Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 2359–2368

TETRAHEDRON: *ASYMMETRY*

Hydroxymethylated cyclic α-amino acid dipeptides by ruthenium ring closing metathesis

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Received 8 May 1998; accepted 19 June 1998

Abstract

Stereoselective syntheses of cyclic α-amino-β-hydroxymethylcyclohexene-α-carboxylic acids are described. The acids were isolated as dipeptides. RCM reactions were effected by Ru(II)-catalysis on hydroxymethylated dienes. The diene substrates were available in stereochemically pure form by stepwise alkylations of (*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine with 4-bromo-1-butene and vinyloxirane.

1. Introduction

In recent reports we have described syntheses of rigidified cyclic α-amino acids *via* Ru(II)-catalyzed ring closing metathesis (RCM) reactions.[1,2] In particular, synthesis of α-amino-β-hydroxy acids has been described where the α-carbon of the amino acid was incorporated into a carbocyclic ring structure. The products can be regarded as conformationally rigid analogues of the amino acids serine or threonine.[2] In this report we describe syntheses of conformationally restricted homoserine analogues which have the hydroxy group located in a side chain corresponding to an α-amino acid γ-carbon, the target molecules being hydroxymethyl derivatives.

2. Results and discussion

By analogy to previous work, the bislactim ether (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine was used to establish the desired stereochemistry at what is going to become the α-carbon in the new amino acid.[1,2] The relevant substrates **5** and **6** for the cyclization reactions eventually leading to cyclic amino acids, were available from alkylation reactions of the lithiated bislactim ether **1** with vinyloxirane

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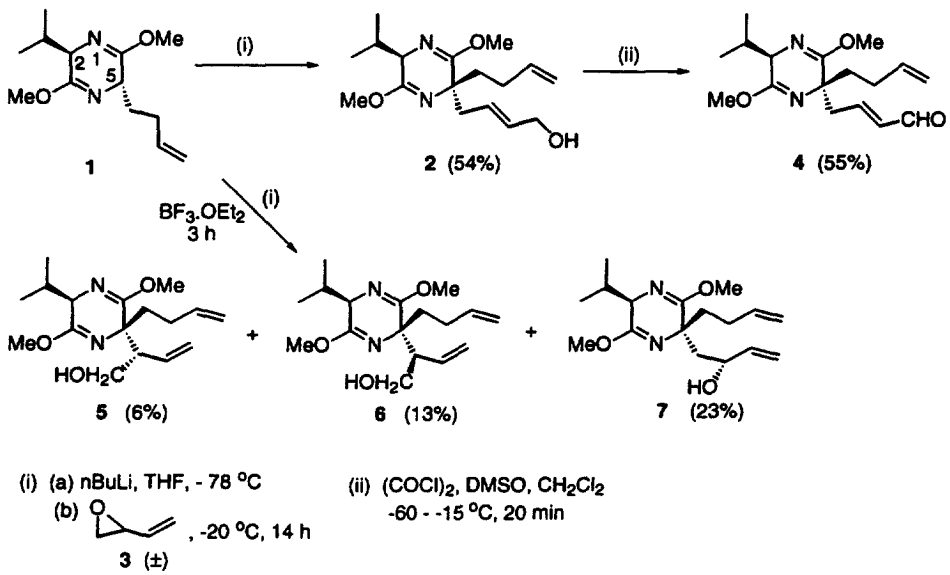
0957-4166/98/$ - see front matter
PII: S0957-4166(98)00248-1

(3; Scheme 1). Alkylation reactions of 2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine and homologues are generally carried out on the lithiated species at low temperature. With vinyloxirane as the alkylating agent, the major product was the allylic alcohol **2**. Its configurational assignment was based on NMR data. ^{13}C NMR showed that the allylic alcohol product was stereochemically homogeneous. Extensive overlap of the olefin proton signals, however, precluded chemical shift and coupling assignments. This was overcome by a successful Swern oxidation to furnish the α,β-unsaturated aldehyde **4**. Chemical shift assignments and proton decoupling experiments of the oxidation product were used to elucidate the configuration of the double bond. The vicinal coupling J=16 Hz is consistent with the *E*-configuration of structure **4**. Hence the allylic alcohol has the *E*-configuration **2**.



Scheme 1.

High stereoselectivity in the second alkylation at C-5 in the bislactim ether is generally the rule as we and previous workers have found on a number of occasions.[1,3] The butenyl and isopropyl groups have a *trans* relationship in this product and hence (*S*)-configuration was generated in the C-5 position.

The formation of the 1,4-addition product **2** corresponds to an S_N2' reaction. This reaction path is not uncommon in ring opening reactions of vinyloxirane. Invariably, with lithiated reactants the conjugated reaction path is important; methyllithium as a hard nucleophile attacks competitively the epoxide carbons whereas stabilized lithiated species undergo mainly conjugate addition.[4] The lithiated bislactim ether is an electronically stabilized species and hence a relatively soft nucleophile which therefore favours conjugate addition with formation of the allylic alcohol **2**. In palladium catalyzed reactions with organometallics,[5] and in reactions with organocopper reagents,[6] conjugate addition is also the mode of reaction.

