Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 2711–2717

Rh(II)-carbenoid insertion into chiron substrates for stereoselective amino acid construction

Mioara Andrei, Christian Römming and Kjell Undheim*

Department of Chemistry, University of Oslo, N-0315 Oslo, Norway

Received 30 June 2004; accepted 14 July 2004

Abstract—Chemoselective and regioselective rhodium(II)-carbenoid insertion reactions have been used for the stereoselective preparation of novel α-cyclopentyl-α-quaternary α-amino acid derivatives. Regio and stereochemistry have been established by X-ray analysis.

1. Introduction

Cyclic α-amino acids with the α-carbon embedded in a ring have restricted conformational freedom when compared to the corresponding acyclic amino acids and can be regarded as belonging to a subclass of α-quaternary amino acids.[1,2] We have reported several methods for the preparation of cyclic α-quaternary α-amino acids.[3–5] In the most recent examples, the amino nitrogen was incorporated into the ring, the products being derivatives of proline and pipecolic acid.[6,7] The conformational freedom of the peptidic material will be significantly affected on insertion of quaternary α-amino acids. Hence the preparation and properties of this class of α-amino acids have attracted great attention.[1,2] Herein we report further results from rhodium carbenoid insertion reactions directed towards the synthesis of amino acid analogues.

2. Results and discussion

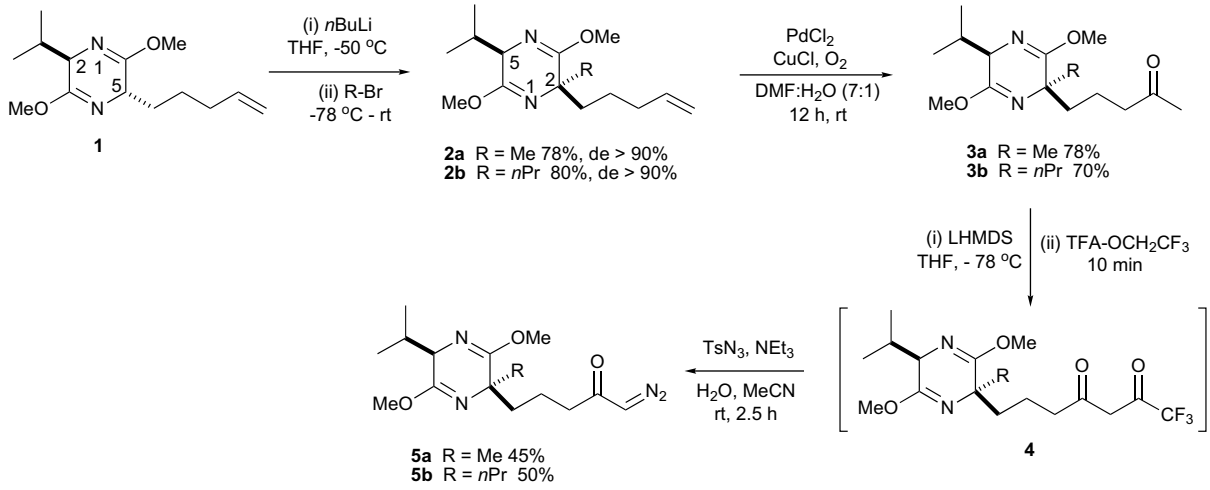
The cyclisation reactions in Scheme 2 were effected on diazoketone substrates using dirhodium tetraacetate as catalyst. The synthesis of the appropriate diazo substrates for the ring formation is shown in Scheme 1. Metallation in substrate **1** can in principle occur at either the 2- or 5-alkylated position. The metallation is fully regioselective for the 5-position because the branching at the α-carbon of the 2-isopropyl group leads to full shielding of the 2-position on the ring. Once lithiated, the new alkylating agent approaches the carbanionic site at C-5 in a *trans* manner with reference to the isopropyl group providing the *gem*-dialkylated products **2** with high diastereoselectivity. Pure stereomers were obtained after flash chromatography on silica gel. The pure stereomers **2** were used in the subsequent work.

Methyl ketones **3** became available via a chemoselective Wacker oxidation. The vinyl moiety in structures **2** served as a precursor, or indirectly as a protective function for the oxo group. Satisfactory yields were obtained under the Wacker conditions without any significant interference from the functionalities in the heterocycle. For the preparation of diazomethyl ketones **5**, the keto methyl group in substrate **3** was initially activated by a reaction with trifluoroethyl trifluoroacetate (TFEA) by analogy to the methodology described by Danheiser and Doyle.[8,9] The acylation was carried out with 1 equiv of base in a reaction with TFEA at −78 °C for 10 min. The product is formulated as structure **4**, which was reacted further in situ with tosyl azide in acetonitrile containing water and triethylamine at ambient temperature. α-Diazo ketones **5** were obtained in moderate overall chemical yields, in the range 45–50%.

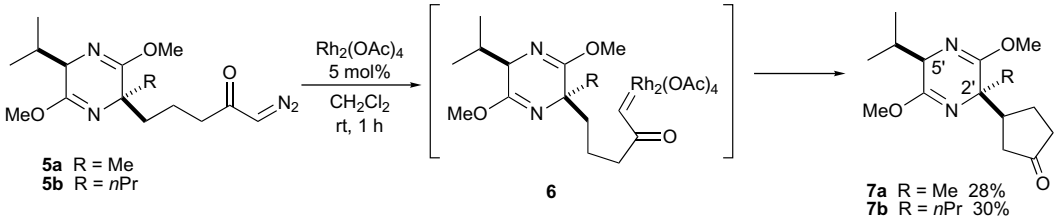
The carbenoid insertion reactions in Scheme 2 were effected using 5 mol% dirhodium tetraacetate in dichloromethane at ambient temperature for 1 h under an argon atmosphere. Intramolecular Rh(II)-carbenoid C–H insertions are in favour of five-membered ring formation. Other ring sizes are less common in the absence

* Corresponding author. Tel.: +47 22 85 55 21; fax: +47 22 85 55 07; e-mail: kjell.undheim@kjemi.uio.no

0957-4166/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2004.07.030



Scheme 1.



