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Stereoselectivity of 1,3-dipolar cycloadditions of L-valine-derived nitrones with methyl acrylate

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Abstract—Chiral nitrones derived from L-valine react with methyl acrylate to afford the corresponding diastereomeric 3,5-disubstituted isoxazolidines. The dibenzylsubstituted nitrone gave also 3,4-disubstituted isoxazolidine in 4% yield, additionally. The stereoselectivity was dependent on the steric hindrance of the nitrone and reaction conditions. High pressure decreased the reaction time of the cycloadditions. The major products were found to have the C-3/C-6 *erythro* and C-3/C-5 *trans* relative configuration. The major cycloadduct undergoes N–O cleavage and deprotection to a chiral diaminodiol derivative.

1. Introduction

The nitrone-olefin 1,3-dipolar cycloaddition is a powerful reaction in that it can create as many as three new contiguous stereogenic centres in a single step.[1] Based on an evaluation of the nitrone cycloaddition, it was felt that the stereochemistry of these new centers could be controlled if the reaction system were properly designed.[1–3] Regio- and stereoselective nitrone cycloaddition, followed by reduction of the N–O bond to produce both an amino and a hydroxy function, allows the synthesis of many products of potential interest. With our continuing efforts to utilize chiral 1,3-dipolar cycloadditions[4–7] we have recently published the preparation of L-valine and L-phenylalanine-derived nitrones.[8] With the goal of developing a simple route to the synthesis of non-proteinogenic γ-substituted β,γ-diamino acids of general formula **1** isosteric to aminostatine **2** via an asymmetric 1,3-dipolar cycloaddition, we now report the stereoselectivity of the cycloaddition of chiral nitrones **3**–**5** (Fig. 2) derived from L-valine with methyl acrylate together with the subsequent transformation of so prepared cycloadducts ((Figs. 1 and 2)).

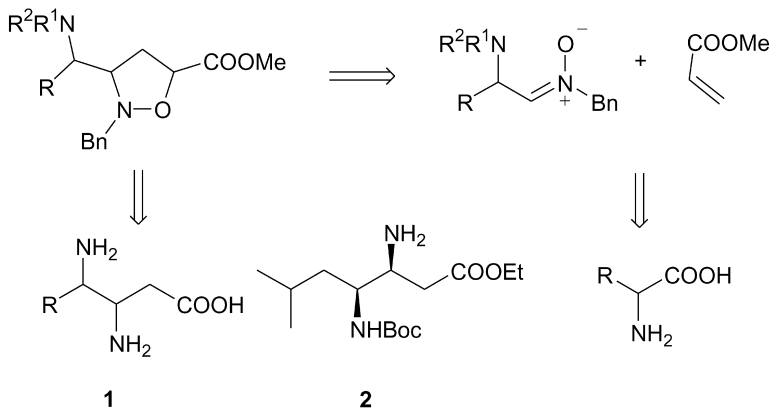

Figure 1.

Keywords: cycloaddition; chiral nitrones; isoxazolidines; high pressure.
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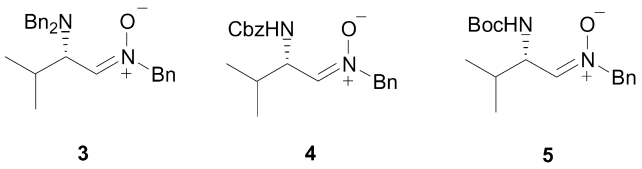
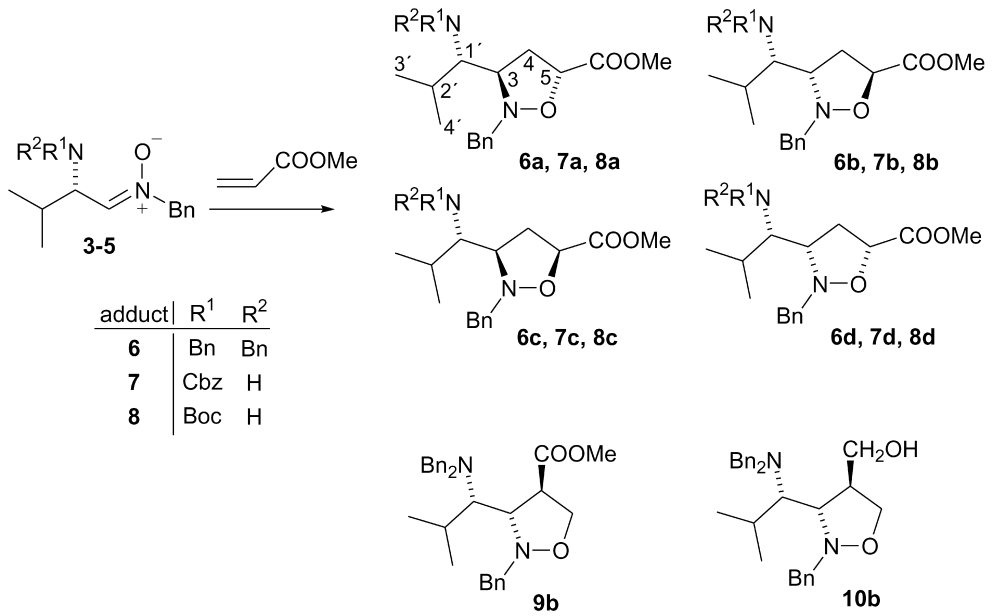


Figure 2.

The stereoselectivity of the cycloaddition is dependent on the substituent being attached on the nitrogen atom in the starting nitrone as well upon reaction conditions (Table 1).

It is noteworthy to mention that our attempts to accelerate the cycloaddition of nitrones **3**–**5** by high pressure were successful. Indeed, high pressure decreased the reaction



adduct	R^1	R^2
6	Bn	Bn
7	Cbz	H
8	Boc	H

Scheme 1.

Diastereoselective synthesis of β,γ-diamino acids has received considerable attention due to the wide range of biological activity of these compounds. For instance the aminostatine (**2**) substrate analogue of statine led to potent aspartyl proteinase inhibition of human renin.[9]

2. Results and discussion

The diastereomerically pure nitrones **3**–**5** were subjected to 1,3-dipolar cycloaddition. Our concern was to study the asymmetric induction from the nitrone part. The cycloadditions afforded the corresponding diastereomeric isoxazolidines **6**–**8** as a mixture of diastereoisomers in a good overall yield (Scheme 1).

