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ASYMMETRIC SYNTHESIS VIA HETEROCYCLIC INTERMEDIATES - XXXIX[1]

ASYMMETRIC SYNTHESIS OF (ENANTIOMERICALLY AND DIASTEREOMERICALLY VIRTUALLY PURE) METHYL 2-AMINO-4,5-EPOXY-3-HYDROXY-ALKANOATES AND METHYL 2-AMINO-3-HYDROXY-4,5-METHYLENE-ALKANOATES BY THE BISLACTIMETHER METHOD

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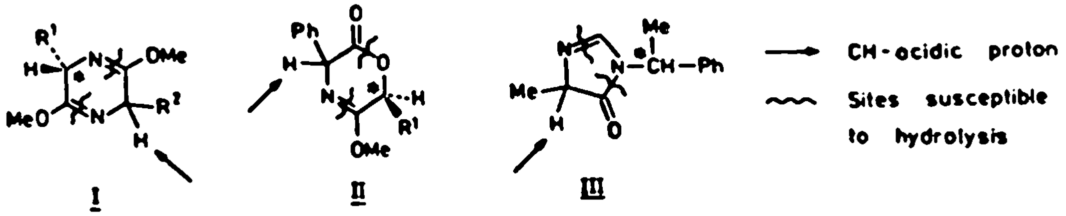
Abstract - α,β-Unsaturated aldehydes react with the titanated bislactim ether 6 of cyclo-(L-val-gly) to give the (2R,1'S)-syn-addition products of type 8. With TBHP (catalyzed by $Ti(OiPr)_4$ with and without (+)- or (-)-DET) these furnish the epoxides 10 or 11 with 1',2'-anti or 1',2'-syn relation. In some cases virtually only one stereoisomer is formed. Upon acid hydrolysis the compounds 10 or 11 give the corresponding methyl (2R,3R)-2-amino-4,5-epoxy-3-hydroxy-alcanoates (type 12 or 13). As experiments with 10c revealed, the oxirane ring in 10 or 11 can be submitted to various regio- and stereo-controlled transformations affording the precursors of type 14 or 17 of amino acids in the sugar series. Cyclopropanation of 8 (diiodo methane/diethyl zinc) proceeds highly diastereoselectively to give the cyclopropanes of type 19. Upon acid hydrolysis these give the corresponding (enantiomerically and diastereomerically pure) methyl (2R,3S,4R,5R)-2-amino-3-hydroxy-4,5-methylene-alcanoates of type 20.

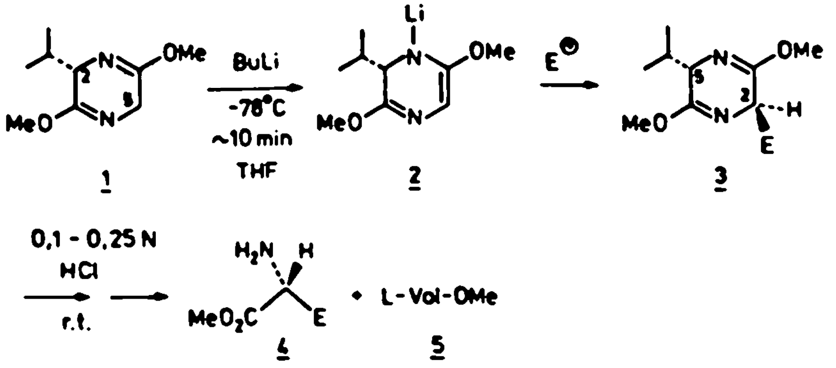
I. Introduction

In 1969 Schöllkopf et al.[2] introduced α-metallated alkyl isocyano alkanoates into synthetic organic chemistry as reagents for the synthesis of amino acids. In the meantime, these reagents have found numerous applications[3], mainly for the synthesis of racemic amino acids.- Some time later we commenced a study, aimed at the *asymmetric* synthesis of amino acids. Our approach is based on heterocyclic chemistry and on the following concept: An heterocycle is built up that contains -besides a chiral inducing center- a latent amino group and a latent carboxyl group, both incorporated in such a way that the hetereocyclic anion is an equivalent of an amino acid carbanion[4] to which an electrophile can be added diastereoselectively. Moreover, the heterocycle must have two sites susceptible to hydrolysis so that it can be cleaved finally liberating the optically active target amino acid and the chiral auxiliary.

So far three types of heterocycles -I, II and III- proved to be suitable in our laboratory.



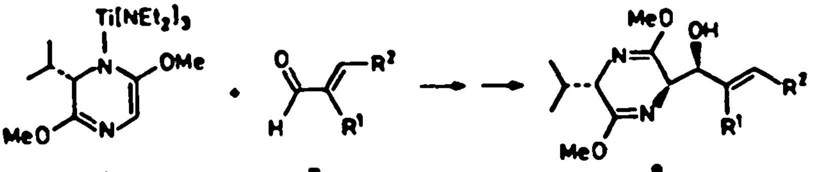
By far the most versatile templates are the dihydropyrazines I, the bislactim ethers of diketopiperazines. The "bislactim ether method"[5] for the asymmetric synthesis of amino acids is based on the fact that a bislactim ether of type I - for instance 1 of cyclo-(L-val-gly)- reacts readily and regioselectively with butyllithium to give the lithium derivative 2. This reagent adds electrophiles E^+ at C-2 trans to the isopropyl group at the residential chiral center (C-5)[6] to give 3 usually with a high degree of asymmetric induction. Subsequently the heterocycle 3 is cleaved at the two iminoether groups by acid hydrolysis, liberating the target amino acid methyl ester 4 and methyl L-valinate 5 (the chiral auxiliary).



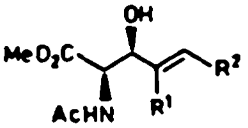
(Remarkably, also those derivatives of the bislactim ether 1 that carry an alkyl group in the 5-position react regioselectively with butyllithium. Their lithium derivatives react with E^+ with a particularly high degree of diastereodifferentiation at the heterocyclic anion).

With aldehydes as electrophiles the degree of diastereoselectivity in the step 2 + E^+ → 3 is raised significantly when Li in 2 is exchanged for $Ti(NEt_2)_3$. With the titanium reagents 6 not only the stereocenter C-2 is generated in virtually only one configuration, but also the stereocenter C-1'. Out of four possible diastereomers, the syn-isomer (type 8) is formed[7,8]. This is also true for chiral aldehydes, even when the aldehyde chirality favors the anti-isomer, i.e. reagent control of stereochemistry prevails[9].

As reported recently[8], α,β-unsaturated aldehydes 7 react with the titanium reagent 6 in a 1,2-fashion to give the 2,1'-syn-products 8 with a double bond in the side chain. Upon acid hydrolysis -subsequent to O-acetylation- these afford the threo-serine esters 9[8].