Scheme 2.

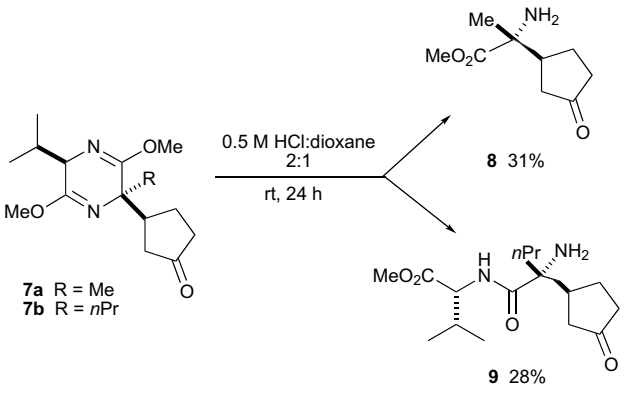
of specially activating heteroatom functions or for stereochemical reasons.[10,11] We have in earlier work observed exclusive five- and six-membered ring formation involving the adjacent annular nitrogen atom.[6,7] In the present case, annulation to the adjacent nitrogen atom would have yielded a seven-membered ring structure. C–H insertion at the α-carbon in the R-group would also lead to an unfavourable seven-membered ring formation. In substrates **5** however, C–H insertion into the functionalised diazopentyl chain can lead to five-membered ring formation (Scheme 2) with the products being cyclopentyl derivatives **7**. No other insertion products were isolated.

The carbenoid insertion was stereoselective with only one stereoisomer being obtained in the insertion at the methylene carbon. The outcome can be rationalised by steric induction from the isopropyl group, which has a *cis* relationship with respect to the reactive diazoketo chain. The heterocycle presumably has an almost planar conformation with the reactive chain pointing out almost in the plane. Preferential carbenoid insertion into the methylene unit from the higher face in a conformation as drawn in structure **6** would provide stereomers **7**.

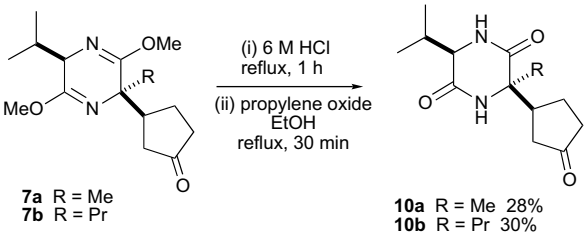
The configuration at the new stereogenic centre in the cyclopentane ring was determined by single crystal X-ray analysis. The substrate for the X-ray analysis was **10b**, a crystalline derivative, which became available after additional reactions, which did not involve the new stereogenic centre (Scheme 4).

Hydrolysis of bislactim ethers into the component amino acid derivatives is best achieved under very mild acidic conditions.[12] However, the course of the hydrolytic reaction is highly sensitive to steric interactions from α-substituents. Herein, 0.5 M HCl in dioxane at ambient temperature provided the α-cyclopentyl-α-alanine methyl ester **8** from methyl substrate **7a**. The higher steric shielding in the propyl homologue **7b** prevented full cleavage (Scheme 3). The product isolated was dipeptide **9**, which was formed by a ring-opening reaction at the less shielded iminoether function at C-6 in substrate **7b**. The second iminoether function formed a peptide bond. For comparison, cleavage of analogues lacking the 2-R substituent in structures **7** proceeds readily in the desired fashion under mild acidic conditions.[13–15] Substrates **7** with R = H were prepared by conjugated addition of the bislactim ether as a copper reagent to 2-cyclopenten-1-one. The adducts were intermediates in the preparation of amino acid derived medicinals.[14,15] Our Rh(II)-approach would provide additional α-substituted analogues.

In contrast to the hydrolytic reaction under mild acidic conditions, hydrolysis under strongly acidic conditions takes another course in that the initial product is the corresponding 2,5-diketopiperazine, which requires drastic acid conditions for further hydrolysis into its amino acid components.[16] In the present work, when bisiminoether substrates **7** were heated with 6 M HCl for 1 h, diketopiperazines **10** were isolated (Scheme 4).



Scheme 3.



Scheme 4.

Diketopiperazines **10** were obtained as solids. Single crystal X-ray analysis of the propyl derivative showed its structure to be **10b**. This established the configuration at the stereogenic centre in the cyclopentane ring. The ORTEP plot of the X-ray structure of compound **10b** is shown in Figure 1. No configurational changes are likely in its formation from the carbenoid insertion product under mild hydrolytic conditions. The latter was therefore assigned as structure **7b**. Reaction conditions in the formation of the methyl and propyl insertion products **7** and their spectroscopic data are closely similar. Hence the methyl insertion product has been assigned the same configuration **7a** as its propyl homologue **7b**.

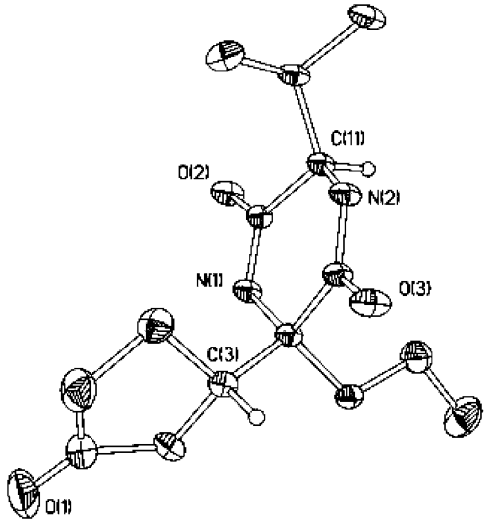


Figure 1. The ORTEP plot of compound **10b**. Ellipsoids are shown at 50% probability. For clarity only the hydrogen atoms at the stereogenic centres C(3) and C(11) are shown.