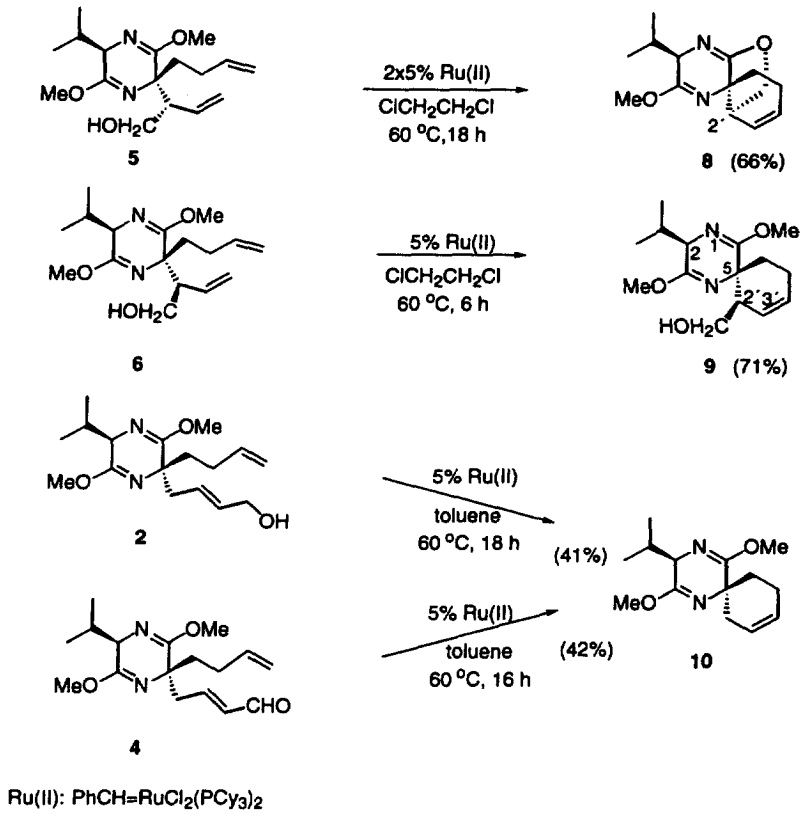
In an effort to change the regiochemistry in the ring opening of vinyloxirane, Lewis acid catalysis was applied. Titanium tetraisopropoxide, however, did not change the course of reaction away from the conjugated addition path. Epoxides as alkylating agents of bislactim ethers have been reported to undergo ring opening at the least substituted epoxide carbon when BF_3-etherate was the Lewis acid catalyst.[7] In the present case, when the reaction of the lithiated bislactim ether **1** was run at −78°C with BF_3-etherate present, the S_N2' reaction was completely subdued. The products were formed from nucleophilic attack at the epoxide carbons.

Acid catalysis in opening of epoxides normally favours nucleophilic attack at the more stabilized incipient carbonium ion which corresponds to the allylic C-2 carbon in vinyloxirane. This may, however, be counteracted by steric interactions between the bulky lithiated bislactim ether **1** and the more substituted electrophilic carbon of the epoxide. The products from the reaction were formed by attack at either epoxide carbon. Attack at the less substituted epoxide carbon gave the β-hydroxy derivative **7**; attack at the more substituted carbon gave the hydroxymethyl derivatives **5** and **6**. The racemic form of vinyloxirane was used in these reactions. Mixtures of the two hydroxymethyl products **5** and **6** were therefore to be expected. The yields of the stereoisomers were low. The difference from unity may reflect either difficulties in their isolation or kinetic differences between the vinyloxiranes enantiomers. An attempt at kinetic resolution using three equivalents of the racemic vinyloxirane was not successful; polymerization reactions of the vinyloxirane under the reaction conditions is a major problem in these reactions. The usual high stereoselectity at C-5, however, was observed (*vide supra*). About 20% of the hydroxymethyl diastereomers **5** and **6** were isolated after chromatographic work up of the reaction mixture. Product **7** was isolated in 24% yield. The other hydroxy epimer of **7** was not separated and isolated presumably because of the chromatographic conditions used. Formation of the alcohol **7** and its diastereomeric alcohol was not further pursued because these alcohols are available by an alternative and more convenient synthetic route.[8]

Cyclization of the hydroxymethyl derivatives **5** and **6** was effected by RCM reactions using the Grubbs catalyst system, *viz.* bis(tricyclohexylphosphine)benzylidene ruthenium dichloride as the Ru(II)-catalyst precursor (Scheme 2).[9] The recently developed RCM reactions have become very useful tools for cyclization reactions, and the ruthenium catalyst systems are compatible with a number of functional groups.[10–12] The present reactions were run with substrates containing free hydroxyl groups (*vide infra*). So far it is not clear when OH-groups need to be protected in the RCM reactions. In some cases a free OH group is allowed,[2,9a,11] in another case protection as a simple ester changed the reaction from failure to a high yielding process.[1b] RCM reactions require that the dienes are conformationally predisposed for ring formation. When hydrogen bonding in the substrate strongly favours unreactive conformers cleavage of the hydrogen bonding may drastically effect the metathetic conversion. Coordination of polar functional groups to the metal of the catalyst may act either to promote the reaction by bringing the reactive functionalities together or to reduce the activity of the catalyst complex by strong coordination.[10] In the present case the RCM reactions proceeded readily with the free OH-group present in the structures **5** and **6**.