6 7 8



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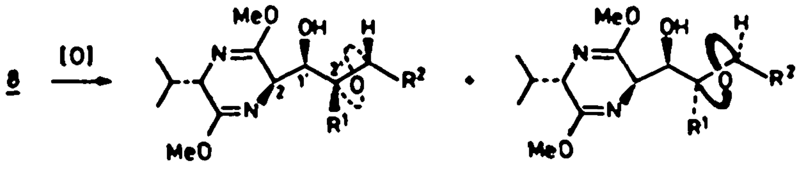
8	R1	R2
a	H	Me
b	H	Ph
c	Me	H
d	Me	Me
e	H	H

The double bond in 8 offers the possibility of functionalisation to give precursors of 2-amino-3-hydroxy acids with additional functional groups (such as hydroxy or amino groups) in the carbon chain.

This communication describes a) the epoxidation of 8 with achiral and chiral Sharpless-epoxidation reagents[10] to give epoxides of type 10 or 11 with either 1',2'-anti or 1',2'-syn-relation, b) the hydrolysis of three of these epoxides, to give the methyl (2R,3R)-2-amino-4,5-epoxy-3-hydroxy-alcanoates of type 12 or 13, c) some transformations of the epoxides 10 in which the oxirane ring is opened by nucleophiles, d) the cyclopropanation of 8 to give diastereoselectively the cyclopropane compounds 19 and e) the hydrolysis of these compounds to give methyl (2R,3R)-2-amino-3-hydroxy-4,5-methylene-alcanoates of type 20.

II. Epoxidation of the Compounds 8

Apart from the acrolein-adduct 8e, the compounds 8 react with tert-butylhydroperoxide (TBHP) with good chemical yields in the presence of $Ti(OiPr)_4$, with or without additional (-)- or (+)-diethyl tartrate (DET), to give either the 1',2'-anti-diastereomers 10 or the 1',2'-syn-diastereomers 11 or a mixture of both (table 1). For 10d the 1',2'-anti-configuration was established by an X-ray-analysis[11]. The 1',2'-syn and 1',2'-anti-isomers 10d and 11d differ in the ^{13}C-NMR spectra in so far, as the C-3 and C-6 signals of the anti-isomer appear at lower field than the ones of the syn-diastereomer. By analogy it was assumed that in each case the isomer with the ^{13}C-NMR C-3 and C-6 signals at lower field is the 1',2'-anti-isomer of type 10. The diastereomer ratios (table 1) were determined by ^1H- or ^{13}C-NMR spectra and/or by capillary GLC.



10 (1',2'-anti)   11 (1',2'-syn)

a-d as for 8

Table 1. Epoxidation of the compounds 8.

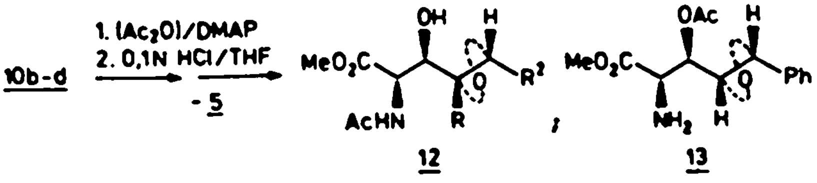
10/11	Method*	Yield	anti/syn	main isomer
a	A	74	1/2.0	syn
	B	61	4.7/1	anti
	C	71	1/>199	syn
b	A	65	32/1	anti
	C	55	1/39	syn
c	A	74	66/1	anti
	B	68	66/1	anti
	C	70	32/1	anti
d	A	83	199/1	anti
	B	76	>199/1	anti
	C	79	39/1	anti
e	A	64	1.6/1	anti

*) A: $Ti(OiPr)_4$/TBHP, B: (-)-DET/$Ti(OiPr)_4$/TBHP, C: (+)-DET/$Ti(OiPr)_4$/TBHP

The stereodirection of the substrates 8 follows from the experiment with $Ti(OiPr)_4$/TBHP (method A). Apart from 8a, which is syn-directing, the substrates 8 are anti-directing (table 1, method A). As for the reagents, according to the Sharpless rule method B with (-)-DET favors the anti-isomers 10, whereas method C with (+)-DET favors the syn-isomer 11.- When 8a is oxidized by method B, the anti-isomer is formed predominantly, i.e. the Sharpless rule holds and the reagent overrides the substrate; when method C is applied (matched case) a high syn-preference is observed.- Likewise, with 8b the reagent overwhelms the asymmetric induction originating from the substrate; with method C the syn-isomer is formed predominantly (mismatched case with reagent control).- With 8c and 8d substrate control prevails; no matter whether (-)- or (+)-DET is used, the anti-isomer is formed predominantly. As expected the degree of diastereoselectivity is exceptionally high when 8d is epoxidized with method B (matched case).

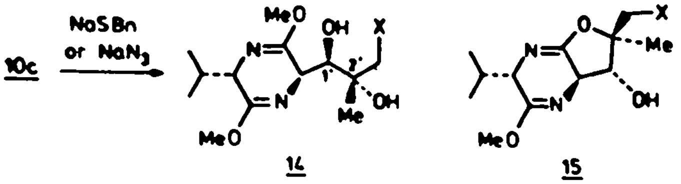
III. Hydrolysis of the Bislactim ethers 10 and 11; Methyl (2R,3R)-(3,4-anti)-2-amino-4,5-epoxy-3-hydroxy-alcanoates of type 12 or 13

Using 10b,c and d as models we could show that the hydrolysis of the bislactim ether moiety can be carried out under so mild conditions (0.1 N HCl, two equivalents, r.t.) that the oxirane ring survives. Prior to hydrolysis the hydroxy group should be protected by acetylation to secure good yields in the hydrolysis step. This has been observed before in analoguous cases[8,9]. With 10c and d the N-acetyl amino acids 12a and b were finally isolated by distillation whereas with 10b the acetyl group stayed at the oxygen atom. Methyl L-valinate 5, a relatively volatile compound, could be separated from the target compounds 12 or 13 by evaporation in the kugelrohr apparatus (30°C, 0.01 torr).