3. Conclusion

In conclusion, we have demonstrated chemoselective and regioselective rhodium(II)-carbenoid insertion reactions, which are useful for stereoselective preparations of novel α-cyclopentyl-α-quaternary α-amino acid derivatives.

4. Experimental

^{1}H NMR spectra were recorded in $CDCl_3$ at 500, 300 or 200 MHz with Bruker DPX 500, DPX 300 or DPX 200. The ^{13}C spectra were recorded in $CDCl_3$ at 125 MHz with a Bruker DPX 500, at 75 MHz with DPX 300 and at 50 MHz with a Bruker DPX 200 instrument. NMR techniques such as DEPT, COSY, HETCOR, COLOC were used. Chemical shifts are reported in parts per million with residual $CHCl_3$ (7.24 ppm) and $CDCl_3$ (77 ppm) as references. *J*-values are given in hertz. Mass spectra under electron-impact conditions (EI) were recorded at 70 eV ionising potential, methane was used for chemical ionisation (CI). The spectra are presented as *m*/*z* (% rel int.). IR spectra were measured on a Perkin–Elmer 1310 infrared spectrophotometer or a Nicolet Magna 550 spectrometer using ATR (attenuated total reflectance). Optical rotations are given in 10^{-1} deg cm^2 g^{-1}. Dry THF was distilled from sodium and benzophenone under argon.

4.1. X-ray crystallographic analysis for compound 10b

X-ray data were collected on a Siemens SMART CCD diffractometer[17] using graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). Data collection method: ω-scan, range 0.6°, crystal to detector distance 5 cm. Data reduction and cell determination were carried out with the SAINT and XPREP programs.[17] Absorption corrections were applied by the use of the SADABS program.[18] The structure was determined and refined using the SHELXTL program package.[19] The nonhydrogen atoms were refined with anisotropic thermal parameters; hydrogen atoms were located from difference Fourier maps and refined with isotropic thermal parameters. Structural data have been deposited at the Cambridge Crystallographic Data Centre, deposition number CCDC 239933.

4.1.1. Crystal data for $C_{15}H_{24}N_2O_3$ 10b. $M = 280.36$, monoclinic, $P2_1$, $a = 6.147(1)$, $b = 14.671(1)$, $c = 8.650(1)$ Å, $\beta = 97.90(1)°$, $V = 772.7(1)$ Å^3, $Z = 2$, $D_x = 1.205$ mg m^{-3}, $\mu = 0.084$ mm^{-1}, $T = 105(2)$ K, measured 13417 reflections in 2θ range 4.8–56.6°, $R_{int} = 0.023$. Two hundred and seventy seven parameters refined against 3789 F^2, $R = 0.030$ for $I_o > 2\sigma(I_o)$ and 0.031 for all data.

4.2. (2*R*,5*R*)-5-Isopropyl-3,6-dimethoxy-2-methyl-2-(4-pent-4-enyl)-2,5-dihydropyrazine 2a

n-BuLi (7.75 mL, 12.44 mmol, 1.6 M in hexane) was added to a solution of (2*R*,5*S*)-2-isopropyl-3,6-dimethoxy-5-(pent-4-enyl)-2,5-dihydropyrazine[20] **1** (2.850 g, 11.31 mmol) in dry THF (30 mL) under argon at −50 °C. The mixture was stirred for 30 min at this temperature, cooled to −78 °C and iodomethane (0.78 mL, 12.44 mmol) in THF (20 mL) added dropwise. The solution was left to return to room temperature overnight and quenched by the addition of 0.1 M phosphate buffer (pH 7, 25 mL). The two phases were separated, the aqueous phase extracted with diethyl ether (3 × 25 mL), the combined organic extracts dried over $MgSO_4$, evaporated and the crude product purified by flash chromatography on silica gel using 10% EtOAc in hexane, R_f 0.48. The product was a colourless oil; yield 2.34 g (78%, de >90%). HRMS(EI): *M* 266.1990. Calcd for $C_{15}H_{26}N_2O_2$: 266.1994. (Found: C, 68.01; H, 10.04. Calcd for $C_{15}H_{26}N_2O_2$: C, 67.63; H, 9.84%.) IR ν_{max} (film/cm^{-1}) 2960, 2945, 2875, 1694, 1642, 1463, 1435, 1380, 1300, 1235; δ_H ($CDCl_3$): 0.64 and 1.05 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 1.23 (3H, s, CH_3), 1.20–1.80 (4H, m, $CH_2CH_2CH_2CH{=}CH_2$), 1.95–2.01 (2H, m, $CH_2CH_2CH_2CH{=}CH_2$), 2.28–2.34 (1H, m, $CH(CH_3)_2$), 3.62 (3H, s, OCH_3), 3.63 (3H, s, OCH_3), 3.87 (1H, d, *J* 3.2, H-5), 4.86–4.99 (2H, m, $CH{=}CH_2$), 5.69–5.82 (1H, m, $CH{=}CH_2$); δ_C ($CDCl_3$): 16.9 and 19.5 ($CH(CH_3)_2$), 24.1 ($CH_2CH_2CH_2$), 28.72 (CH_3), 30.5 ($CH(CH_3)_2$), 33.7 and 40.1 ($CH_2CH_2CH_2$), 52.1 (2 × OCH_3), 58.2 (C-2), 60.3 (C-5), 114.1 ($CH{=}CH_2$), 138.9 ($CH{=}CH_2$), 161.7 and 165.7 (2 × C=N); MS(EI): 266 (46%, M), 252 (8), 251 (42), 223 (22), 209 (13), 197 (26), 194 (29), 155 (100), 140 (13), 124 (9).