The RCM reactions were run in dry degassed 1,2-dichloroethane or toluene at 60°C, the products being the hydroxymethyl heterospirane **9** and the tricyclic spirane structure **8**. Formation of the tricyclic product **8** requires that the hydroxymethyl substituent is located in the vicinity of the lactim carbon at C-6. Under the conditions of the reaction a reesterification occurs with expulsion of methanol. This course of reaction allows the tricyclic isomer to be assigned structure **8** with elucidation of the stereochemistry at C-2 in the cyclohexyl spirane ring. The other isomer, which does not undergo this cyclization, is therefore assigned structure **9**, which has the opposite stereochemistry at the epimeric hydroxy carbon. Their precursors before the RCM reaction, are therefore assigned structures **5** and **6**, respectively.

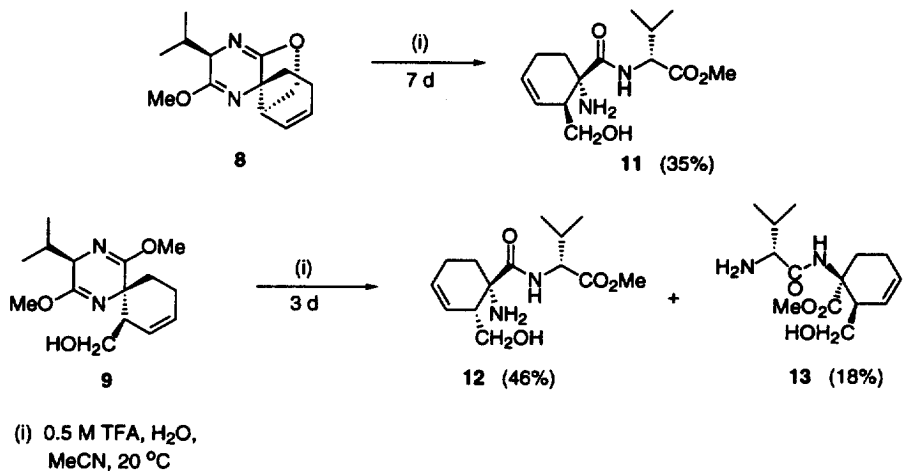
RCM reactions with compound **2**, which has the hydroxymethyl group situated at the terminal olefin carbon, proceeded at elevated temperature with expulsion of the hydroxymethylene group together with the terminal olefin carbon to yield the spirocyclohexene **10**.[1a] This shows that the Ru(II)-catalyst is also capable of removing a hydroxymethyl substituted terminal olefin carbon in the RCM reaction. Furthermore, even the α,β-unsaturated carbonyl derivative **4**, which has the formyl group at the terminal olefin carbon, underwent the RCM reaction at about the same rate and in yields comparable with the hydroxymethyl case **2**. Allyl alcohol and acrolein are probably the expulsion products in these cyclization



Scheme 2.

reactions. Previously it has been reported that another ruthenium precatalyst system could be used to effect an RCM reaction involving a terminal olefin carbon substituted by an electron withdrawing group, *viz.* a carboxylic ester group under relatively vigorous conditions.[13] But generally ruthenium based catalysts are used to effect RCM reactions on olefins unsubstituted at the terminal carbon.[9–12] Milder reaction conditions are then frequently used as we found in our previous preparation of the cyclohexene **10** using the 5-allyl-5-butenyl analogue of **2** (**4**); the RCM reaction proceeded at ambient temperature to the extent of 95% conversion.[1a]

Sterically congested bislactim-spiranes may resist hydrolytic cleavage of the lactim functionalities under the usual mild acid conditions used for liberation of the new amino acid from the bislactim ring.[14] Under stronger acid conditions the reaction takes another course resulting in lactam formation. The resistance towards hydrolytic cleavage of the bislactim ring can be translated into a method for dipeptide formation involving the new amino acid. Under mild acid conditions for hydrolysis of the spirane **9** formation of the major product **12** (46%) corresponds to a hydrolytic cleavage with ring opening of the bislactim ether at the 3,4-positions (Scheme 3). The minor product **13** (18%) comes from hydrolytic cleavage of the 1,6-lactim positions. Further cleavage would require stronger acidic conditions. The 1,6-lactim function is sterically the more hindered site for reaction in the spirane **9**, which may be rationalized to mean that hydrolysis in the 3,4-lactim position is the faster reaction. Ring cleavage in this position leads to a dipeptide which has the new amino acid at the *N*-terminus whereas reaction at the 1,6-lactim position leads to a dipeptide with the new amino acid at the *C*-terminus. In the hydrolytic opening of the tricyclic product **8**, only the dipeptide **11** was seen which corresponds to the first mode of ring opening.