Purification by flash chromatography allowed the isolation of the pure diastereoisomers **6ab**, **7ab**, **8ab** and **9b**, while the isolation and/or characterization of minor isomers was possible only for some of them. The regioselectivity of the cycloaddition of the nitrones **4**,**5** was high; indeed 5-substituted isoxazolidines were formed exclusively. On the other hand, although the cycloaddition of the nitrone **3** proceeded with the formation of the 5-substituted isoxazolidines **6a**–**d**, surprisingly the 4-substituted isoxazolidine **9b** was formed in 4% yield. The oily isoxazolidine **9b** was reduced with DIBALH to yield the primary alcohol **10b** and the unexpected structure of the 4-substituted regioisomer was subsequently confirmed by X-ray crystallographic analysis of **10b** (Fig. 3).

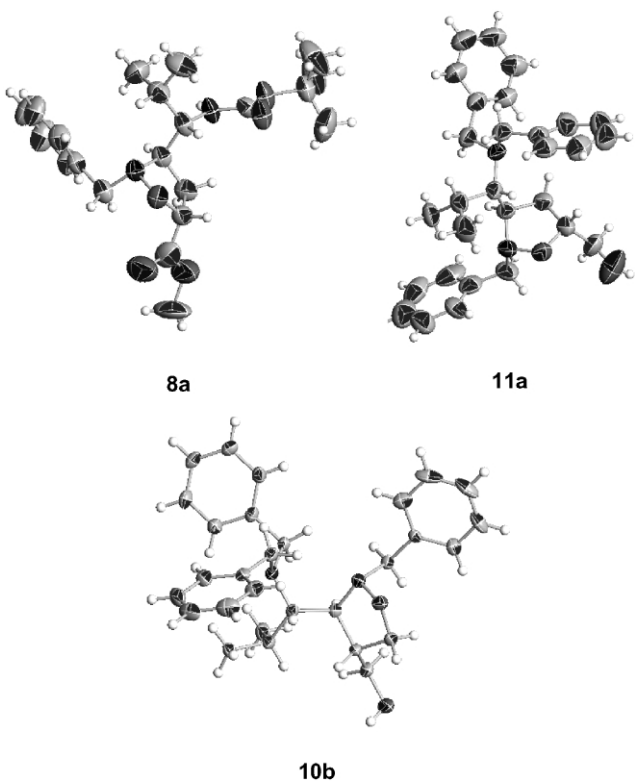


Figure 3.

Table 1. 1,3-Dipolar cycloaddition of chiral L-valine-derived nitrones **3**–**5** to methyl acrylate

Entry	Nitrone	Adduct	Reaction condition	yield (%)	**a**	**b**	**c**	**d**
1	**3**	**6**	110°C, 3 days[a]	82	59	22	12	7
2	**3**	**6**	rt, 30 days[a]	–	–	–	–	–
3	**3**	**6**	rt, 2 days, 10 Kbar[a]	84	54	19	14	13
4	**3**	**6**	60°C, 2 days, 10 Kbar[a]	80	52	20	15	13
5	**4**	**7**	110°C, 1 h[a]	89	51	44	5	–
6	**4**	**7**	40°C, 12 h[b]	91	62	34	5	–
7	**4**	**7**	rt, 4 days[b]	84	64	36	–	–
8	**4**	**7**	rt, 2 days, 10 Kbar[b]	85	54	36	6	–
9	**4**	**7**	60°C, 2 days, 10 Kbar[b]	87	54	41	5	–
10	**5**	**8**	110°C, 1 h[a]	92	45	50	5	–
11	**5**	**8**	40°C, 12 h[b]	90	58	37	5	–
12	**5**	**8**	rt, 4 days[b]	85	64	36	–	–

[a] Toluene.
[b] CH_2Cl_2.

times of the cycloadditions (Table 1, entry 1, 2 versus 3, 4). On the other hand, high pressure changed only slightly the ratio of diastereoisomers of the nitrone cycloaddition. Selectivity of the cycloadditions with nitrone **5** depend on the reaction conditions. The cycloaddition in boiling toluene gave *threo*–*trans* diastereoisomer **8b** as a major product in contrast to the cycloaddition in CH_2Cl_2 where *erythro*–*trans* isoxazolidine **8a** were formed as a major adduct (Table 1, entry 10 versus 11, 12).

The ratio of diastereoisomers was determined from quantitative ^{13}C NMR spectra, by integration of the peaks from C-3 and C-4 of the isoxazolidines, respectively. The structural assignments of the products are based on analysis of NMR spectra. The stereochemistries of the cycloadducts were deduced by NOE experiments. The most important and decisive information obtained from these experiments is the presence or absence of the NOE interaction between the protons H-4/H-3, H-4/H-5 and H-3/H-5 in the corresponding cycloadducts. For instance the *trans* relationship of the substituents at C-3 and C-5 in **8a** has been assigned on the basis of NOEDS. A 27% enhancement on signal H-4_B and 7% enhancement on signal H-3 following saturation of signal H-4_A show a *trans* relationship between the H-3 and H-5 protons; irradiation of H-4_B causes only enhancement on H-4_A (22%). Moreover, the missing interactions between H-4_A and H-5 and between H-4_B and each of H-3 and H-5 confirming this *trans* relationship between the H-3 and H-5 protons. Subsequently the stereochemistry was confirmed by X-ray-crystallographic analysis in the cases of **8a**, **10b** and **11a** (the oily methyl ester **6a** was converted with DIBALH into the hydroxymethyl derivative **11a**).

X-Ray analyses of **8a** and hydroxymethyl derivative **11a** shows C-1′/C-3 *erythro* and C-3/C-5 *trans* stereochemistry and therefore reveals that the isoxazolidines **6a**–**8a** (TS 1) and also **6b**–**8b** (TS 2) result from an *exo* attack of methyl acrylate to (*Z*)-nitrone **3**–**5** (Fig. 4). It should be mentioned that the corresponding (*E*)-nitrones were not detected by ^1H NMR analysis. Moreover, there was no thermal interconversion between the adducts in refluxing toluene, thus indicating that the cycloaddition proceeded irreversibly under the reaction conditions to give the kinetically controlled products **6**–**9**.