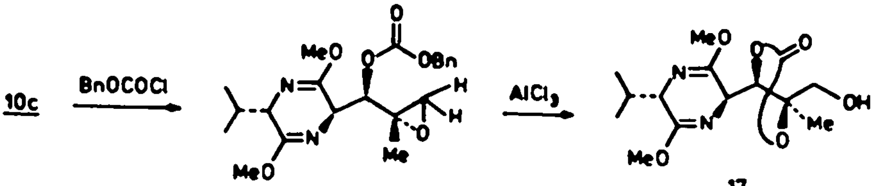
12	a	b
R^1	Me	Me
R^2	H	Me

In a set of orientational experiments we studied some transformations of the compounds 10, utilizing 10c as a model compound. Reaction of 10c with benzylthiolate gave the compound 14a that cyclized on standing (within two days) to the compound 15a. To prevent this cyclisation, the 2'-hydroxy group of 14a should be protected. After protection of both hydroxy groups (by, for instance, acetyl groups), hydrolysis of the bislactim ether moiety should proceed cleanly to give the corresponding amino acid methyl ester. Likewise sodium azide reacted with 10c to furnish the azido compound 14b. As expected, 14b cyclized on standing to 15b.



14,15	a	b
X	SBn	N_3

Moreover, 10c was converted with carbobenzoxy chloride into the carbonate 16 and this in turn ($AlCl_3$ induced) into the cyclic carbonate 17[12]. Upon hydrolysis 17 should yield (the masked) methyl D-2-deoxy-2-amino-4-methyl-xylonate 18. Starting with ent-1 the enantiomer of 18 should be obtainable.



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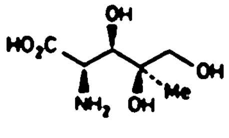

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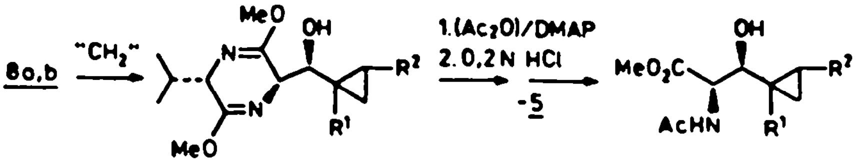
IV. Cyclopropanation of the Compounds 8

Cyclopropanation of the C=C double bond in 8a,b and c with the "methylene" generated from diethyl zinc and diiodo methane[13] proceeded with a high degree of diastereoselectivity to give the compounds 19. In the ^1H- and ^{13}C-NMR spectra only one diastereomer of 19 is detectable. Based on (speculative) mechanistic considerations about the cyclopropanation step, we tentatively assign the 1',2'-syn-configuration to the compounds 19. Hydrolysis of the compounds 19, subsequent to O-acetylation, proceeded cleanly to give the methyl (2R,3S)-2-amino-3-hydroxy-4,5-methylene-alcanoates 20. Note: After completion of the manuscript the proposed 3,4-syn-configuration for 20 was established for 20a by an X-ray analysis[14].



19 a,b as for 8 20

EXPERIMENTAL

The bislactim ether 1 was prepared according to lit.[15] or purchased from Merck-Schuchardt[16].- ^1H- and ^{13}C-NMR spectra: Varian XL 100 and XL 200.- IR spectra: Perkin Elmer 298.- Mass spectra: Varian MAT 731.- Capillary GLC: Carlo Erba Fractovap 2300; Chrompack CPSil 5CB column, 50 m, 0.22 mm diameter; H_2; for integration of signals of flame-ionisation-detector: Shimadzu Data Processor Chromtopac C-R3A.- Liquid chromatography was performed as low pressure chromatography (1-2 bar) on silica gel (Merck, 0.040-0.063 mm, 240-400 mesh).- Experiments with organometallic reagents were performed under argon, using the syringe-technique.- All distillations were performed as bulb-to-bulb distillations.- All NMR spectra were recorded in $CDCl_3$.

Sharpless-Epoxidation of Compounds 8; Compounds 10,11

Compounds 8 were prepared as described in lit.[8] but in larger runs. In each run 1 (9.20 g, 50.0 mmol), butyllithium (29.4 ml of an 1.70 N solution in hexane, 50.0 mmol) and THF (100 ml) were used to generate 2. To the solution of 2 $ClTi(NEt_2)_3$ (15.0 g, 50.0 mmol) in hexane (20 ml) was added to generate 6. After 1 h stirring at -70°C, aldehyde 7 (48.0 mmol) was added dropwise. Workup was performed as described in lit.[8]. The crude compounds 8 were not distilled because of the danger of retro-aldol-cleavage but were used without further purification.- The TBHP-solution in dichloroethane was prepared as described in lit.[17] starting with commercial TBHP-solution free from di-t-butyl-peroxide.- Epoxidations; General procedure: 10a-e /11a,b: A solution of $Ti(OiPr)_4$ (0.56 g, 2.0 mmol) in dichloromethane (20 ml) was prepared (for method A). To this solution the bislactim ether 8 (2.0 mmol) in dichloro-methane (5 ml) was added dropwise at -20°C and stirring was continued for 20 min at -20°C. Then a solution of TBHP in dichloroethane (1 ml, 5.5 mmol) was injected and the reaction mixture kept at -20°C for 1-4 d. An aqueous solution of tartaric acid (5 ml, 10 %) was added to the mixture. After stirring at r.t., the water layer was separated and the organic layer was washed with some water. The solvent was removed in vacuo. Ether (30 ml) was added to the residue. The solution was stirred with a 1N sodium hydroxide solution (6 ml, 6.0 mmol) saturated with sodium chloride for 30 min at 0°C. The water layer was separated, the ether layer washed with a saturated solution of sodium chloride and dried with magnesium sulfate. The ether was removed in vacuo and the crude 10/11 purified by bulb-to-bulb distillation.- For method B, (-)-DET (0.41 g, 2 mmol) was added to the solution of $Ti(OiPr)_4$ prior to addition of 8; for method C, (+)-DET was used instead.- ^{1}H-NMR for the bislactim ether moiety: δ = 0.70-0.74 and 1.04-1.07 (2d, J = 7 Hz; 6H, $CH(CH_3)_2$), 2.1-3.0 (d or b, J = 8 Hz; 1H, OH), 2.25-2.30 (dsp, J = 3.5 Hz, J = 7 Hz; 1H, $CH(CH_3)_2$), 3.68-3.75 and 3.75-3.77 (2s; 6H, 3- and 6-OCH_3), 4.00-4.04 (dd, ^{3}J = ^{5}J = 3.5 Hz; 1H, H-5), 4.14-4.18 (dd, ^{3}J = 2 Hz, ^{5}J = 3.5 Hz; 1H, H-2).