Scheme 3.

In conclusion we have developed a method for stereoselective synthesis of cyclic α-amino-β-hydroxymethylcyclohexene-α-carboxylic acids isolated as dipeptides.

3. Experimental

^{1}H NMR spectra were recored in $CDCl_3$ at 500 MHz, 300 MHz or 200 MHz with Bruker DRX 500, DPX 300 or DPX 200. The ^{13}C spectra were recorded in $CDCl_3$ at 125 MHz, 75 MHz or 50 MHz. Chemical shifts are reported in ppm using residual $CHCl_3$ (7.24 ppm) and $CDCl_3$ (77 ppm) as references. The mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing potential; methane was used for chemical ionization (CI). The spectra are presented as *m/z* (% rel. int.). Dry THF and toluene were distilled from sodium and benzophenone under argon. Dry 1,2-dichloroethane was distilled from calcium hydride under argon. Solvents were degassed by bubbling argon through them. Bis(tricyclohexylphosphine)benzylidene ruthenium dichloride was purchased from Strem Chemicals Inc., 7 Mulliken Way, Newburyport, MA.

3.1. (2R,5S)-5-(3-Butenyl)-2,5-dihydro-3,6-dimethoxy-5-E-(4-hydroxy-2-butenyl)-2-isopropylpyrazine 2

nBuLi (0.75 ml, 1.80 mmol, 2.4 M in heptane) was added dropwise to a solution of (2*R*,5*S*)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine[1a] (385 mg, 1.62 mmol) in dry THF (10 ml) under argon at −50°C. The solution was cooled to −78°C after 45 min and vinyloxirane (0.145 ml, 1.80 mmol) in THF (2 ml) was added dropwise. The mixture was allowed to reach ambient temperature overnight. 0.1 M Phosphate buffer (pH 7; 10 ml) was added and the aqueous phase extracted with dichloromethane (3×20 ml). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography using dichloromethane:diethyl ether 9:1 and 4:1 as eluents; yield 270 mg (54%) of a colourless oil. Found: C, 66.03; H, 9.37. Calc. for $C_{17}H_{28}N_2O_3$: C, 66.20; H, 9.15%. $[\alpha]_D$=−2.7 (c=1.11, $CHCl_3$). ^{1}H NMR (300 MHz): δ 0.61 (d, *J* 7 Hz, 3H, CH_3), 1.03 (d, *J* 7 Hz, 3H, CH_3), 1.60–2.44 (m, 8H, 3×CH_2, CH, OH), 3.62 (s, 3H, CH_3O), 3.65 (s, 3H, CH_3O), 3.71 (d, *J* 3 Hz, 1H, 1/2CH_2), 3.76 (d, *J* 3 Hz, 1H, CH), 3.95 (d, *J* 6 Hz, 1H, 1/2CH_2), 4.91–5.85 (m, 5H, CH_2=, 3×CH). ^{13}C NMR (75 MHz): δ 16.89 (CH_3), 19.47 (CH_3), 29.07 (CH_2), 30.53 (CH), 38.81

(CH_2), 43.80 (CH_2), 52.17 (CH_3O), 52.37 (CH_3O), 60.60 (C-2), 61.99 (C-5), 63.34 (CH_2–OH), 114.14 (CH_2=), 127.14 (CH=), 133.00 (CH=), 138.64 (CH=), 162.87 (C), 163.79 (C). MS (EI): 308 (0.5, M^+), 237 (57), 196 (12), 195 (100), 153 (27).

3.2. (2R,5S)-5-(3-Butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-E-(4-oxo-2-butenyl)pyrazine 4