4.3. (2*R*,5*R*)-5-Isopropyl-3,6-dimethoxy-2-(pent-4-enyl)-2-propyl-2,5-dihydropyrazine 2b

Compound **2b** was made as above from *n*-BuLi (9.51 mL, 12.65 mmol, 1.33 M in hexane), (2*R*,5*S*)-2-isopropyl-3,6-dimethoxy-5-(pent-4-enyl)-2,5-dihydropyrazine **1** (2.9 g, 11.50 mmol) in dry THF (30 mL) and the reaction mixture worked up as above. The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexane, R_f 0.53. The product was a colourless oil; yield 2.68 g (80%, de >90%). HRMS(EI): *M* 294.2293. Calcd for $C_{17}H_{30}N_2O_2$: 294.2302. (Found: C, 69.05; H, 10.08. Calcd for $C_{17}H_{30}N_2O_2$: C, 69.35; H, 10.27%.) IR ν_{max} (film/cm^{-1}) 2960, 2945, 2873, 1694, 1640, 1465, 1435, 1380, 1305, 1237; δ_H ($CDCl_3$): 0.64 and 1.04 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 0.76–1.90 (11H, m, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH{=}CH_2$), 1.92–1.99 (2H, m, $CH_2CH{=}CH_2$), 2.30–2.35 (1H, m, $CH(CH_3)_2$ 3.62 (3H, s, OCH_3), 3.63 (3H, s, OCH_3), 3.85 (1H, d, *J* 3.1, H-5), 4.85–4.98 (2H, m, $CH{=}CH_2$), 5.68–5.79 (1H, m, $CH{=}CH_2$); δ_C ($CDCl_3$): 14.1 ($CH_2CH_2CH_3$), 17.0 and 19.6 ($CH(CH_3)_2$), 17.3 ($CH_2CH_2CH_3$), 23.9 ($CH_2CH_2CH_2$), 30.6 ($CH(CH_3)_2$), 33.8 and 39.8 ($CH_2CH_2CH_2$), 43.5 ($CH_2CH_2CH_3$), 52.05 and 52.15 (2 × OCH_3), 60.7 (C-5), 62.1 (C-2), 114.1 ($CH{=}CH_2$), 139.0 ($CH{=}CH_2$), 162.3 and 164.4 (2 × C=N); MS(EI): 294 (71%, M), 279 (42), 251 (100), 225 (36), 222 (24), 197 (13), 183 (88), 154 (16).

4.4. (2′*R*,5′*R*)-5-(5-Isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)pentan-2-one 3a

Palladium dichloride (0.119 g, 0.673 mmol) and copper chloride (0.666 g, 6.73 mmol) in water (2.00 mL) and DMF (14.00 mL) were stirred together at room temperature for 1 h before (2*R*,5*R*)-5-isopropyl-3,6-dimethoxy-2-methyl-2-(4-pent-4-enyl)-2,5-dihydropyrazine **2a** (1.790 g, 6.73 mmol) was added. The mixture was stirred under oxygen at room temperature for 12 h and then extracted with diethyl ether. The organic layer was dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography on silica gel using hexane–EtOAc 5:1, R_f 0.24. The product was a colourless oil; yield 1.480 g (78%). HRMS(EI) 282.1946. Calcd for $C_{15}H_{26}N_2O_3$: 282.1943. (Found: C 63.48; H 8.9. Calcd for $C_{15}H_{26}N_2O_3$: C, 63.80; H, 9.28%.) IR ν_{max} (film/cm^{-1}) 2969, 2945, 2871, 1720, 1691, 1462, 1436, 1245, 1205, 1130, 1006; δ_H ($CDCl_3$): 0.63 and 1.05 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 1.21 (3H, s, CH_3), 1.22–1.85 (4H, m, $CH_2CH_2CH_2CO$), 2.06 (3H, s, $COCH_3$), 2.29–2.36 (3H, m, $CH(CH_3)_2$ and CH_2CO), 3.61 (3H, s, OCH_3), 3.62 (3H, s, OCH_3), 3.86 (1H, d, *J* 3.14, H-5); δ_C ($CDCl_3$): 16.8 and 19.5 ($CH(CH_3)_2$), 19.6 (CH_2) 28.6 and 29.5 (CH_3 and H_3CCO), 30.4 ($CH(CH_3)_2$), 39.8 (CH_2), 43.9 (CH_2), 52.2 (2 × OCH_3), 58.1 (C-2), 60.3 (C-5), 161.9 and 165.4 (C=N), 209.0 (C=O); MS(EI): 282 (28%, M), 267 (31), 197 (45), 155 (100), 85 (43), 43 (57).

4.5. (2′*R*,5′*R*)-5-(5-Isopropyl-3,6-dimethoxy-2-propyl-2,5-dihydropyrazin-2-yl)pentan-2-one 3b

Compound **3b** was prepared as above from palladium dichloride (0.169 g, 0.955 mmol), copper chloride (0.945 mg, 9.55 mmol) and (2*R*,5*R*)-5-isopropyl-3,6-dimethoxy-2-(pent-4-enyl)-2-propyl-2,5-dihydropyrazine **2b** (2.790 g, 9.55 mmol) in water (2.00 mL) and DMF (14.00 mL). The crude product was purified by flash chromatography on silica gel using hexane–EtOAc 5:1, R_f 0.22; yield 2.070 g (70%) of a colourless oil. HRMS(EI) *M* 310.2241. Calcd for $C_{17}H_{30}N_2O_3$: 310.2256. (Found: C 65.38; H 9.55. Calcd for $C_{17}H_{30}N_2O_3$: C, 65.77; H, 9.74%.) IR ν_{max} (film/cm^{-1}) 2969, 2945, 2870, 1718, 1690, 1460, 1245, 1206, 1006; δ_H ($CDCl_3$): 0.62 and 1.03 (2d, *J* 6.8, $CH(CH_3)_2$), 0.74–1.02 (5H, m, $CH_2CH_2CH_3$), 1.10–1.80 (6H, m, $CH_2CH_2CH_2CO$ and $CH_2CH_2CH_3$), 2.04 (3H, s, $COCH_3$), 2.28–2.33 (3H, m, $CH(CH_3)_2$ and CH_2CO), 3.60 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 3.82 (1H, d, *J* 3.2, H-5′); δ_C ($CDCl_3$): 14.0 (CH_3), 16.9 and 19.5 ($CH(CH_3)_2$), 17.2 (CH_2), 19.4 (CH_2), 29.4 (H_3CCO), 30.5 ($CH(CH_3)_2$), 39.6 (CH_2), 43.2 (CH_2), 43.9 (CH_2CO), 52.0 and 52.1 (2 × OCH_3), 60.6 (C-5′), 61.9 (C-2′), 162.5 and 164.0 (2 × C=N), 208.9 (C=O); MS(EI): 310 (10%, M), 295 (24), 281 (8), 268 (15), 267 (69), 238 (17), 225 (100), 183 (91), 167 (9).