(2R,5S,1'R,2'R,3'R)-2-(2',3'-Epoxy-1'-hydroxy-but-1'-yl)-2,5-dihydro-5-isopropyl-3,6-dimethoxy-pyrazine (10a): Method B, with 0.51 g of 8a, 2 d at -20°C ; yield 0.33 g (61 %) of 10a; b.p. 150°C/0.01 torr; diastereomer ratio (^{13}C-NMR, capillary GLC) 4.7:1 (10a:11a). ^{1}H-NMR: δ = 1.38 (d, J = 5 Hz; 3H, H-4'), 3.0 (dd, J = 2 Hz, J = 3.5 Hz; A-part of AB, 1H, H-2'), 3.1 (dq, J = 2 Hz, J = 5 Hz; B-part of AB, 1H, H-3'), 3.9-4.0 (m; 1H, H-1').-
^{13}C-NMR: 16.85 and 17.35 ($CH(CH_3)_2$), 19.04 (C-4'), 32.01 ($CH(CH_3)_2$), 52.54 and 52.70 (3- and 6-OCH_3), 53.51 (C-2'), 57.80 (C-5), 59.58 (C-3'), 61.00 (C-2), 71.06 (C-1'), 161.32 and 166.32 (C-3 and -6).
$C_{13}H_{22}N_2O_4$ (270.2): Calcd. C 57.77 H 8.14 Found C 57.68 H 8.14

(2R,5S,1'R,2'S,3'S)-2-(2',3'-Epoxy-1'-hydroxy-but-1'-yl)-2,5-dihydro-5-isopropyl-3,6-dimethoxy-pyrazine (11a): Method C, with 0.51 g of 8a, 2 d at -20°C; yield 0.38 g (71 %) of 11a; b.p. 150°C/0.01 torr; diastereomer ratio (capillary GLC) 1:199 (10a:11a). ^{1}H-NMR: δ = 1.34 (d, J = 5 Hz; 3H, H-4'), 2.98 (dd, J = 2 Hz, J = 3.5 Hz; A-part of AB, 1H, H-2'), 3.05 (dq, J = 2 Hz, J = 5 Hz; B-part of AB, 1H, H-3'), 4.00 (ddd, J = 8 Hz, J = 3.5 Hz, J = 3.5 Hz; 1H, H-1').- ^{13}C-NMR: 16.68 and 17.19 ($CH(CH_3)_2$), 19.04 (C-4'), 31.80 ($CH(CH_3)_2$), 51.39 (C-2'), 52.66 and 52.71 (3- and 6-OCH_3), 58.77 (C-5), 60.02 (C-3'), 60.76 (C-2), 70.96 (C-1'), 161.11 and 165.69 (C-3 and -6).

(2R,5S,1'R,2'R,3'R)-2-(2',3'-Epoxy-1'-hydroxy-3'-phenyl-prop-1'-yl)-2,5-dihydro-5-isopropyl-3,6-dimethoxy-pyrazine (10b): Method A, with 0.63 g of 8b, 1 d at -20°C; yield 0.43 g (65 %) of 10b; b.p. 180°C/0.01 torr; diastereomer ratio (capillary GLC) 32:1 (10b:11b). ^{1}H-NMR: δ = 3.31 (dd, J = 2 Hz, J = 2 Hz; 1H, H-2'), 3.92 (d, J = 2 Hz; 1H, H-3'), 4.14 (dd, J = 2 Hz, J = 3.5 Hz; 1H, H-1'), 7.1-7.4 (m; 5H, phenyl).- ^{13}C-NMR: 16.76 and 19.01 ($CH(CH_3)_2$), 31.99 ($CH(CH_3)_2$), 52.77 and 52.81 (3- and 6-OCH_3), 55.11 (C-2'), 58.36 (C-5), 60.97 (C-2), 62.81 (C-3'), 70.59 (C-1'), 125.76, 128.20, 128.46 and 136.94 (phenyl), 161.04 and 165.96 (C-3 and -6).
$C_{18}H_{24}N_2O_4$ (332.4): Calcd. C 65.06 H 7.22 Found C 65.03 H 7.18

(2R,5S,1'R,2'S,3'S)-2-(2',3'-Epoxy-1'-hydroxy-3'-phenyl-prop-1'-yl)-2,5-dihydro-5-isopropyl-3,6-dimethoxy-pyrazine (11b): Method B, with 0.63 g of 8b, 4 d at -20°C; yield 0.37 g (55 %) of 11b; b.p. 180°C/0.01 torr; diastereomer ratio (capillary GLC) 1:39 (10b:11b). ^{1}H-NMR: δ = 3.29 (dd, J = 3 Hz, J = 2 Hz; 1H, H-2'), 3.91 (d, J = 2 Hz; 1H, H-3'), 4.1-4.3 (m; 2H, H-1' and -2), 7.2-7.4 (m; 5H, phenyl).- ^{13}C-NMR: 16.75 and 19.06 ($CH(CH_3)_2$), 31.90 ($CH(CH_3)_2$), 52.70 and 52.74 (3- and 6-OCH_3), 55.28 (C-2'), 58.60 (C-5), 60.91 (C-2), 62.93 (C-3'), 70.91 (C-1'), 125.82, 128.19, 128.46 and 137.06 (phenyl), 161.09 and 165.89 (C-3 and -6).

(2R,5S,1'R,2'S)-2-(2',3'-Epoxy-1'-hydroxy-2'-methyl-prop-1'-yl)-2,5-dihydro-5-isopropyl-3,6-dimethoxy-pyrazine (10c): Method A, with 0.51 g of 8c, 1 d at -20°C; yield 0.41 g (74 %) of 10c; b.p. 140°C/0.01 torr; diastereomer ratio (capillary GLC) 66:1 (10c:11c). ^{1}H-NMR: δ = 1.49 (s; 3H, 2'-CH_3), 2.71 and 3.03 (2d, J = 5 Hz; AB-signal, H-3'), 4.15 (d, J = 2 Hz; 1H, H-1').- ^{13}C-NMR: 16.61, 18.38 and 19.09 ($CH(CH_3)_2$ and 2'-CH_3), 31.44 ($CH(CH_3)_2$), 51.65 (C-3'), 52.37 and

52.61 (3- and 6-OCH$_3$), 57.08 (C-5), 57.75 (C-2'), 60.44 (C-2), 72.06 (C-1'), 161.16 and 165.43 (C-3 and -6).
$C_{13}H_{22}N_2O_4$ (270.2): Calcd. C 57.77 H 8.14 Found C 57.83 H 8.11

(2R,5S,1'R,2'R,3'R)-2-(2',3'-Epoxy-1'-hydroxy-2'-methyl-but-1'-yl)-2,5-dihydro-5-isopropyl-3,6-dimethoxy-pyrazine (10d): Method A, with 0.54 g of 8d. 1 d at -20°C; yield 0.47 g (82 %) of 10d; b.p. 140°C/0.01 torr, m.p. 75°C; diastereomer ratio (capillary GLC) 199:1 (10d:11d). ^{1}H-NMR: δ = 1.35 (d, J = 5.5 Hz; 3H, H-4'), 1.41 (s; 3H, 2'-CH$_3$), 3.28 (q, J = 5.5 Hz; 1H, H-3'), 4.17 (m; 2H, H-1' and -2).- ^{13}C-NMR: 13.40, 14.44, 16.57 and 19.10 (CH(CH$_3$)$_2$, 3'-CH$_3$ and 2'-CH$_3$), 31.40 (CH(CH$_3$)$_2$), 52.20 and 52.59 (3- and 6-OCH$_3$), 56.00 (C-2'), 56.76 (C-5), 60.40 (C-2), 61.21 (C-2'), 72.99 (C-1'), 161.19 and 165.22 (C-3 and -6).
$C_{14}H_{24}N_2O_4$ (282.4): Calcd. C 59.15 H 8.45 Found C 58.99 H 8.50