Next, we decided to exploit our knowledge of these cycloadditions in the development of a synthetic method to γ-substituted β,γ-diamino acids of general formula **1** from amino acid precursors. Our retrosynthetic strategy is outlined in Figure 1. As shown in Scheme 2, 1,3-dipolar cycloaddition of amino acid derived nitrone **3** prepared from L-valine with methyl acrylate gave the diastereomerically pure isoxazolidine **6a** in 52%. NO-heterocycles are prone to hydrogenolysis since the relatively weak N–O bond is easily cleaved.[7c] The C–COOMe functionalized isoxazolidine **6a** was reduced with DIBALH to yield the primary alcohol **11a** confirmed by X-ray crystallographic analysis. Direct hydrogenolysis of **11a** in the presence of catalyst palladium on carbon in methanol in the presence of Boc_2O resulted in a cascade reaction sequence involving isoxazolidine N–O bond cleavage, *N*-debenzylation and *N*-Boc protection affording chiral diamino diol **12** in 56% yield.

Unfortunately, the last transformation to β,γ-diamino acid **13** was not successful. Although different agents were used

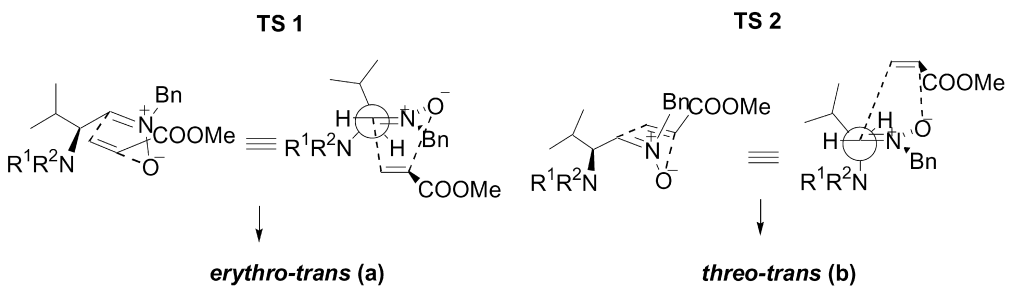
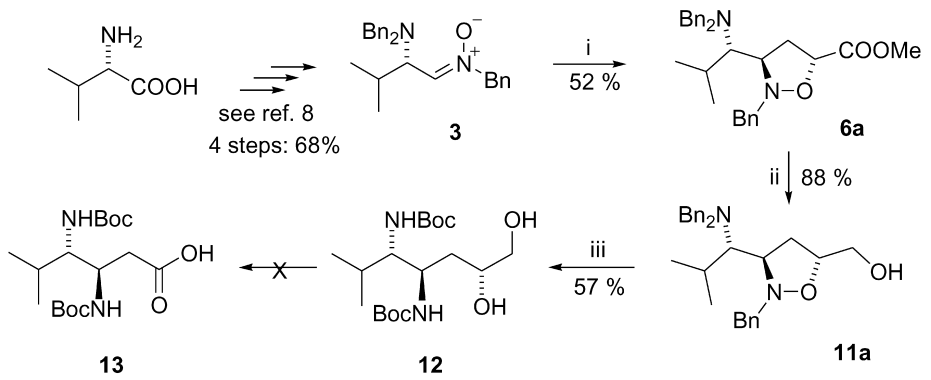


Figure 4.



Scheme 2. (i) Methyl acrylate, toluene, 110°C, 5 days; (ii) DIBALH, THF, 1 h, −10°C; (iii) (1) H_2–Pd/C, MeOH, 48 h, rt, (2) Boc_2O, dioxane – H_2O, 10 h, rt.

for oxidation of chiral diamino diol **12** such as $NaIO_4$–Ag_2O,[10] $NaIO_4$–$NaClO_2$–NaH_2PO_4,[11] $NaIO_4$–Br_2–$NaHCO_3$[12] and $NaIO_4$–$RuCl_3$[13] reactions afforded only mixture of three unstable products, but β,γ-diamino acid **13** was not formed.

3. Conclusion

Chiral nitrones derived from L-valine react with methyl acrylate to afford the corresponding diastereomeric 3,5-disubstituted isoxazolidines. The dibenzylsubstituted nitrone gave also 3,4-disubstituted isoxazolidine in 4% yield, additionally. The stereoselectivity of the cycloaddition was dependent on the steric hindrance of the nitrone and reaction conditions. High pressure decreased the reaction time of the cycloadditions. The major products were found to have the C-3/C-6 *erythro* and C-3/C-5 *trans* relative configuration. An efficient synthetic pathway to chiral diamino diol **12** member of very rare class of chiral compounds,[14] has been established from L-valine via enantiomerically pure isoxazolidine intermediate **9a** in 8 steps with overall yield of 18%.

4. Experimental

4.1. General methods

All starting materials and reagents are commercially available (Fluka, Merck or Avocado) and were used without further purification. Solvents were dried using standard procedures. Thin-layer chromatography (TLC) was used for monitoring of reaction courses and was carried out on aluminium plates coated with silica $60F_{254}$ (0.25 mm thickness, Merck). Eluents are indicated in the text. All column chromatography was done by using the flash chromatography technique, and was carried out on silica 60 (0.040–0.063 mm, Merck). Melting points were determined on a Kofler hot plate apparatus and are uncorrected. Elemental analyses were performed by the microanalysis service of the Department of Analytical Chemistry, Slovak University of Technology, Bratislava.

The ^1H and ^{13}C NMR spectra of deuterochloroform solutions were obtained using Varian VXR 300 (300 MHz) and Bruker DRX-400 (400 MHz) instruments, tetramethylsilane being the internal reference. The IR spectra of tetrachloromethane solutions were obtained using Perkin Elmer 781 Infrared Spectrophotometer. Optical rotations [α] were measured on an IBZ Messtechnik Polar-LμP polarimeter at the sodium D line (589 nm) using a 1 dm cell with chloroform as solvent.