4.6. (2′*R*,5′*R*)-1-Diazo-5-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)pentan-2-one 5a

n-BuLi (2.06 mL, 3.3 mmol, 1.6 M in hexane) was added to a solution of HMDS (0.691 mL, 3.3 mmol) in THF (10 mL) under argon at 0 °C. The solution was stirred at 0 °C for 10 min, cooled to −78 °C and a solution of (2′*R*,5′*R*)-5-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)pentan-2-one **3a** (0.850 g, 3.014 mmol) in THF (15 mL) added dropwise over 15 min. The mixture was stirred at −78 °C for 30 min before TFEA (0.447 mL, 3.3 mmol) was rapidly injected by means of a syringe. The reaction mixture was stirred at this temperature for 10 min and transferred to a separating funnel containing 5% aqueous HCl (20 mL) and diethyl ether (20 mL). The funnel was shaken, the layers separated, the aqueous layer extracted with diethyl ether (2 × 15 mL), the combined organic solutions washed with saturated aqueous NaCl (25 mL) and the solution evaporated. The residual oil was dissolved in MeCN (15 mL) and transferred to a three-necked flask. Subsequently, water (0.054 mL, 3.014 mmol) and triethylamine (0.628 mL, 4.5 mmol) were added followed by dropwise addition over 10 min of a solution of tosyl azide (0.886 g, 4.5 mmol) in MeCN (5 mL). The resultant mixture was stirred at room temperature for 2.5 h, the solvent distilled off, the residue dissolved in diethyl ether (10 mL) and the ether solution shaken with 5% aqueous NaOH (15 mL) and then with aqueous saturated NaCl (15 mL). The solution was dried over $MgSO_4$, evaporated and the residual material subjected to flash chromatography on silica gel using 20% EtOAc in hexane, R_f 0.20. The product was a yellow oily material, yield 0.418 g (45%); HRMS(EI): *M* 308.1839. Calcd for $C_{15}H_{24}N_4O_3$: 308.1843. ν_{max} (film/cm^{-1}) 2970, 2946, 2875, 2101, 1690, 1645, 1436, 1364, 1245, 1202, 1136, 1005; δ_H ($CDCl_3$): 0.64 and 1.06 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 1.23 (3H, s, CH_3), 1.25–1.89 (4H, m, $CH_2CH_2CH_2CO$), 2.26–2.34 (3H, m, $CH(CH_3)_2$ and $CH_2CH_2CH_2CO$), 3.62 and 3.64 (2 × 3H, 2s, 2 × OCH_3), 3.86 (1H, d, *J* 3.4, H-5′), 5.17 (1H, b s, CH=N_2); δ_C ($CDCl_3$): 16.9 and 19.5 (2 × CH_3), 20.7 (CH_2), 28.6 (CH_3), 30.5 ($CH(CH_3)_2$), 36.5 and 39.9 (2 × CH_2), 52.2 (2 × OCH_3), 53.2 (CH=N_2), 58.1 (C-2′), 60.3 (C-5′), 162.0 and 165.4 (2 × C=N), 195.0 (CO); *m*/*z* (EI) 308 (3%, M), 265 (23), 237 (28), 223 (9), 209 (20), 197 (29), 181 (8), 155 (100), 126 (11).

4.7. (2′*R*,5′*R*)-1-Diazo-5-(5-isopropyl-3,6-dimethoxy-2-propyl-2,5-dihydropyrazin-2-yl)pentan-2-one 5b

n-BuLi (4.45 mL, 7.13 mmol, 1.6 M in hexane) was added to a solution of HMDS (1.48 mL, 7.13 mmol) in THF (20 mL) under argon at 0 °C. The mixture was stirred for 10 min, the solution cooled to −78 °C and a solution of (2′*R*,5′*R*)-5-(5-isopropyl-3,6-dimethoxy-2-propyl-2,5-dihydropyrazin-2-yl)pentan-2-one **3b** (2.010 g, 6.48 mmol) in THF (15 mL) added dropwise over 15 min. The mixture was stirred at −78 °C for 30 min before TFEA (0.960 mL, 7.13 mmol) was rapidly injected by means of a syringe. The reaction mixture was stirred for 10 min and transferred to a separating funnel containing 5% aqueous HCl (40 mL) and diethyl ether (40 mL). The funnel was shaken, the layers separated, the aqueous layer extracted with diethyl ether (2 × 25 mL), the combined organic solutions washed with saturated aqueous NaCl (40 mL) and the solution evaporated. The residual oil was dissolved in MeCN (25 mL), and transferred to a three-necked flask. Subsequently, water (0.116 mL, 6.48 mmol) and triethylamine (1.352 mL, 9.72 mmol) were added followed by the dropwise addition over 10 min of a solution of tosyl azide (1.99 g, 9.72 mmol) in MeCN (10 mL). The resultant reaction mixture was stirred at ambient temperature for 2.5 h, the solvent distilled off, the residue dissolved in diethyl ether (10 mL) and the ether solution shaken with 5% aqueous NaOH (30 mL) and then with aqueous saturated NaCl (30 mL). The solution was dried over $MgSO_4$ evaporated and the residual material subjected to flash chromatography on silica gel using 20% EtOAc in hexane, R_f 0.15. The product was a yellow oily material; yield 1.088 g (50%); HRMS(EI): *M* 336.2158. Calcd for $C_{17}H_{28}N_4O_3$: 336.2161. ν_{max} (film/cm^{-1}) 2970, 2946, 2875, 2100, 1690, 1645, 1436, 1364, 1245, 1136, 1006; δ_H ($CDCl_3$): 0.64 and 1.05 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 0.77–1.04 (5H, m, $CH_2CH_2CH_3$), 1.25–1.83 (6H, m, $CH_2CH_2CH_2COCHCN_2$ and $CH_2CH_2CH_3$), 2.25–2.40 (3H, m, $CH(CH_3)_2$ and $CH_2CH_2CH_2COCHN_2$), 3.62 and 3.64 (2 × 3H, 2s, 2 × OCH_3), 3.84 (1H, d, *J* 3.4, H-5′), 5.17 (1H, b s, CH=N_2); δ_C ($CDCl_3$): 14.0 (CH_3), 16.9 and 19.5 ($CH(CH_3)_2$), 17.2 (CH_2), 20.5 (CH_2), 30.5 ($CH(CH_3)_2$), 35.2, 39.63 and 43.3 (3 × CH_2), 52.1 and 52.2 (2 × OCH_3), 54.1 (CH=N_2), 60.7 (C-5′), 61.9 (C-2′), 162.6 and 164.0 (2 × C=N), 195.0 (CO); *m*/*z* (EI) 336 (5%, M), 308 (17), 293 (24), 223 (40), 195 (13), 197 (43), 183 (62), 155 (100), 55 (32).