(2R,5S,1'R,2'R)-2-(2',3'-Epoxy-1'-hydroxy-prop-1'-yl)-2,5-dihydro-5-isopropyl-3,6-dimethoxy-pyrazine (10e): Method A, with 0.48 g of 8e, 1 d at -20°C; yield 0.33 g (64 %) of 10e; b.p. 130°C/0.01 torr; diastereomer ratio (^{13}C-NMR, ^{1}H-NMR) 1.6:1 (10e:11e). ^{1}H-NMR: δ = 2.8 (m; 2H, H-3'), 3.3 (m; 1H, H-2'), 3.95 (m; 1H, H-1').- ^{13}C-NMR: 16.92 and 19.01 (CH(CH$_3$)$_2$), 32.16 (CH(CH$_3$)$_2$), 46.04 (C-2'), 52.28, 52.71 and 52.83 (3- and 6-OCH$_3$ and C-3'), 57.71 (C-5), 61.12 (C-2), 71.41 (C-1'), 161.18 and 166.60 (C-3 and -6).- Poor yield with method B and C.
$C_{12}H_{20}N_2O_4$ (256.3): Calcd. C 56.25 H 7.81 Found C 56.05 H 7.88

Hydrolysis of Compounds 10; Methyl (2R,3R)-2-amino-3-hydroxy-4,5-epoxy-alcanoates of type 12/13
O-Acetyl-10; General procedure: Acetanhydride (0.22 ml, 2.3 mmol) was added to a solution of 10 (2.0 mmol) and 4-(dimethylamino)-pyridine (81 mg, 0.66 mmol) in pyridine (15 ml). Stirring was continued for 12 h at r.t.. The mixture was poured into water (0°C, 15 ml)/dichloromethane (15 ml). After shaking the layers were separated and the water layer extracted twice with dichloromethane (20 ml each time). The combined organic layer was dried with magnesium sulfate, the solvent and the pyridine evaporated in vacuo and the crude O-acetyl-10 distilled.- IR (film): 1690-1695 (C=N), 1750 cm^{-1} (O-acetyl).

(2R,5S,1'R,2'S)-2-(1'-Acetoxy-2',3'-epoxy-2'-methyl-prop-1'-yl)-2,5-dihydro-5-isopropyl-3,6-dimethoxy-pyrazine (O-acetyl-10c): With 0.54 g of 10c; yield 0.56 g (90 %) of O-acetyl-10c; b.p. 140°C/0.01 torr.- ^{1}H-NMR: 0.65 and 1.04 (2d, J = 7 Hz; 6H, CH(CH$_3$)$_2$), 1.50 (s; 3H, 2'-CH$_3$), 1.94 (s; 3H, O-Ac), 2.30 (dsp, J = 7 Hz, J = 3.5 Hz; 1H, CH(CH$_3$)$_2$), 2.6 and 2.9 (2d, J = 6 Hz; AB-signal, H-3'), 3.66 and 3.69 (2s; 6H, 3- and 6-OCH$_3$), 3.94 (dd, J = ^{5}J = 3 Hz; 1H, H-5), 4.36 (dd, J = ^{5}J = 3 Hz; 1H, H-2), 5.34 (d, J = 3 Hz; 1H, H-1').- ^{13}C-NMR: 16.43, 18.69 and 19.09 (CH(CH$_3$)$_2$ and 2'-CH$_3$), 20.67 (O$_2$CCH$_3$), 51.99, 52.50 and 52.53 (3- and 6-OCH$_3$ and C-3'), 55.52 and 56.64 (C-5 and -2'), 60.39 (C-2), 72.95 (C-1'), 160.41 and 164.63 (C-3 and -6), 169.35 (O$_2$CCH$_3$).
$C_{15}H_{24}N_2O_5$ (312.4): Calcd. C 57.69 H 7.69 Found C 57.61 H 7.82

(2R,5S,1'R,2'S,3'R)-2-(1'-Acetoxy-2',3'-epoxy-2'-methyl-but-1'-yl)-2,5-dihydro-5-isopropyl-3,6-dimethoxy-pyrazine (O-acetyl-10d): With 0.57 g of 10d; yield 0.62 g (95 %) of O-acetyl-10d; b.p. 140°C/0.01 torr.- ^{1}H-NMR: 0.60 and 0.98 (2d, J = 7 Hz; 6H, CH(CH$_3$)$_2$), 1.21 (d, J = 6 Hz; 3H, H-4'), 1.35 (s; 3H, 2'-CH$_3$), 1.94 (s; 3H, O-Ac), 2.23 (dsp, J = 7 Hz, J = 3.5 Hz; 1H, CH(CH$_3$)$_2$), 3.02 (q, J = 6 Hz; 1H, H-3'), 3.60 and 3.63 (2s; 6H, 3- and 6-OCH$_3$), 3.87 (dd, J = ^{5}J = 3.5 Hz; 1H, H-5), 4.26 (dd, J = ^{5}J = 3.5 Hz; 1H, H-2), 5.29 (d, J = 3 Hz; 1H, H-1').
$C_{16}H_{26}N_2O_5$ (326.4): Calcd. C 58.89 H 7.97 Found C 59.04 H 8.02

(2R,5S,1'R,2'S,3'R)-2-(1'-Acetoxy-2',3'-epoxy-3'-phenyl-prop-1'-yl)-2,5-dihydro-5-isopropyl-3,6-dimethoxy-pyrazine (O-acetyl-10b): With 0.66 g of 10b; yield 0.69 g (92 %) of O-acetyl-10b; b.p. 185°C/0.01 torr.- ^{1}H-NMR: 0.66 and 1.04 (2d, J = 7 Hz; 6H, CH(CH$_3$)$_2$), 2.08 (s; 3H, O-Ac), 2.29 (dsp, J = 7 Hz, J = 3.5 Hz; 1H, CH(CH$_3$)$_2$), 3.02 (dd, J = 2 Hz, J = 7 Hz; 1H, H-2'), 3.68 and 3.70 (2s; 6H, 3- and 6-OCH$_3$), 3.92 (dd, J = ^{5}J = 3.5 Hz; 1H, H-5), 3.97 (d, J = 2 Hz; 1H, H-2'), 4.33 (dd, J = ^{5}J = 3.5 Hz; 1H, H-2), 5.22 (d, J = 3 Hz; 1H, H-1'), 7.2-7.4 (m; 5H, phenyl).
$C_{20}H_{26}N_2O_5$ (374.4): Calcd. C 64.17 H 6.95 Found C 64.02 H 6.93