4.2. General procedure for atmospheric pressure cycloadditions of nitrones 3–5 to methyl acrylate

To a stirred solution of the nitrone (1.0 mmol) in toluene or in CH_2Cl_2 (5 mL) was added methyl acrylate (2 mmol), and the solution was heated at reflux. The resulting mixture was evaporated under reduced pressure. The crude mixture was purified by column chromatography on silica gel eluting with EtOAc/hexanes to give mixture of diastereoisomers. The ratio of diastereoisomers and reaction conditions are summarised in the Table 1. Chromatography conditions and physical properties of products are shown below.

4.3. General procedure for high pressure cycloadditions of nitrones 3–5 to methyl acrylate

Reactions of nitrones with methyl acrylate were carried out at rt or 60°C in toluene, or in CH_2Cl_2 for several days under 10 Kbar pressure. The reaction mixture (1 mmol of nitrone, 2 mmol of dipolarophile and 0.5 mL of solvent) was placed in a Teflon ampoule which was inserted into the high-pressure vessel filled with *n*-hexane as a transmission medium. After decompression, the mixture was purified by flash column chromatography on silica gel eluting with EtOAc/hexanes to give mixture of diastereoisomers.

4.3.1. (3*R*,5*R*,1′*S*)-[2-Benzyl-3-(1′-dibenzylamino-2′-methylpropylidene)-isoxazolidin-5-yl]-carboxylic acid methyl ester (6a). The product **6a** was isolated by flash column chromathography on silica gel eluting with EtOAc/hexanes (4:96) as a colourless oil in 46% yield. $[\alpha]_D^{25}$=+32.1, ($CHCl_3$, *c* 0.3); ν_{max} (CCl_4) 1741, 1505, 1218, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.35–7.21 (m, 15H, H–Ph), 4.06, 3.73 (2×d, 2×1H, *J*=13.2 Hz, NCH_2Ph), 3.77 [d, 2H, *J*=13.4 Hz, $N(CH_2Ph)_2$], 3.69 (s, 3H, $COOCH_3$), 3.66 (m, 1H, H-3), 3.60 (app dd, 1H, $J_{4A,5}$=$J_{4B,5}$=8.8 Hz, H-5), 3.42 [d, 2H, *J*=13.4 Hz, $N(CH_2Ph)_2$], 3.17 (m, 1H, $J_{3,4A}$=8.8 Hz, $J_{4A,5}$=8.8 Hz, $J_{4A,B}$=12.2 Hz, H-4_A), 2.56 (ddd, 1H, $J_{3,4B}$=6.9 Hz, $J_{4B,5}$=8.9 Hz, $J_{4A,B}$=12.3 Hz, H-4_B), 2.41 (dd, 1H, $J_{1',2'}$=1.2 Hz, $J_{3,1'}$=10.8 Hz, H-1′), 2.28 (m, 1H, $J_{1',2'}$=1.2 Hz, $J_{2',3'}$=7.2 Hz, $J_{2',4'}$=7.0 Hz, H-2′), 1.08, 0.99 (2×d, 2×3H,

$J_{2',3'}$=7.2 Hz, $J_{2',4'}$=7.0 Hz, H-3′, H-4′); ^{13}C NMR (125 MHz, $CDCl_3$): δ=173.8 (CO), 139.8–127.1 (C-Ph), 77.0 (C-5), 65.9 (C-3), 62.2 (N*C*H$_2$Ph), 59.6 (C-1′), 54.5 [N(*C*H$_2$Ph)$_2$], 52.1 (COO*C*H$_3$), 33.8 (C-4), 25.5 (C-2′), 23.9, 18.9 (C-3′, C-4′); for $C_{30}H_{36}N_2O_3$ (472.62) calcd C, 76.24, H, 7.68, N, 5.93; found: C, 76.47, H, 7.77, N, 5.69.

4.3.2. (3*S*,5*S*,1′*S*)-[2-Benzyl-3-(1′-dibenzylamino-2′-methylpropylidene)-isoxazolidin-5-yl]-carboxylic acid methyl ester (6b). The product **6b** was isolated by flash column chromathography on silica gel eluting with EtOAc/hexanes (4:96) as a colourless oil in 18% yield. $[\alpha]_D^{25}$=+72.9, ($CHCl_3$, *c* 0.55), ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.34 (m, 15H, H–Ph), 4.58 ('t', 1H, $J_{4A,5}$=7.3 Hz, $J_{4B,5}$=8.5 Hz, H-5), 4.12, 3.92 (2×d, 2×1H, *J*=13.7 Hz, NC*H*$_2$Ph), 3.80 (s, 3 H, COOCH$_3$), 3.81, 3.73 [2×d, 2×2H, *J*=13.7 Hz, N(C*H*$_2$Ph)$_2$], 3.63 (m, 1H, H-3), 2.63 (m, 1H, $J_{3,4A}$=7.3 Hz, $J_{4A,5}$=7.3 Hz, $J_{4A,B}$=12.8 Hz, H-4$_A$), 2.50 (ddd, 1H, $J_{3,4B}$=4.3 Hz, $J_{4B,5}$=8.5 Hz, $J_{4A,B}$= 12.8 Hz, H-4$_B$), 2.40 (t, 1H, $J_{3,1'}$=6.4 Hz, $J_{1',2'}$=1.2 Hz, H-1′), 1.88 (m, 1H, $J_{1',2'}$=1.2 Hz, $J_{2',3'}$=$J_{2',4'}$=6.8 Hz, H-2′), 1.00, 0.82 (2×d, 2×3H, $J_{2',3'}$=$J_{2',4'}$=6.8 Hz, H-3′, H-4′); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.2 (CO), 140.5–126.8 (C–Ph), 76.5 (C-5), 65.6 (C-3), 61.9 (N*C*H$_2$Ph), 61.1 (C-1′), 55.4 [N(*C*H$_2$Ph)$_2$], 52.4 (COO*C*H$_3$), 35.9 (C-4), 29.2 (C-2′), 21.6, 20.3 (C-3′,C-4′); for $C_{30}H_{36}N_2O_3$ (472.62) calcd C, 76.24, H, 7.68, N, 5.93; found: C, 76.41, H, 7.53, N, 6.04.