4.8. (2′*R*,3*S*,5′*R*)-3-(5-Isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)cyclopentan-1-one 7a

A solution of (2′*R*,5′*R*)-1-diazo-5-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)pentan-2-one **5a** (0.340 g, 1.10 mmol) in dry dichloromethane (20 mL) was added dropwise to a solution of $Rh_2(OAc)_4$ (0.025 g, 0.055 mmol) in dry dichloromethane (30 mL) under argon at room temperature. The mixture was stirred at room temperature for 1 h before the solution was evaporated to dryness at reduced pressure. The residual material was subjected to flash chromatography on silica gel using EtOAc–CH_2Cl_2 1:6, R_f 0.5. The product was a colourless oil; yield 0.086 g (28%); HRMS(EI): *M* 280.1791. Calcd for $C_{15}H_{24}N_2O_3$: 280.1786. (Found: C, 64.54; H, 8.39. Calcd for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63%.) $[\alpha]_D^{20} = -78.5$ (*c* 0.6, CH_2Cl_2); ν_{max} (film/cm^{-1}) 2965, 2855, 1732, 1681, 1456, 1435, 1290, 1241, 1205. δ_H ($CDCl_3$): 0.62 and 1.07 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 1.20 (1H, s, CH_3), 1.38–1.42 (1H, m, CHC*H*HCHHCO), 1.72–1.74 (1H, m, CHCHHC*H*HCO), 2.10–2.27 (3H, m, CHCH*H*CHHCO, CHCHHCH*H*CO and CHC*H*HCO), 2.35–2.39 (1H, m, $CH(CH_3)_2$), 2.53–2.63 (1H, m, CHCH*H*CO), 2.73–2.78 (1H, m, CH), 3.59 (3H, s, OCH_3), 3.67 (1H, s, OCH_3), 3.86 (1H, d, *J* 3.6, H-5′); δ_C ($CDCl_3$): 16.6 and 19.6 ($CH(CH_3)_2$), 24.9 ($CHCH_2CH_2CO$), 27.2 (CH_3), 30.2 ($CH(CH_3)_2$), 38.3 and 39.1 (CH_2COCH_2), 43.9 (CH), 52.3 and 52.4

($2\times OCH_3$), 58.7 (C-2′), 59.9 (C-5′), 162.6 and 165.1 ($2\times C{=}N$), 219.8 (CO); *m/z* (EI) 280 (7%, M), 265 (16), 237 (7), 208 (18), 197 (46), 181 (8), 156 (9), 155 (100), 55 (10).

4.9. (2′*R*,3*S*,5′*R*)-3-(5-Isopropyl-3,6-dimethoxy-2-propyl-2,5-dihydropyrazin-2-yl)cyclopentan-1-one 7b

A solution of (2′*R*,5′*R*)-1-diazo-5-(5-isopropyl-3,6-dimethoxy-2-propyl-2,5-dihydropyrazin-2-yl)pentan-2-one **5b** (0.900 g, 2.67 mmol) in dry dichloromethane (50 mL) was added dropwise to a solution of $Rh_2(OAc)_4$ (0.059 g, 0.133 mmol) in dry dichloromethane (40 mL) under argon at room temperature. The mixture was stirred at room temperature for 1 h, the solution evaporated to dryness at reduced pressure and the residual material subjected to flash chromatography on silica gel using EtOAc–CH_2Cl_2 1:6, R_f 0.42. The product was a colourless oil; yield 0.246 g (30%); HRMS(EI): *M* 308.2097. Calcd for $C_{17}H_{28}N_2O_3$: 308.2099. (Found: C, 66.48; H, 8.99. Calcd for $C_{17}H_{28}N_2O_3$: C, 66.20; H, 9.15%.) $[\alpha]_D^{20} = -71.3$ (*c* 0.4, CH_2Cl_2) ν_{max} (film/cm^{-1}); 2968, 2857, 1732, 1680, 1459, 1435, 1291, 1241, 1203; δ_H ($CDCl_3$): 0.62 and 1.07 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 0.79–1.06 (5H, m, $CH_2CH_2CH_3$), 1.37–1.80 (4H, m, $CH_2CH_2CH_3$ and $CHCH_2CH_2CO$), 2.07–2.28 (3H, m, $CHCH_2CH_2CO$ and CHCHHCO), 2.30–2.42 (1H, m, $CH(CH_3)_2$), 2.51–2.62 (1H, m, CHCHHCO), 2.70–2.78 (1H, m, CH), 3.58 (3H, s, OCH_3), 3.66 (1H, s, OCH_3), 3.84 (1H, d, *J* 3.6, H-5′); δ_C ($CDCl_3$): 14.0 (CH_3), 16.8 and 19.5 ($CH(CH_3)_2$), 17.3 ($CH_2CH_2CH_3$), 24.8 ($CHCH_2CH_2CO$), 30.3 ($CH(CH_3)_2$), 38.2, 39.2 and 42.0 (CH_2COCH_2 and $CH_2CH_2CH_3$), 44.1 (CH), 52.21 and 52.3 ($2\times OCH_3$), 60.5 (C-5′), 62.6 (C-2′), 163.1 and 163.4 ($2\times C{=}N$), 219.8 (CO); *m/z* (EI) 308 (8%, M), 293 (16), 265 (26), 236 (14), 225 (69), 223 (60), 183 (100), 55 (16).