Hydrolysis; 12a,b and 13: 0.1 N HCl (40 ml, 40 mmol) was added to a solution of

O-acetyl-10 (2.0 mmol) in THF (5 ml) and stirring continued for 24 h at r.t.. The mixture was extracted with ether (30 ml) which was discarded. The water layer was saturated with sodium chloride, ether was added (30 ml) and the solution brought to pH 8-10 with conc. ammonia. The ether layer was separated and the water layer extracted four times with ether (30 ml each time). The combined ether layer was dried with magnesium sulfate and the ether evaporated in vacuo. Methyl valinate 5 was evaporated at 30°C/0.01 torr (Kugelrohr apparatus) and the crude 12a,b or 13 purified by flash chromatography on silica gel. Upon addition of up to 45 mol% Eu(tfc)$_3$ the ^{1}H-NMR signals shifted but did not split; i.e. ee > 95 %.- IR for 21a,b (film): 1655 (N-Ac), 1740 (CO_2Me), 3150-3550 cm^{-1} (OH and NH).

Methyl (2R,3R,4S)-2-acetamino-4,5-epoxy-3-hydroxy-4-methyl-pentanoate (12a): With 0.62 g of O-acetyl-10c, yield 0.22 g (51 %) of 12a; chromatography: ether/methanol 12:1 (R_f = 0.41).- ^{1}H-NMR: 1.48 (s; 3H, 3-CH_3), 2.07 (s; 3H, N-Ac), 2.65 and 2.93 (2d, J = 5.5 Hz; 2H, H-4), 3.83 (s; 3H, CO_2CH_3), 3.85 (s; 1H, OH), 4.39 (d, J = 2 Hz; 1H, H-3), 4.99 (dd, J = 2 Hz, J = 9 Hz; 1H, H-2), 6.35 (d, J = 9 Hz; 1H, NH).
$C_9H_{15}NO_5$ (217.2): Calcd. C 49.74 H 6.91 Found C 49.88 H 6.88

Methyl (2R,3R,4S,5R)-2-acetamino-4,5-epoxy-3-hydroxy-4-methyl-hexanoate (12b): With 0.65 g of O-acetyl-10d, yield 0.28 g (60 %) of 12b; chromatography: ether/methanol 12:1 (R_f = 0.54).- ^{1}H-NMR: 1.26 (d, J = 6 Hz; 3H, H-6), 1.42 (s; 3H, 4-CH_3), 2.05 (s; 3H, N-Ac), 2.37 (b; 1H, OH), 3.18 (q, J = 6 Hz; 1H, H-5), 3.82 (s; 3H, CO_2CH_3), 4.25 (d, J = 1.5 Hz; 1H, H-3), 4.99 (dd, J = 1.5 Hz, J = 9 Hz; 1H, H-2), 6.21 (d, J = 9 Hz; 1H, NH).
$C_{1017}NO_5$ (231.3): Calcd. C 51.94 H 7.35 Found C 51.76 H 7.49

Methyl (2R,3R,4S,5R)-3-acetoxy-2-amino-4,5-epoxy-5-phenyl-pentanoate (13): With 0.75 g of O-acetyl-10b, yield 0.30 g (54 %) of 13; chromatography: ether (R_f = 0.46).- IR (film): 1740 (CO_2Me and O-Ac), 3250-3450 cm^{-1} (NH_2).- ^{1}H-NMR: 2.05 (s; 3H, O-Ac), 3.1 (b; 2H, NH_2), 3.70 (dd, J = 2 Hz, J = 4 Hz; 1H, H-4), 3.80 (s; 3H, CO_2CH_3), 4.08 (d, J = 2 Hz; 1H, H-5), 4.31 (d, J = 6.5 Hz; 1H, H-2), 5.2 (dd, J = 4 Hz, J = 6.5 Hz; 1H, H-3), 7.3-7.6 (m; 5H, phenyl).

Compounds 14a and 15a; Sodium hydride (50 mg, 2.1 mmol) and magnesium sulfate (0.25 g, 2.1 mmol) were added to a solution of benzylthiol (0.27 g, 2.2 mmol) in abs. methanol (10 ml). To this mixture a solution of 10c (0.54 g, 2.0 mmol) in methanol (2 ml) was added and stirring continued for 10 h at r.t.. Glacial acetic acid (0.13 g, 2.1 mmol) was added and the mixture poured into water (10 ml)/ether (20 ml). The ether layer was separated and the water layer extracted twice with ether (30 ml each time). The combined ether layer was dried with magnesium sulfate, the solvent evaporated (<25°C) and the residue purified by flash chromatography on silica gel (ether/ petrolether, b.p. 40-55°C, 2:1; R_f(14a) = 0.23, R_f(15a) = 0.43). Yield 0.63 g (80 %) of 14a and 73 mg (10 %) of 15a; 14a cyclized quantitatively on standing at r.t. within 2 d to 15a.

(2R,5S,1'R,2'R)-2-(3'-Benzylthio-1',2'-dihydroxy-2'-methyl-prop-1'-yl)-2,5-dihydro-5-isopropyl-3,6-dimethoxy-pyrazine (14a): IR (film): 1680 (C=N), 3200-3500 cm^{-1} (OH).- ^{1}H-NMR: 0.69 and 1.01 (2d, J = 7 Hz; 6H, $CH(C\underline{H}_3)_2$), 1.13 (s; 3H, 2'-CH_3), 2.20 (dsp, J = 7 Hz, J = 3.5 Hz; 1H, $C\underline{H}(CH_3)_2$), 2.43 (d, J = 10 Hz; 1H, OH), 2.69 and 2.82 (2d, J = 12 Hz; AB-signal, H-3'), 3.61 and 3.75 (2s; 6H, 3- and 6-OCH_3), 3.78 (s; 2H, S-$C\underline{H}_2$-phenyl), 4.04 (b; 2H, H-5 and H-1'), 5.27 (b; 1H, OH), 7.2-7.4 (m; 5H, phenyl).