DMSO (120 μl, 1.70 mmol) in dichloromethane (2 ml) was added dropwise to a solution of oxalyl chloride (72 μl, 0.83 ml) in dichloromethane (8 ml) under argon at −60°C and the mixture stirred for 5 min before a solution of (2*R*,5*S*)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-5-(4-hydroxy-2-butenyl)-2-isopropylpyrazine (233 mg, 0.76 mmol) in dichloromethane (5 ml) was added dropwise. After stirring for 5 min the temperature was raised to −15°C, the mixture stirred for 20 min, cooled to −60°C and triethylamine (0.38 ml, 2.72 mmol) added. The mixture was allowed to warm to ambient temperature and water (5 ml) was added. The aqueous layer was extracted with diethyl ether (3×15 ml) and the combined organic layers dried ($MgSO_4$) and evaporated. The product was isolated by flash chromatography using hexane:ethyl acetate (9:1) as eluent; yield 127 mg (55%) of a colourless oil. $[\alpha]_D$=+18.7 (c=1.27, $CHCl_3$). ^{1}H NMR (300 MHz): δ 0.63 (d, *J* 7 Hz, 3H, CH_3), 1.04 (d, *J* 7 Hz, 3H, CH_3), 1.70–1.93 (m, 4H, 2×CH_2), 2.29 (m, 1H, CH), 2.51–2.73 (m, 2H, CH_2), 3.63 (s, 6H, 2×CH_3O), 3.79 (d, *J* 3 Hz, 1H, H-2), 4.97 (m, 2H, CH_2=), 6.03 (ddd, J_{CHO} 8 Hz, $J_{H\beta}$ 16 Hz, $J_{H\gamma}$ 1 Hz, 1H, H_α), 6.53 (m, 1H, H_β), 9.39 (d, *J* 8 Hz, 1H, CHO). ^{13}C NMR (75 MHz): δ 16.94 (CH_3), 19.47 (CH_3), 28.83 (CH_2), 30.59 (CH), 39.16 (CH_2), 44.02 (CH_2), 52.34 (CH_3O), 52.44 (CH_3O), 60.68 (C-2), 61.33 (C-5), 114.44 (CH_2=), 135.58 (CH=), 138.22 (CH=), 153.18 (CH=), 162.84 (C), 163.38 (C), 193.61 (CHO). MS (EI): 306 (8, M^+), 291 (14), 263 (27), 237 (48), 196 (12), 195 (100).

3.3. (2R,5S,1′S)-5-(3-Butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(1-hydroxymethyl-2-propenyl)pyrazine 5; (2R,5S,1′R)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(1-hydroxymethyl-2-propenyl)pyrazine 6; (2R,5S,2′R)-5-(3-butenyl)-5-(2-hydoxy-3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine 7

nBuLi (2.92 ml, 7.00 mmol, 2.4 M in heptane) was added to a solution of (2*R*,5*S*)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine[1a] (1.56 g, 6.56 mmol) in dry THF (15 ml) under argon at −50°C. The solution was kept at this temperatre for 45 min, cooled to −78°C and a solution of vinyloxirane (0.56 ml, 7.00 mmol) in dry THF (0.5 ml) added dropwise followed by dropwise addition of boron trifluoride ethyl etherate (0.88 ml, 7.00 mmol). Acetic acid (1 ml) was added after 3 h at −78°C and the cold bath removed. 0.1 M Phosphate buffer (pH 7; 10 ml) was added and the aqueous layer extracted with dichloromethane (3×30 ml). The combined organic layers were dried ($MgSO_4$) and evaporated. Three alcohols were separated after repeated (3×) flash chromatography with hexane:ethyl acetate (7:1 and 4:1) as eluents.

3.3.1. (2R,5S,2′R)-5-(3-Butenyl)-5-(2-hydroxy-3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine 7

Compound **7** was eluted first; yield 473 mg (23%) of a colourless oil. Found: C, 66.17; H, 9.23. Calc. for $C_{17}H_{28}N_2O_3$: C, 66.20; H, 9.15%. $[\alpha]_D$=−14.3 (c=1.03, $CHCl_3$). ^{1}H NMR (300 MHz): δ 0.65 (d, *J* 7 Hz, 3H, CH_3), 1.04 (d, *J* 7 Hz, 3H, CH_3), 1.61–1.99 (m, 6H, 3×CH_2), 2.30 (m, 1H, CH), 3.61 (s, 3H, CH_3O), 3.62 (s, 3H, CH_3O), 3.86 (d, *J* 3 Hz, 1H, H-2), 4.44 (m, 1H, C*H*–OH), 4.55 (bs, 1H, OH), 4.86–5.21 (m, 4H, 2×CH_2=), 5.70 (m, 2H, 2×CH=). ^{13}C NMR (75 MHz): δ 17.10 (CH_3), 19.47 (CH_3), 29.05 (CH_2), 30.44 (CH), 36.81 (CH_2), 46.57 (CH_2), 52.26 (CH_3O), 52.41 (CH_3O), 60.14 (C-2), 61.19

(C-5), 69.69 (CH), 113.80 (CH_2=), 114.42 (CH_2=), 138.12 (CH=), 140.60 (CH=), 163.32 (C), 163.43 (C). MS (EI): 308 (0.82, M^+), 237 (27), 211 (18), 197 (12), 196 (13), 195 (100).