4.10. (1′*S*,2*R*)-2-Amino-2-(3-oxocyclopent-1-yl)propanoic acid methyl ester 8

HCl (0.5 M, 2 mL, 1 mmol) was added to a solution of (2′*R*,3*S*,5′*R*)-3-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)cyclopentan-1-one **7a** (0.140 g, 0.5 mmol) in dioxane (1 mL). The mixture was stirred at ambient temperature for 24 h and the pH adjusted to 10 by the addition of aq ammonia. The mixture was extracted with dichloromethane (3×5 mL), and the extracts dried over $MgSO_4$ and evaporated. The title compound was isolated after flash chromatography on silica gel using CH_2Cl_2–MeOH 20:1, R_f 0.17; yield 0.028 g (31%); HRMS(CI-CH_4): M+H 186.1138. $C_9H_{15}N_1O_3$+H requires 186.1130; $[\alpha]_D^{20} = -50.5$ (*c* 0.53, CH_2Cl_2); ν_{max} (film/cm^{-1}) 3409, 2961, 1732, 1660, 1652, 1523, 1456, 1260; δ_H ($CDCl_3$): 1.29 (1H, s, CH_3), 1.51–2.53 (9H, m, CH, CH_2CH_2CO, CH_2CO and NH_2), 3.76 (3H, s, CO_2CH_3); δ_C ($CDCl_3$): 23.9 ($CHCH_2CH_2CO$), 25.1 (CH_3), 38.6 and 39.3 (CH_2COCH_2), 45.2 (CH), 52.4 (OCH_3), 58.5 (C-2), 175.3 (CO_2CH_3), 218.6 (CO); *m/z* (CI) 186 (66%, M^++H), 174 (31), 169 (17), 168 (6), 141 (10), 126 (100), 109 (23), 102 (40).

4.11. (1″*S*,2*R*,2′*R*)-2-[2-Amino-2-(3-oxocyclopent-1-yl)pentanoylamino]-3-methylbutyric acid methyl ester 9

HCl (0.5 M, 2 mL, 1 mmol) was added to a solution of (2′*R*,3*S*,5′*R*)-3-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)cyclopentan-1-one **7b** (0.155 g, 0.5 mmol) in dioxane (1 mL). The mixture was stirred at ambient temperature for 24 h before the pH was adjusted to 10 by the addition of aq ammonia. The mixture was extracted with dichloromethane (3×5 mL), and the extracts dried over $MgSO_4$ and evaporated. The title compound was isolated after flash chromatography on silica gel using CH_2Cl_2–MeOH 20:1, R_f 0.50; yield 0.040 g (25%); HRMS(CI-CH_4): M+H 313.2132. $C_{16}H_{28}N_2O_4$+H requires 313.2127; $[\alpha]_D^{20} = -13.6$ (*c* 0.28, CH_2Cl_2); ν_{max} (film/cm^{-1}); 3367, 3327, 2962, 2874, 1740, 1660, 1652, 1506, 1467, 1437, 1209; δ_H ($CDCl_3$): 0.83 and 0.93 (9H, m, $CH(CH_3)_2$ and $CH_2CH_2CH_3$), 1.10–2.34 (13H m, $CH_2CH_2CH_3$, CH, CH_2CH_2CO, CH_2CO and NH_2), 2.70–2.85 (1H, m, CH), 3.71 (3H, s, CO_2CH_3), 4.42–4.48 (1H, dd, *J* 9.0, 4.8, NHCH), 8.06 (1H, bd, *J* 7.2, NH); δ_C ($CDCl_3$): 14.3 (CH_3), 16.9 and 19.25 ($2\times CH_3$), 17.75 ($CH_2CH_2CH_3$), 23.8 ($CHCH_2CH_2CO$), 30.75 ($CH(CH_3)_2$), 38.6, 39.05 and 42.5 (CH_2COCH_2 and $CH_2CH_2CH_3$), 44.9 (CH), 52.05 (OCH_3), 57.0 (CHNH), 62.1 (C-2), 172.3 (CO_2CH_3), 217.6 (CO); *m/z* (CI) 313 (78%, M^++H), 281 (2), 253 (3), 229 (3), 155 (10), 154 (100), 111 (3), 95 (3).

4.12. (1′*S*,3*R*,6*R*)-6-Isopropyl-3-methyl-3-(3-oxocyclopent-1-yl)piperazine-2,5-dione 10a

A solution of (2′*R*,3*S*,5′*R*)-3-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)cyclopentan-1-one **7a** (0.100 g, 0.35 mmol) in THF (1 mL) was added to 6 M HCl (3 mL) and the mixture refluxed for 1 h. The solvents were removed under reduced pressure, and the residue dissolved in ethanol (3 mL). Propylene oxide (1 mL) was added to the solution, the mixture heated under reflux for 30 min, the solvents removed under reduced pressure and the residue subjected to flash chromatography using hexane–EtOAc–AcOH 5:5:1. The product was a white solid with mp 256–259 °C (dec), R_f 0.51; yield 0.025 g (28%). (Found: C 62.04; H 8.13. Calcd for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99%.) δ_H (CF_3CO_2D–$CDCl_3$): 1.02 and 1.18 (6H, 2d, *J* 7.1, $CH(CH_3)_2$), 1.29 (3H, s, CH_3), 2.02–2.11 (2H, m, $CHCH_2CH_2CO$), 2.37–2.68 (5H, m, $CHCH_2CH_2CO$, $CHCH_2CO$ and $CH(CH_3)_2$), 3.01–3.10 (1H, m, $CHCH_2CO$), 4.32 (1H, d, *J* 2.8, H-6); δ_C (CF_3CO_2D–$CDCl_3$): 15.9 and 17.6 ($CH(CH_3)_2$), 24.5 ($CHCH_2CH_2CO$), 28.3 (CH_3), 32.35 ($CH(CH_3)_2$), 38.8 and 39.2 (CH_2COCH_2), 45.7 (CH), 60.75 (C-6), 66.1 (C-3), 172.6 and 172.75 ($2\times CONH$), 227.4 (CO).