(2R,3R,3aR,6S)-2-Benzylthiomethyl-2,3,3a,6-tetrahydro-3-hydroxy-6-isopropyl-5-methoxy-2-methyl-furo [2,3-b] -pyrazine (15a): IR (film): 1650 and 1700 (C=N), 3100-3300 cm^{-1} (OH).- ^{1}H-NMR: 0.90 and 0.98 (2d, J = 7 Hz; 6H, $CH(C\underline{H}_3)_2$), 1.41 (s; 3H, 2-CH_3), 2.08 (dsp, J = 7 Hz, J = 3.5 Hz; 1H, $C\underline{H}(CH_3)_2$), 2.63 and 2.73 (2d, J = 14 Hz; AB-signal, 2-CH_2), 3.73 (s; 3H, OCH_3), 3.75 and 3.85 (2d, J = 13 Hz; 2H, S-$C\underline{H}_2$-phenyl), 4.00 (dd, ^{5}J = 3 Hz, J = 5.5 Hz; 1H, H-6), 4.11 (dd, ^{5}J = 3 Hz, J = 10 Hz; 1H, H-3a), 4.26 (d, J = 10 Hz; 1H, H-3), 4.56 (b; 1H, OH), 7.3-7.4 (m; 5H, phenyl).- ^{13}C-NMR: 18.61, 19.43 and 20.70 (2-CH_3 and $CH(\underline{C}H_3)_2$), 33.45 ($\underline{C}H(CH_3)_2$), 37.28 (2-CH_2), 39.04 (S-$\underline{C}H_2$-phenyl), 53.50 (OCH_3), 59.68 and 64.06 (C-3 and -6), 76.51 (C-3), 87.86 (C-2), 126.99, 128.39, 129.23 and 137.92 (phenyl), 166.50 and 169.30 (C-2 and -5).
$C_{19}H_{26}N_2O_3S$ (362.2): Calcd. C 62.98 H 7.18 Found C 63.02 H 7.17

Compounds 14b and 15b: Sodium azide (0.20 g, 3.0 mmol) and magnesium sulfate (0.36 g, 3.0 mmol) were added to a solution of 10c (0.54 g, 2.0 mmol) in abs. methanol (15 ml). The mixture was heated under reflux for 24 h. Then glacial acetic acid (0.18 g, 3.0 mmol) was added and the solvent evaporated in vacuo. The residue was shaken with ether (25 ml)/water (15 ml), the layers were separated and the water layer extracted three times with ether (25 ml each time). The ether extract was dried with magnesium sulfate and the ether evaporated in vacuo. Yield ≈ 40% of 14b and ≈ 40% of 15b (^1H-NMR). After standing for 4 d at r.t. 14b had cyclized quantitatively to 15b, which was purified by flash chromatography (silica gel, ether/petrolether 2:1; R_f = 0.15); yield 0.39 g (70 %) of pure 15b.

(2S,3R,3aR,6S)-2-Azidomethyl-2,3,3a,6-tetrahydro-3-hydroxy-6-isopropyl-5-methoxy-2-methyl-furo[2,3-b]-pyrazine (15b): IR (film): 1650 and 1700 (C=N), 2100 (N_3), 3100-3300 cm^{-1} (OH).- ^1H-NMR: 0.72 and 1.01 (2d, J = 7 Hz; 6H, $CH(C\underline{H}_3)_2$), 1.43 (s; 3H, 2-CH_3), 2.12 (dsp, J = 7 Hz, J = 5.5 Hz; 1H, $C\underline{H}(CH_3)_2$), 3.31 and 3.56 (2d, J = 12 Hz; AB-signal, 2-CH_2), 3.78 (s; 3H, OCH_3), 4.05 (dd, ^5J = 2 Hz, J = 5.5 Hz; 1H, H-6), 4.15 (dd, ^5J = 2 Hz, J = 10 Hz; 1H, H-3a), 4.23 (d, J = 10 Hz; 1H, H-3), 4.99 (b; 1H, OH).-
High resolution MS (70 eV): Found M^+ 281.148789 Calcd. M^+ 281.148789 for $C_{12}H_{19}N_5O_3$

(2R,5S,1'R,2'S)-2-(1'-Carbobenzoxy-2',3'-epoxy-2'-methyl-prop-1'-yl)-2,5-dihydro-5-isopropyl-3,6-dimethoxy-pyrazine (16): A solution of 10c (0.54 g, 2.0 mmol) in THF (5 ml) was injected to NaH (50 mg, 2.1 mmol) and THF (10 ml) and stirring was continued for 2 h at r.t.. Then carbobenzoxychloride (0.39 g, 2.3 mmol) in THF (5 ml) was added at 0°C and the crude 16 chromatographied in ether/petrolether 1:1 (R_f = 0.61). Yield 0.72 g (90 %) of 16.- IR (film): 1700 (C=N), 1760 cm^{-1} (C=O).- ^1H-NMR: 0.68 and 1.04 (2d, J = 7 Hz; 6H, $CH(C\underline{H}_3)_2$), 1.54 (s; 3H, 2'-CH_3), 2.30 (dsp, J = 7 Hz, J = 3.5 Hz; 1H, $C\underline{H}(CH_3)_2$), 2.65 and 2.96 (2d, J = 6 Hz; AB-signal, H-3'), 3.63 and 3.67 (2s; 6H, 3- and 6-OCH_3), 3.96 (dd, ^5J = 3.5 Hz, J = 3.5 Hz; 1H, H-5), 4.37 (dd, ^5J = 3.5 Hz, J = 3.5 Hz; 1H, H-2), 5.12 and 5.18 (2d, J = 12 Hz; AB-signal, O-$C\underline{H}_2$-phenyl), 5.27 (d, J = 3.5 Hz; 1H, H-1'), 7.38 (s; 5H, phenyl).-
High resolution MS (70 eV): Found M^+ 404.194723 Calcd. M^+ 404.194723 for $C_{21}H_{28}N_2O_6$

(2R,5S,1'R,2'R)-2-(1',2'-Carbonyldioxy-3'-hydroxy-2'-methyl-prop-1'-yl)-2,5-dihydro-5-isopropyl-3,6-dimethoxy-pyrazine (17): A solution of $AlCl_3$ (0.27 g, 2.0 mmol) in ether (5 ml) was added to a solution of 16 (0.40 g, 1.0 mmol) in ether (10 ml) and stirring continued for 3 h at r.t.. Then phosphate buffer (10 ml, pH 7) and ether (10 ml) were added to the mixture. The ether layer was separated and the water layer extracted three times with ether (20 ml each time). The ether extract was dried with magnesium sulfate and the solvent evaporated in vacuo. The crude 17 was purified by chromatography with ether (R_f = 0.43). Yield 0.16 g (50 %) of 17.- IR (film): 1690 (C=N), 1790 (C=O), 3300-3550 cm^{-1} (OH).- ^1H-NMR: 0.70 and 1.04 (2d, J = 7 Hz; 6H, $CH(C\underline{H}_3)_2$), 1.73 (s; 3H, 2'-CH_3), 2.29 (dsp, J = 7 Hz, J = 3.5 Hz; 1H, $C\underline{H}(CH_3)_2$), 2.58 (b; 1H, OH), 3.69 and 3.76 (2s; 8H, 3- and 6-OCH_3 and H-3'), 4.06 (dd, ^5J = 3.5 Hz, J = 3.5 Hz; 1H, H-5), 4.16 (dd, ^5J = 3.5 Hz, J = 1 Hz; 1H, H-2), 5.03 (d, J = 1 Hz; 1H, H-1').-
High resolution MS (70 eV): Found M^+ 314.147788 Calcd. M^+ 314.147788 for $C_{14}H_{22}N_2O_6$