3.3.2. (2R,5S,1′S)-5-(3-Butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(1-hydroxymethyl-2-propenyl)pyrazine **5**

Compound **5** was eluted second; yield 122 mg (6%). Found: C, 66.13; H, 8.92. Calc. for $C_{17}H_{28}N_2O_3$: C, 66.20; H, 9.15%. $[\alpha]_D$=+9.1 (c=0.95, $CHCl_3$). ^{1}H NMR (200 MHz): δ 0.62 (d, *J* 7 Hz, 3H, CH_3), 1.03 (d, *J* 7 Hz, 3H, CH_3), 1.63–2.01 (m, 4H, 2×CH_2), 2.21–2.50 (m, 2H, 2×CH), 3.59 (s, 3H, CH_3O), 3.61 (s, 3H, CH_3O), 3.82 (d, *J* 3 Hz, 1H, H-2), 4.10, 4.15 (dd, *J* 4 Hz, 2H, CH_2), 4.86–5.10 (m, 4H, CH_2=), 5.68–5.82 (m, 2H, 2×CH=). ^{13}C NMR (50 MHz): δ 17.14 (CH_3), 19.46 (CH_3), 29.22 (CH_2), 30.37 (CH), 36.56 (CH_2), 52.04 (CH_3O), 52.47 (CH_3O), 52.50 (CH), 59.98 (C-2), 63.05 (CH_2OH), 65.41 (C-5), 114.44 (CH_2=), 118.14 (CH_2=), 135.52 (CH=), 138.14 (CH=), 161.85 (C), 164.08 (C). MS (EI): 208 (0.4, M^+), 237 (60), 234 (10), 196 (12), 195 (100), 153 (21).

3.3.3. (2R,5S,1′R)-5-(3-Butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(1-hydroxymethyl-2-propenyl)pyrazine **6**

Compound **6** was the third compound collected; yield 263 mg (13%) of a colourless oil. Found: C, 66.58; H, 8.90. Calc. for $C_{17}H_{28}N_2O_3$: C, 66.20; H, 9.15%. $[\alpha]_D$=−36.4 (c=1.36, $CHCl_3$). ^{1}H NMR (200 MHz): δ 0.63 (d, *J* 7 Hz, 3H, CH_3), 1.05 (d, *J* 7 Hz, 3H, CH_3), 1.58–2.01 (m, 4H, 2×CH_2), 2.31 (m, 1H, CH), 2.54 (m, 1H, CH), 3.17–3.50 (m, 2H, CH_2O), 3.63 (s, 3H, CH_3O), 3.64 (s, 3H, CH_3O), 3.81 (d, *J* 3 Hz, 1H, H-2), 4.84–5.24 (m, 4H, 2×CH_2=), 5.66–5.88 (m, 2H, CH=). ^{13}C NMR (50 MHz): δ 17.06 (CH_3), 19.48 (CH_3), 28.93 (CH_2), 30.45 (CH), 37.08 (CH_2), 52.27 (CH_3O), 52.34 (CH_3O), 55.00 (CH), 60.36 (CH), 61.91 (CH_2), 62.37 (C-5), 114.23 (CH_2=), 119.75 (CH_2=), 135.43 (CH=), 138.52 (CH=), 163.02 (2×C). MS (EI): 308 (1, M^+), 265 (11), 238 (10), 237 (63), 235 (11), 233 (22), 196 (12), 195 (100), 153 (23).

3.4. (2R,5S,2′S)-6,2′-Oxymethylene-[2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(3-cyclohexene)] **8**

Bis(tricyclohexylphosphine)benzylidene ruthenium dichloride (47 mg, 0.057 mmol) in dry degassed 1,2-dichloroethane (2 ml) was added to a solution of (2*R*,5*S*,1′*S*)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(1-hydroxymethyl-2-propenyl)pyrazine (350 mg, 1.14 mmol) in dry degassed 1,2-dichloroethane (20 ml) at 60°C. TLC monitoring showed the presence of unreacted substrate after 18 h at 60°C. Another portion of catalyst (47 mg, 0.057 mmol) in 1,2-dichloroethane (2 ml) was added and stirring was continued at 60°C for 4 h. The solvent was evaporated and the residue purified by flash chromatography using hexane:ethyl acetate (1:1) as eluent; yield 185 mg (66%) of a colourless oil. Found: C, 67.32; H, 8.13. Calc. for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12%. $[\alpha]_D$=−152.3 (c=1.21, $CHCl_3$). ^{1}H NMR (300 MHz): δ 1.02 (d, *J* 7 Hz, 3H, CH_3), 1.04 (d, *J* 7 Hz, 3H, CH_3), 1.45–2.74 (m, 6H, 2×CH_2, 2×CH), 3.64 (s, 3H, CH_3O), 3.75 (d, *J* 8 Hz, 1H, CH), 3.93, 3.97 (dd, *J* 8 Hz, 1H, 1/2CH_2O), 4.41, 4.44 (dd, *J* 8 Hz, 1H, 1/2CH_2O), 5.64 (m, 1H, CH=), 5.96 (m, 1H, CH=). ^{13}C NMR (75 MHz): δ 20.46 (CH_3), 20.78 (CH_3), 21.06 (CH_2), 29.93 (CH_2), 35.54 (CH), 43.64 (CH), 52.88 (CH_3O), 57.07 (C), 64.89 (CH), 73.39 (CH_2), 122.04 (CH=), 129.64 (CH=), 167.76 (C), 172.83 (C). MS (EI): 249 (11), 248 (63, M^+), 206 (31), 205 (100), 191 (37), 177 (16). HRMS: *M* 248.1520. Calc. for $C_{14}H_{20}N_2O_2$: 248.1525.