4.13. (1′*S*,3*R*,6*R*)-6-Isopropyl-3-(3-oxocyclopent-1-yl)-3-propylpiperazine-2,5-dione 10b

A solution of (2′*R*,3*S*,5′*R*)-3-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)cyclopentan-3-one **7b** (0.155 g, 0.5 mmol) in THF (1 mL) was added to 6 M HCl (3 mL) and the mixture heated under reflux for

30 min. The solvents were removed under reduced pressure and the residue was dissolved in ethanol (3 mL). Propylene oxide (1 mL) was added to the solution and the mixture heated under reflux for 1 h before the solvents were distilled off under reduced pressure. The residual material was subjected to flash chromatography on silica gel using hexane–EtOAc–AcOH 5:5:1. The product was a white solid, R_f 0.58; mp >300 °C (dec); yield 0.042 g (30%). (Found: C 63.96; H 8.59. Calcd for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63%.) $[\alpha]_D^{20} = -14.6$ (*c* 0.38, AcOH); δ_H (CF_3CO_2D–$CDCl_3$): 0.98–1.01 (3H, t, *J* 7.3, $CH_2CH_2CH_3$), 1.03 and 1.18 (6H, 2d, *J* 7.1, $CH(CH_3)_2$), 1.29–1.51 (2H, m, $CH_2CH_2CH_3$), 1.70–1.75 (1H, m, $CHHCH_2CH_3$), 2.02–2.24 (3H, m, $CHHCH_2CH_3$ and $CHCH_2CH_2CO$), 2.41–2.75 (5H, m, $CHCH_2CH_2CO$, $CHCH_2CO$ and $CH(CH_3)_2$), 3.01–3.13 (1H, m, $CHCH_2CO$), 4.34 (1H, d, *J* 2.8, H-6); δ_C (CF_3CO_2D–$CDCl_3$): 12.6 (CH_3), 15.7 and 17.9 ($CH(CH_3)_2$), 17.6 ($CH_2CH_2CH_3$), 24.7 ($CHCH_2$-CH_2CO), 32.2 ($CH(CH_3)_2$), 38.8, 39.2 and 42.0 (CH_2COCH_2 and $CH_2CH_2CH_3$), 45.8 (CH), 60.75 (C-6), 65.8 (C-3), 172.65 and 172.8 (2 × CONH), 227.25 (CO).

References

1. Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599.
2. Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732.
3. Møller, B.; Undheim, K. *Eur. J. Org.* **2003**, 332–336.
4. Hammer, K.; Undheim, K. *Tetrahedron: Asymmetry* **1998**, *9*, 2359–2368.
5. (a) Hoven, G. B.; Efskind, J.; Rømming, C.; Undheim, K. *J. Org. Chem.* **2002**, *67*, 2459–2463, 2703; (b) Efskind, J.; Römming, C.; Undheim, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2697–2703.
6. Andrei, M.; Efskind, J.; Viljugrein, T.; Römming, C.; Undheim, K. *Tetrahedron: Asymmetry* **2004**, *15*, 1301–1313.
7. Andrei, M.; Römming, C.; Undheim, K. *Tetrahedron: Asymmetry* **2004**, *15*, 1359–1370.
8. (a) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G. *Org. Synth.* **1996**, *73*, 134–143; (b) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959–1964.
9. Doyle, M. P.; Mckervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Comounds. From Cyclopropanes to ylides*; Wiley–Interscience: New York, 1998; pp 15–17.
10. Taber, D. F.; Petty, E. H.; Ramon, K. *J. Am. Chem. Soc.* **1985**, *107*, 196–199; Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808–4809.
11. (a) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765–1808; (b) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296–3305.
12. (a) Schöllkopf, U. *Tetrahedron* **1983**, *39*, 2085–2091; (b) Beulshausen, T.; Groth, U.; Schöllkopf, U. *Liebigs Ann. Chem.* **1991**, 1207–1209.
13. Schöllkopf, U.; Pettig, D.; Schulze, E.; Klinge, M.; Egert, E.; Benecke, B.; Noltemeyer, M. *Angew. Chem.* **1988**, *100*, 1238–1239.
14. Eustache, J.; Grob, A.; Larn, C.; Sellier, O.; Schulz, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2961–2966.
15. Ashton, W. T.; Dong, H.; Sisco, R. M.; Doss, G. A.; Leiting, B.; Patel, R. A.; Wu, J. K.; Marsilio, F.; Thornberry, N. A.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 859–863.
16. Bull, S. D.; Davies, S. G.; Epstein, S. W.; Leech, M. A.; Ouzman, J. V. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2321–2330.
17. SMART and SAINT Area Detector Control and Integration Software Version 5.054. Bruker Analytical X-ray Instruments Inc., Madison, Wisconsin, USA, 1998.
18. Sheldrick, G. M. SADABS Version 2.01. Program for Empirical Correction of Area Detector Data, University of Göttingen, Germany, 2000.
19. Sheldrick, G. M. SHELXTL, Structure Determination Programs Version 5.10. Bruker Analytical X-ray Instruments Inc., Madison, Wisconsin, USA, 1997.
20. Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 2309–2322.