhou, X.-T.; Dai, L.-X.; Sun, J. *J. Org. Chem.* **1997**, *62*, 1799–1803. Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Uozumi, Y. *Tetrahedron Lett.* **1996**, *37*, 4969–4972. Es-Sayed, M.; Gratkowski, C.; Krass, N.; Meyers, A. I.; Meiere, A. *Synlett* **1992**, 962–964. Fernandez-Megia, E.; Paz, M. M.; Sardina, F. J. *J. Org. Chem.* **1994**, *59*, 7643–7652.
12. Martinková, M.; Gonda, J. *Tetrahedron Lett.* **1997**, *38*, 875–878.
13. Moriwake, T.; Hamano, S.; Miki, D.; Saito, S. *Chem. Lett.* **1986**, 815–818.
14. Drobnica, L'.; Kristian, P.; Augustin, J. In *The Chemistry of Cyanates and their Thio Derivatives*; Patai, S., Ed.; Wiley: New York, 1977; pp 1005–1221. DeWolfe, R.; Young, W. G. In *The Chemistry of Alkenes*; Patai, S., Ed.; Wiley: New York, 1964; pp 681–753.
15. Engdahl, K. A.; Bivehed, H.; Ahberg, P.; Saunders, Jr., W. H. *J. Am. Chem. Soc.* **1983**, *105*, 4767–4774.