4.3.3. (3*R*,5*S*,1′*S*)-[2-Benzyl-3-(1′-dibenzylamino-2′-methylpropylidene)-isoxazolidin-5-yl]-carboxylic acid methyl ester (6c). The product **6c** was isolated by flash column chromathography on silica gel eluting with EtOAc/hexanes (4:96). Following NMR signals came from enriched mixture of diastereoisomers. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ=7.31 (m, 15H, H–Ph), 4.58 ('t', $J_{4A,5}$=$J_{4B,5}$=8.1 Hz, H-5), 3.92, 3.80 (2×d, 2×1H, *J*= 13.2 Hz, NC*H*$_2$Ph), 3.55 (s, 3H, H-COOC*H*$_3$), 3.77 3.54 [2×d, 2×2H, *J*=13.2 Hz, N(C*H*$_2$Ph)$_2$], 3.51 (m, 1H, H-3), 2.79 (m, 2H, H-4$_{A,B}$), 2.66 (dd, 1H, $J_{3,1'}$=10.3 Hz, $J_{1',2'}$=1.7 Hz, H-1′), 2.29 (m, 1H, $J_{1',2'}$=1.7 Hz, $J_{2',3'}$= $J_{2',4'}$=6.8 Hz, H-2′), 1.10, 0.99 (2×d, 2×3H, $J_{2',3'}$=$J_{2',4'}$=6.8 Hz, H-3′,4′); ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ=171.2 (*C*OOCH$_3$), 139.9–126.8 (C–Ph), 74.5 (C-5), 65.5 (C-3), 63.7 (C-1′), 60.4 (N*C*H$_2$Ph), 55.1 (N(*C*H$_2$Ph)$_2$), 52.2 (COO*C*H$_3$), 36.0 (C-4), 26.7 (C-2′), 23.1, 19.6 (C-3′,4′); for $C_{30}H_{36}N_2O_3$ (472.62) calcd C, 76.24, H, 7.68, N, 5.93; found: C, 76.11, H, 7.78, N, 5.81.

4.3.4. (3*S*,4*S*,1′*S*)-[2-Benzyl-3-(1′-dibenzylamino-2′-methylpropylidene)-isoxazolidin-4-yl]-carboxylic acid methyl ester (9b). The product **9b** was isolated by flash column chromathography on silica gel eluting with EtOAc/hexanes (4:96) as a colourless oil in 4% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.31 (m, 15H, H–Ph), 4.22 (dd, 1H, $J_{5A,4}$=6.7 Hz, $J_{5A,B}$=8.5 Hz, H-5$_A$), 4.06 (m, 1H, $J_{4,5A}$=6.7 Hz, $J_{4,5B}$=9.6 Hz, $J_{4,3}$=1.8 Hz, H-4), 3.99 (dd, 1H, $J_{3,1'}$=10.5 Hz, $J_{3,4}$=1.8 Hz, H-3), 3.95, 3.77 (2×d, 2×1H, *J*=13.2 Hz, NC*H*$_2$Ph), 3.82, 3.43 [2×d, 2×2H, *J*=12.9 Hz, N(C*H*$_2$Ph)$_2$], 3.80 (s, 3H, COOC*H*$_3$), 3.55 (dd, 1H, $J_{5B,4}$=9.4 Hz, $J_{5A,B}$=8.5 Hz, H-5$_B$), 2.43 (dd, 1H, $J_{3,1'}$=10.5 Hz, $J_{1',2'}$=1.5 Hz, H-1′), 2.35 (m, 1H, H-2′), 1.14, 1.06 (2×d, 2×3H, $J_{2',3'}$=$J_{2',4'}$=6.8 Hz, H-3′, H-4′); ^{13}C NMR (125 MHz, $CDCl_3$): δ=175.5 (CO), 140.0–127.4, (C–Ph), 69.4 (C-3), 67.1 (C-5), 61.9 (C-1′), 59.5 (N*C*H$_2$Ph), 54.6 [N(*C*H$_2$Ph)$_2$], 52.7 (COO*C*H$_3$), 51.0 (C-4), 25.8 (C-2′), 24.5, 19.5 (C-3′, C-4′); for $C_{30}H_{36}N_2O_3$ (472.62) calcd C, 76.24, H, 7.68, N, 5.93; found: C, 75.99, H, 7.85, N, 6.14.

4.3.5. (3*R*,5*R*,1′*S*)-[2-Benzyl-3-(1′-benzyloxycarbonyl-amino-2′-methylpropylidene)-isoxazolidin-5-yl]-carboxylic acid methyl ester (7a). The product **7a** was isolated by flash column chromathography on silica gel eluting with EtOAc/hexanes (10:90→20:80) as a colourless solid in 42% yield. Mp 126–127°C (from EtOAc/hexanes), $[\alpha]_D^{25}$=−60.7 ($CHCl_3$, *c* 0.5); ν_{max} (CCl_4) 3475, 1737, 1507, 1216, 1180, 1095 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.32 (m, 10H, H–Ph), 5.12 (s, 2H, OC*H*$_2$Ph), 4.70 (app t, 1H, $J_{4A,5}$=$J_{4B,5}$=8.1 Hz, H-5), 4.57 (d, 1H, $J_{1',NH}$=10.3 Hz, NH), 4.24, 3.80 (2×d, 2×1H, *J*=12.4 Hz, NC*H*$_2$Ph), 3.73 (s, 3H, COOC*H*$_3$), 3.57 (m, 1H, $J_{1',2'}$=2.6 Hz, $J_{3,1'}$=9.8 Hz, $J_{1',NH}$=10.3 Hz, H-1′), 3.18 (m, 1H, H-3), 2.58 (m, 2H, H-4$_{A,B}$), 2.21 (m, 1H, H-2′), 0.88, 0.38 (2×d, 2×3H, $J_{2',3'}$= $J_{2',4'}$=6.8 Hz, H-3′, H-4′); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.2 (CO), 156.9 (CO), 136.9–127.5 (C-Ph), 77.2 (C-5), 66.8 (OCH$_2$Ph), 65.6 (C-3), 62.3 (NCH$_2$Ph), 56.0 (C-1′), 52.3 (COOCH$_3$), 33.6 (C-4), 27.6 (C-2′), 20.9, 14.5 (C-3′, C-4′); for $C_{24}H_{30}N_2O_5$ (426.51) calcd C, 67.59, H, 7.09, N, 6.57; found: C, 67.47, H, 7.07, N, 6.69.