3.5. (2R,5S,2′R)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(2-hydroxymethyl-3-cyclohexene) 9

Bis(tricyclohexylphosphine)benzylidene ruthenium dichloride (12 mg, 0.015 mmol) in dry degassed 1,2-dichloroethane (1 ml) was added to a solution of (2*R*,5*S*,1′*R*)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(1-hydroxymethyl-2-propenyl)pyrazine (93 mg, 0.30 mmol) in dry degassed 1,2-dichloroethane (5 ml) at 60°C. The mixture was stirred at 60°C for 6 h, the solvent evaporated and the residue purified by flash chromatography using hexane:diethyl ether (1:1 and 1:2) as eluents; yield 60 mg (71%) of a colourless oil. Found: C, 64.20; 8.60. Calc. for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63%. $[\alpha]_D=-86.2$ (c=0.60, $CHCl_3$). ^1H NMR (300 MHz): δ 0.70 (d, *J* 7 Hz, 3H, CH_3), 1.06 (d, *J* 7 Hz, 3H, CH_3), 1.40–2.32 (m, 6H, 2×CH_2, CH, OH), 2.30 (bs, 1H, CH), 3.48 (m, 2H, CH_2–OH), 3.61 (s, 3H, CH_3O), 3.65 (s, 3H, CH_3O), 4.01 (d, *J* 4 Hz, 1H, H-2), 5.56 (m, 1H, CH=), 5.86 (m, 1H, CH=). ^{13}C NMR (75 MHz): δ 17.45 (CH_3), 19.41 (CH_3), 21.41 (CH_2), 31.29 (CH), 34.74 (CH_2), 43.51 (CH), 52.15 (CH_3O), 52.66 (CH_3O), 59.29 (C-5), 60.86 (C-2), 63.52 (CH_2OH), 125.84 (CH=), 127.66 (CH=), 163.51 (C), 165.23 (C). MS (EI): 280 (9, M^+), 250 (19), 238 (14), 237 (100), 219 (15), 196 (16), 154 (48), 153 (79), 125 (9), 123 (14).

3.6. (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(3-cyclohexene) 10

From allylic alcohol **2**: Bis(tricyclohexylphosphine)benzylidene ruthenium dichloride (39 mg, 0.047 mmol) in dry degassed toluene (1 ml) was added to a solution of (2*R*,5*S*)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-5-(4-hydroxy-2-butenyl)-2-isopropylpyrazine (289 mg, 0.94 mmol) in dry degassed toluene (10 ml) under argon at 60°C. The mixture was stirred at 60°C for 18 h before the solvent was distilled off. The residual material was subjected to flash chromatograhy using 2% ethyl acetate in hexane as eluent; yield 95 mg (41%) of a colourless oil. The physical data for the product were in full agreement with our previously published data.[1a] Part of the starting material (100 mg, 35%) was recovered.

From α,β-unsaturated aldehyde **4**: Bis(tricyclohexylphosphine)benzylidene ruthenium dichloride (16 mg, 0.020 mmol) in dry degassed toluene (1 ml) was added to a solution of (2*R*,5*S*)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(4-oxo-2-butenyl)pyrazine (120 mg, 0.39 mmol) in dry degassed toluene (10 ml) under argon at 60°C. The solvent was evaporated after 16 h and the residue purified by flash chromatography using 2% and 10% ethyl acetate in hexane as eluent; yield 41 mg (42%) of the title compound. Part of the starting material 43 mg (36%) was recovered.

3.7. Methyl (R)-N-[(1S,2S)-1-amino-2-hydroxymethyl-3-cyclohexene-1-carbonyl]valinate 11

(2*R*,5*S*,2′*S*)-6,2′-Oxymethylene-[2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(3-cyclohexene)] (103 mg, 0.42 mmol) was stirred with trifluoroacetic acid (21 ml, 4.20 mmol, 0.2 M) and acetonitrile (21 ml) at ambient temperature for 3 days. The mixture was evaporated almost to dryness and water (5 ml) and dichloromethane (10 ml) added. The aqueous phase was made alkaline by addition of conc. ammonia (pH 10) and the aqueous layer extracted with dichloromethane (3×10 ml). The combined dichloromethane layers were dried ($MgSO_4$), evaporated and the residue purified by flash chromatography using 3% and 5% methanol in dichloromethane as eluents; yield 41 mg (35%) of a colourless oil. $[\alpha]_D=+70.2$ (c=0.54, $CHCl_3$). ^1H NMR (300 MHz): δ 0.88 (d, *J* 7 Hz, 3H, CH_3), 0.94 (d, *J* 7 Hz, 3H, CH_3), 1.47–2.46 (m, 9H, 2×CH_2, NH_2, 2×CH, OH), 3.62 (m, 2H, CH_2), 3.70 (s, 3H, CH_3O), 4.37, 4.40 (dd, *J* 5 Hz, 1H, CH), 5.51 (m, 1H, CH=), 5.81 (m, 1H, CH=), 8.29 (d, *J* 7 Hz, 1H, NH). ^{13}C NMR (75 MHz): δ 17.82 (CH_3), 19.13 (CH_3), 21.67 (CH_2), 30.62 (CH_2, CH), 47.71 (CH),