4.3.6. (3*S*,5*S*,1′*S*)-[2-Benzyl-3-(1′-benzyloxycarbonyl-amino-2′-methylpropylidene)-isoxazolidin-5-yl]-carboxylic acid methyl ester (7b). The product **7b** was isolated by flash column chromathography on silica gel eluting with EtOAc/hexanes (10:90→20:80) as a colourless solid in 40% yield. Mp 42–44°C (from EtOAc/hexanes), $[\alpha]_D^{25}$=−35.8 ($CHCl_3$, *c* 0.5); ν_{max} (CCl_4) 3430, 1727, 1516, 1458, 1230, 1053 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.32 (m, 10H, H–Ph), 5.13 (d, 1H, $J_{1',NH}$=10.3 Hz, NH), 5.09 (s, 2H, OC*H*$_2$Ph), 4.43 (app dd, 1H, $J_{4A,5}$=7.7 Hz, $J_{4B,5}$=8.9 Hz, H-5), 4.23 (d, 1H, *J*=12.8 Hz, NC*H*$_2$Ph), 3.76 (s, 3H, COOC*H*$_3$), 3.69 (d, 1H, *J*=12.8 Hz, NC*H*$_2$Ph), 3.60 (m, 1H, H-3), 3.26 (ddd, 1H, $J_{1',2'}$=1.7 Hz, $J_{3,1'}$=11.1 Hz, $J_{1',NH}$=10.3 Hz, H-1′), 2.82 (m, 1H, $J_{4A,5}$=7.7 Hz, $J_{4A,B}$= 13.2 Hz, H-4$_A$), 2.45 (m, 1H, $J_{4B,5}$=8.9 Hz, H-4$_B$), 1.71 (m, 1H, H-2′), 0.83, 0.51 (2×d, 2×3H, $J_{2',3'}$=6.8 Hz, $J_{2',4'}$=6.4 Hz, H-3′, H-4′); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.3 (CO), 156 (CO), 136.9–127.7 (C–Ph), 77.9 (C-5), 66.6 (OCH$_2$Ph), 64.3 (C-3), 63.4 (NCH$_2$Ph), 60.9 (C-1′), 52.4 (COOCH$_3$), 36.1 (C-4), 31.0 (C-2′), 19.4, 19.3 (C-3′, C-4′); for $C_{24}H_{30}N_2O_5$ (426.51) calcd C, 67.59, H, 7.09, N, 6.57; found: C, 67.63, H, 7.26, N, 6.10.

4.3.7. (3*R*,5*R*,1′*S*)-{2-Benzyl-3-[1′-(*tert*-butoxycarbonyl-amino)-2′-methylpropylidene]-isoxazolidin-5-yl}-carboxylic acid methyl ester (8a). The product **8a** was isolated by flash column chromathography on silica gel eluting with EtOAc/hexanes (15:85) as a colourless solid in 39% yield. Mp 82–83°C (from EtOAc/hexanes), $[\alpha]_D^{25}$=−69.8 ($CHCl_3$, *c* 0.5); ν_{max} (CCl_4) 3475, 1750, 1733, 1504, 1373, 1210, 1172 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.36 (m, 5H, H–Ph), 4.69 (app t, 1H, $J_{4A,5}$=$J_{4B,5}$=8.3 Hz, H-5), 4.32 (d, 1H, $J_{1',NH}$=10.2 Hz, NH), 4.23, 3.78 (2×d, 2×1H, *J*=12.4 Hz, NC*H*$_2$Ph), 3.79 (s, 3H, COOC*H*$_3$), 3.48 (ddd, 1H, $J_{1',2'}$=2.9 Hz, $J_{3,1'}$=$J_{1',NH}$=10.2 Hz, H-1′), 3.15 (ddd, 1H, $J_{3,6}$=9.3 Hz, $J_{3,4A}$=2.9 Hz, $J_{3,4B}$=6.1 Hz, H-3), 2.61

(m, 2H, H-$4_{A,B}$), 2.21 (m, 1H, H-2′), 0.88, 0.37 (2×d, 2×3H, $J_{2',3'}$=7.0 Hz, $J_{2',4'}$=6.7 Hz, H-3′, H-4′); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.8 (CO), 156.8 (CO), 137.4–128.8 (C–Ph), 79.7 [$C(CH_3)_3$], 77.7 (C-5), 66.5 (C-3), 62.7 (NCH_2Ph), 55.7 (C-1′), 52.8 ($COOCH_3$), 34.1 (C-4), 28.8 [$C(CH_3)_3$], 28.0 (C-2′), 20.7, 14.9 (C-3′, C-4′); for $C_{21}H_{32}N_2O_5$ (392.49) calcd C, 64.26, H, 8.22, N, 7.14; found: C, 64.05, H, 8.43, N, 6.95.

4.3.8. (3*S*,5*S*,1′*S*)-{2-Benzyl-3-[1′-(*tert*-butoxycarbonylamino)-2′-methylpropylidene]-isoxazolidin-5-yl}-carboxylic acid methyl ester (8b). The product **8b** was isolated by flash column chromatography on silica gel eluting with EtOAc/hexanes (15:85) as a colourless solid in 31% yield. Mp 72–74°C (from EtOAc/hexanes), $[\alpha]_D^{25}$=−44.5 ($CHCl_3$, *c* 0.2); ν_{max} (CCl_4) 3462, 1740, 1718, 1495, 1370, 1211, 1168 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.35 (m, 5H, H–Ph), 4.91 (d, 1H, $J_{1',NH}$=10.5 Hz, NH), 4.43 (app dd, 1H, $J_{4A,5}$=7.7 Hz, $J_{4B,5}$=9.4 Hz, H-5), 4.24, 3.71 (2×d, 2×1H, *J*=12.8 Hz, NCH_2Ph), 3.78 (s, 3H, $COOCH_3$), 3.60 (m, 1H, H-3), 3.20 (ddd, 1H, $J_{1',2'}$=2.1 Hz, $J_{3,1'}$=8.5 Hz, $J_{1',NH}$=10.5 Hz, H-1′), 2.85 (dt, 1H, $J_{3,4A}$=7.9 Hz, $J_{4A,5}$=7.7 Hz, $J_{4A,B}$=12.8 Hz, H-4_A), 2.45 (ddd, 1H, $J_{3,4B}$=1.7 Hz, $J_{4B,5}$=9.4 Hz, $J_{4A,B}$=12.8 Hz, H-4_B), 1.68 (m, 1H, H-2′), 0.83, 0.51 (2×d, 2×3H, $J_{2',3'}$=$J_{2',4'}$=6.8 Hz, H-3′, 4′); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.4 (CO), 156.5 (CO), 137.1–127.6 (C–Ph), 78.9 [$C(CH_3)_3$], 77.9 (C-5), 64.6 (C-3), 63.5 (NCH_2Ph), 60.2 (C-1′), 52.4 ($COOCH_3$), 36.3 (C-4), 31.0 (C-2′), 28.4 [$C(CH_3)_3$], 19.4 (C-3′, C-4′); for $C_{21}H_{32}N_2O_5$ (392.49) calcd C, 64.26, H, 8.22, N, 7.14; found: C, 64.57, H, 8.18, N, 6.91.

4.4. General procedure for reduction of 6a and 9b with DIBALH

A stirred solution of ester (0,21 mmol) in anhydrous THF (15 mL) was cooled to −10°C before dropwise adding of DIBALH (0.44 mL). The reaction was quenched after 1 h stirring at −10°C by addition of MeOH (~1 mL). The resulting mixture was poured into an 20% aqueous solution of potassium tartrate (30 mL) and allowed to stir for 30 min. Then CH_2Cl_2 (15 mL) was added to the mixture and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The organic layers were dried and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel. Chromatography conditions and physical properties of the products are shown below.

4.4.1. (3*R*,5*R*,1′*S*)-2-Benzyl-3-(1′-dibenzylamino-2′-methylpropylidene)-5-hydroxymethyl isoxazolidine (11a). The product **11a** was isolated by flash column chromatography on silica gel eluting with EtOAc/hexanes (20:80) as a colourless solid in 88% yield. Mp 98–99°C (from EtOAc/hexanes), $[\alpha]_D^{25}$=+50.5 ($CHCl_3$, *c* 0.5); ν_{max} (CCl_4) 3590, 1485, 1455, 1387, 1361, 1104 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.40 (m, 15H, H–Ph), 3.97 (s, 2H, NCH_2Ph), 3.85, 3.54 [2×d, 2×2H, *J*=12.8 Hz, $N(CH_2Ph)_2$], 3.68 (m, 2H, H-3, CH_AOH), 3.49 (m, 1H, H–CH_BOH), 3.40 (m, 1H, H-5), 2.89 (dd, 1H, $J_{3,4A}$=7.4 Hz, $J_{4A,B}$=12.2 Hz, H-4_A), 2.60 (d, 1H, $J_{3,1'}$=10.8 Hz, H-1′), 2.39 (m, 1H, $J_{2',3'}$=$J_{2',4'}$=6.8 Hz, H-2′), 2.30 (ddd, 1H, $J_{3,4B}$=6.7 Hz, $J_{4B,5}$=2.7 Hz, $J_{4A,B}$=12.2 Hz, H-4_B), 1.72 (br s, 1H, OH), 1.21, 1.12 (2×d, 2×3H, $J_{2',3'}$=$J_{2',4'}$=6.8 Hz, H-3′, 4′); ^{13}C NMR (75 MHz, $CDCl_3$): δ=139.9–127.3 (C–Ph), 80.1 (C-5), 66.0 (C-3), 64.9 (CH_2OH), 63.2 (NCH_2Ph), 59.9 (C-1′), 54.5 [$N(CH_2Ph)_2$], 31.2 (C-4), 25.8 (C-2′), 23.8, 19.4 (C-3′, C4′); for $C_{29}H_{36}N_2O_2$ (444.61) calcd C 78.34, H 8.16, N 6.30; found: C 78.17, H 8.31, N 6.42.

4.4.2. (3*R*,4*R*,1′*S*)-2-Benzyl-3-(1′-dibenzylamino-2′-methylpropylidene)-4-hydroxymethyl isoxazolidine (10b). The product **10b** was isolated by flash column chromatography on silica gel eluting with EtOAc/hexanes (20:80) as a colourless solid in 71% yield. Mp 167–168°C (from EtOAc/hexanes), ^{1}H NMR (500 MHz, $CDCl_3$/TMS): δ=7.33 (m, 15H, H–Ph), 4.26, 3.78 [2×d, 2×2H, *J*=12.9 Hz, H–$N(CH_2Ph)_2$], 4.11 (dd, 1H, $J_{5A,B}$=8.5 Hz, $J_{5A,4}$=8.2 Hz, H-5_A), 4.05, 3.97 (2×d, 2×2H, *J*=14.3 Hz, H–NCH_2Ph), 3.86 (dd, 1H, $J_{5A,B}$=8.5 Hz, $J_{5B,4}$=8.8 Hz, H-5_B), 3.43, 3.40 (2×dd, 2×1H, $J_{4,CH2}$=7.6 Hz, $J_{4,CH2}$=5.6 Hz, J_{CH2}=10.8 Hz, CH_2OH), 3.08 (app t, 1H, $J_{3,4}$=$J_{3,1'}$=5.3 Hz, H-3), 2.72 (m, 1H, H-4), 2.41 (dd, 1H, $J_{1',2'}$=7.6 Hz, $J_{1',3}$=5.0 Hz, H-1′), 2.20 (m, 1H, H-2′), 1.61 (br s, 1H, OH), 1.20, 0.88 (2×d, 2×3H, $J_{2',3'}$=6.7 Hz, $J_{2',4'}$=6.4 Hz, H-3′, 4′). ^{13}C NMR (125 MHz, $CDCl_3$/TMS): δ=141.1–126.7 (C–Ph), 69.5 (C-3), 68.0 (C-5), 63.7 (C-CH_2OH), 63.2 (C-1′), 61.3 (NCH_2Ph), 56.1 ($N(CH_2Ph)_2$), 49.6 (C-4), 33.0 (C-2′), 22.2, 21.7 (C-3′,4′); for $C_{29}H_{36}N_2O_2$ (444.61) calcd C 78.34, H 8.16, N 6.30; found: C 78.59, H 8.07, N 6.44.