52.11 (CH_3O), 57.26 (CH), 58.00 (C), 63.67 (CH_2OH), 125.93 (CH=), 127.90 (CH=), 172.32 (C=O), 176.96 (C=O). MS (EI): 284 (0.3, M^+), 249 (59), 207 (15), 126 (100), 109 (17), 108 (41), 96 (17), 95 (14), 94 (37). HRMS: *M* 284.1678. Calc. for $C_{14}H_{24}N_2O_4$: 284.1736.

3.8. Methyl (R)-N-[(1S,2R)-1-amino-2-hydroxymethyl-3-cyclohexene-1-carbonyl]valinate **12** *and methyl (1S,2R)-N-[(R)-valinyl]-1-amino-2-hydroxymethyl-3-cyclohexene-1-carboxylate* **13**

(2*R*,5*S*,2′*R*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(2-hydroxymethyl-3-cycloheptene) (158 mg, 0.56 mmol) was stirred with trifluoroacetic acid (28 ml, 5.60 mmol) and acetonitrile (28 ml) at ambient temperature for 7 days. The mixture was concentrated almost to dryness and water (10 ml) and dichloromethane (20 ml) added. The aqueous layer was made alkaline (pH 10) by addition of conc. ammonia, the aqueous phase extracted with dichloromethane (2×20 ml), the organic phases combined, dried ($MgSO_4$) and evaporated. The products were isolated by flash chromatography using 3% and 10% methanol in dichloromethane as eluents.

3.8.1. Methyl (R)-N-[(1S,2R)-1-amino-2-hydroxymethyl-3-cyclohexene-1-carbonyl]valinate **12**

Compound **12** was the first product eluted; yield 73 mg (46%) of a colourless oil. $[\alpha]_D=-59.9$ (c=0.73, $CHCl_3$). ^1H NMR (300 MHz): δ 0.87 (d, *J* 7 Hz, 3H, CH_3), 0.91 (d, *J* 7 Hz, 3H, CH_3), 1.52–2.20 (m, 8H, 2×CH_2, NH_2, CH, OH), 2.96 (m, 1H, CH), 3.53–3.70 (m, 2H, CH_2), 3.68 (s, 3H, CH_3O), 4.42, 4.43 (dd, *J* 5 Hz, 1H, CH), 5.50 (m, 1H, CH=), 5.77 (m, 1H, CH=), 8.11 (d, *J* 9 Hz, 1H, NH). ^{13}C NMR (75 MHz): δ 17.64 (CH_3), 19.06 (CH_3), 21.38 (CH_2), 30.76 (CH), 32.85 (CH_2), 42.99 (CH), 52.04 (CH_3O), 56.96 (CH), 58.05 (C), 63.11 (CH_2OH), 126.35 (CH=), 126.81 (CH=), 172.49 (C=O), 177.60 (C=O). MS (EI): 225 (2.5, M^+-CH_3OCO), 127 (8), 126 (100), 108 (18). MS (CI-CH_4): 285 (15, *M*+1), 126 (100).

3.8.2. Methyl (1S,2R)-N-[(R)-valinyl]-1-amino-2-hydroxymethyl-3-cyclohexene-1-carboxylate **13**

Compound **13** was the second product eluted; yield 28 mg (18%) of a colourless oil. ^1H NMR (500 MHz): δ 0.86 (d, *J* 7 Hz, 3H, CH_3), 0.94 (d, *J* 7 Hz, 3H, CH_3), 1.47 (bs, 4H, NH_2, NH, OH), 1.64–2.21 (m, 5H, 2×CH_2, CH), 3.09 (m, 1H, CH), 3.17 (d, *J* 5 Hz, 1H, CH), 3.72 (s, 3H, CH_3O), 3.94–4.23 (m, 2H, CH_2), 5.35 (m, 1H, CH=), 5.82 (m, 1H, CH=). ^{13}C NMR (125 MHz): 17.00 (CH_3), 19.37 (CH_3), 21.33 (CH_2), 31.84 (CH), 32.74 (CH_2), 40.84 (CH), 56.92 (C), 59.84 (CH), 64.35 (CH_2OH), 124.04 (CH=), 127.77 (CH=), 175.43 (C=O), 177.34 (C=O). MS (EI): 284 (0.4, M^+), 224 (18), 223 (81), 167 (21), 152 (16), 108 (98), 72 (100). HRMS: *M* 284.1726. Calc. for $C_{14}H_{24}N_2O_4$: 284.1736.

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