4.4.3. (2*R*,4*R*,5*S*)-4,5-di-(*N*-*tert*-Butoxycarbonylamino)-6-methylheptane-1,2-diol (12). The alcohol **11a** was dissolved in MeOH, Pd/C and Boc_2O were added and the apparatus flushed three times with H_2. The reaction mixture was hydrogenated under atmospheric pressure at room temperature for 48 h, filtered through a pad of Celite and then concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 97:3) to give diamino diol **12** as colourless solid in 57% yield. Mp 184–185°C (from CH_2Cl_2/MeOH), $[\alpha]_D^{25}$=+6.9 (c=0.25, $CHCl_3$); ν_{max} (CCl_4) 3605, 3450, 3361, 1707, 1690, 1506, 1398, 1371, 1146 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/TMS)): δ=5.38, 4.55 (2×d, 2×1H, *J*=9.0 Hz, *J*=9.82 Hz, H–NH), 3.92 (m, 1H, H-4), 3.69 (m, 1H, H-2), 3.54 (dd, 1H, $J_{1,2}$=3.0 Hz, $J_{1A,B}$=11.1 Hz, H-1_A), 3.46 (m, 2H, H-1_B, H-5), 1.76 (m, 1H, H-6), 1.42 (s, 2×9H, H–$C(CH_3)_3$), 1.23 (m, 1H, H-3), 0.94, 0.88 (2×d, 2×3H, $J_{6,7}$=6.8 Hz, $J_{6,8}$=6.8 Hz, H-7, H-8), ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ=157.5, 156.8 (2C, C=O), 80.1, 79.8 (2C, $C(CH_3)_3$), 68.3 (C-2), 66.6 (C-1), 59.7 (C-5), 48.7 (C-4), 34.5 (C-3), 28.8 (C-6), 28.4 (2C, $C(CH_3)_3$), 19.9, 18.0 (2C, C-7, C-8), for $C_{18}H_{36}N_2O_3$ (376.49) calcd C 57.42, H 9.64, N 7.44; found: C 57.53, H 10.09, N 7.16.

4.5. X-Ray diffraction study

Crystallographic data for the structures **8a**,**10b** and **11a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 191162 (**8a**), CCDC 191163 (**11a**) and CCDC 191164 (**10b**). Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (email: deposit@ccdc.cam.ac.uk).

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References

1. (a) Tufariello, J. J. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley/Interscience: New York, 1984; p 83 Chapter 9. (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates*; VCH: New York, 1988. (c) Gothelf, K. V.; Jorgensen, K. V. *Chem. Rev.* **1988**, *98*, 863.
2. Frederickson, M. *Tetrahedron* **1997**, *53*, 403.
3. (a) Baggiolini, E. G.; Iacobelli, J. A.; Hennesy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098. (b) Brandi, A.; Cicchi, S.; Goti, A.; Pietrusiewicz, K. M. *Tetrahedron: Asymmetry* **1991**, *2*, 1063. (c) Saito, S.; Ishikawa, T.; Kishimoto, N.; Kohara, T.; Moriwake, T. *Synlett* **1994**, 282. (d) Kametani, T.; Chu, S. D.; Honda, T. *Heterocycles* **1987**, *25*, 241. (e) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1988**, *63*, 2371. (f) Bernet, B.; Vasella, A. *Helv. Chim. Acta.* **1979**, *62*, 2411.
4. Fišera, L.; Al-Timari, U. A. R.; Ertl, P. *Cycloadditions in Carbohydrate Chemistry*; *ACS Monograph*, ACS: Washington, 1992; p 158.
5. (a) Al-Timari, U. A. R.; Fišera, L.; Ertl, P.; Goljer, I.; Prónayová, N. *Monatsh. Chem.* **1992**, *123*, 999. (b) Kubán, J.; Blanáriková, I.; Fišera, L.; Prónayová, N. *Chem. Papers* **1997**, *51*, 378.
6. (a) Kubán, J.; Blanáriková, I.; Fengler-Veith, M.; Jäger, V.; Fišera, L. *Chem. Papers* **1998**, *52*, 780. (b) Blanáriková, I.; Dugovič, B.; Fišera, L.; Hametner, C. *ARKIVOC* **2001**, *2*, 1091.
7. (a) Kubán, J.; Blanáriková, I.; Fišera, L.; Jarošková, L.; Fengler-Veith, M.; Jäger, V.; KozÍšek, J.; Humpa, O.; Langer, V. *Tetrahedron* **1999**, *55*, 9501. (b) Kubán, J.; Kolarovic, A.; Fišera, L.; Jäger, V.; Humpa, O.; Prónayová, N.; Ertl, P. *Synlett* **2001**, 1862. (c) Kubán, J.; Kolarovic, A.; Fišera, L.; Jäger, V.; Humpa, O.; Prónayová, N. *Synlett* **2001**, 1866. (d) Fischer, R.; Drucková, A.; Fišera, L.; Rybár, A.; Hametner, C.; Cyranski, M. K. *Synlett* **2002**, 1113. (e) Fischer, R.; Drucková, A.; Fišera, L.; Hametner, C. *ARKIVOC* **2002**, *8*, 80.
8. Blanáriková, I.; Fišera, L.; Kopanicáková, Z.; Salanski, P.; Jurczak, J.; Hametner, C. *ARKIVOC* **2001**, *V*, 51.
9. (a) Shinigawa, S.; Tanamura, T.; Harada, S.; Asai, M.; Okazaki, H. *J. Med. Chem.* **1984**, *30*, 1458. (b) 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.
10. Yang, S.; Hayen, W.; Griegl, H. *Monatsh. Chem.* **1994**, *124*, 469.
11. Zimmermann, P. J.; Blanáriková, I.; Jäger, V. *Angew. Chem. Int. Ed.* **2000**, *39*, 910.
12. Lichtenthaler, F. W.; Jarglis, P.; Lorenz, K. *Synthesis* **1988**, 790.
13. Bunuel, E.; Gil, M. A.; Diaz-de-Villegas, M. D.; Cativiela, C. *Tetrahedron* **2001**, *57*, 6417.
14. Kuzuhara, H.; Ohrui, H.; Emoto, S. *Agric. Biol. Chem.* **1971**, *35*, 8.