Cyclopropanation of Compounds 8; Compounds 19: General procedure: A solution of diethyl zinc in hexane (3.71 g, 4.5 mmol, 15% wt/wt) was injected into a solution of 8 (3.0 mmol) in dry hexane (20 ml) at -20 or 0°C. Then diiodomethane (1.61 g, 6.0 mmol) was added dropwise at the same temperature and stirring continued for 3-20 h at 0 or 20°C. The mixture was poured into a saturated aqueous solution of ammonium chloride (30 ml) and the water layer extracted four times with ether (50 ml each time). The ether extract was dried with magnesium sulfate and the solvent evaporated in vacuo. The crude 19 was purified by chromatography (column 5 cm in diameter; 50 g silica gel, 0.05-0.2 mm, 70-270 mesh). The silica gel was eluated with ether/petrolether 1:2 (400 ml) which was discarded, followed by eluation with ether (200 ml) yielding pure 19.- In the ^1H- and ^{13}C-NMR spectra only one diastereomer of 19 was detectable.- IR (film): 1695 (C=N), 3060 or 3070 (cyclopropyl-H), 3200-3600 cm^{-1} (OH).

(2R,5S,1'R,2'R,3'R)-2,5-Dihydro-2-(1'-hydroxy-2',3'-methylene-but-1'yl)-5-isopropyl-3,6-dimethoxy-pyrazine (19a): With 0.76 g of 8a; addition at 0°C, stirring for 20 h at 20°C. Yield 0.55 g (68 %) of 19a.- ${}^{1}H$-NMR: 0.25-0.34 (m; 1H, cyclopropyl), 0.52-0.64 (m; 1H, cyclopropyl), 0.7-1.0 (m; 2H, cyclopropyl), 0.72 and 1.03 (2d, J = 7 Hz; 6H, $CH(C\underline{H}_3)_2$), 1.06 (d, J = 8 Hz; 3H, H-4), 2.25 (d, J = 8 Hz; 1H, OH), 2.29 (dsp, J = 7 Hz, J = 3.5 Hz; 1H, $C\underline{H}(CH_3)_2$), 3.27 (ddd, J = 3.5 Hz, J = 8 Hz, J = 8 Hz; 1H, H-1'), 3.73 (s; 6H, 3- and 6-OCH_3), 4.00 (dd, ${}^{5}J$ = J = 3.5 Hz; 1H, H-5), 4.13 (dd, ${}^{5}J$ = J = 3.5 Hz; 1H, H-2).- ${}^{13}C$-NMR: 11.15 (CH_2, cyclopropyl), 11.28 (C-4'), 16.70, 18.39, 19.10 and 22.98 ($CH(\underline{C}H_3)_2$, C-3' and -2'), 31.78 ($\underline{C}H(CH_3)_2$), 52.52 (3- and 6-OCH_3), 60.36 and 60.82 (C-2 and -5), 76.78 (C-1'), 162.00 and 165.18 (C-3 and -6).
$C_{14}H_{24}N_2O_3$ (268.3): Calcd. C 62.66 H 9.01 Found C 62.80 H 9.17

(2R,5S,1'R,2'R,3'R)-2,5-Dihydro-2-(1'-hydroxy-2',3'-methylene-3'-phenyl-prop-1'yl)-5-isopropyl-3,6-dimethoxy-pyrazine (19b): With 0.95 g of 8b; addition at -20°C, stirring for 3 h at 20°C. Yield 0.60 g (61 %) of 19b.- ${}^{1}H$-NMR: 0.69 and 1.01 (2d, J = 7 Hz; 6H, $CH(C\underline{H}_3)_2$), 1.0 (ddd, ${}^{2}J$ = 5 Hz, J = 8.5 Hz, J = 5 Hz; A-part of ABCD, 1H, CH_2-cyclopropyl), 1.1 (ddd, ${}^{2}J$ = 5 Hz, J = 8.5 Hz, J = 5.5 Hz; B-part of ABCD, 1H, CH_2-cyclopropyl), 1.6 (dddd, J = 4.5 Hz, J = 8.5 Hz, J = 5.5 Hz, J = 8 Hz; C-part of ABCD, 1H, H-2'), 1.9 (ddd, J = 4.5 Hz, J = 8.5 Hz, J = 5 Hz; D-part of ABCD, 1H, H-3'), 2.29 (dsp, J = 7 Hz, J = 3.5 Hz; 1H, $C\underline{H}(CH_3)_2$), 2.36 (bd, J = 8 Hz; 1H, OH), 3.5-3.7 (m; 1H, H-1'), 3.72 (2s; 6H, 3- and 6-OCH_3), 3.91 (dd, ${}^{5}J$ = J = 3.5 Hz; 1H, H-5), 4.16 (dd, ${}^{5}J$ = J = 3.5 Hz; 1H, H-2), 7.0-7.4 (m; 5H, phenyl).- ${}^{13}C$-NMR: 13.74 (CH_2, cyclopropyl), 16.76 and 19.06 ($CH(\underline{C}H_3)_2$), 21.10 and 25.65 (C-2' and -3'), 31.86 ($\underline{C}H(CH_3)_2$), 52.57 (3- and 6-OCH_3), 60.01 and 60.88 (C-2 and -5), 75.74 (C-1'), 125.54, 126.02, 128.26 and 142.57 (phenyl), 161.70 and 165.49 (C-3 and -6).
$C_{19}H_{26}N_2O_3$ (330.4): Calcd. C 69.07 H 7.93 Found C 69.06 H 8.08

(2R,5S,1'S)-2,5-Dihydro-2-(1'-hydroxy-2'-methyl-2',3'-methylene-prop-1'yl)-5-isopropyl-3,6-dimethoxy-pyrazine (19c): With 0.76 g of 8c; addition at 0°C, stirring for 20 h at 20°C. Yield 0.61 g (76 %) of 19c.- ${}^{1}H$-NMR: 0.25-0.65 (m; 4H, cyclopropyl), 0.72 and 1.05 (2d, J = 7 Hz; 6H, $CH(C\underline{H}_3)_2$), 1.20 (s; 3H, 2'-CH_3), 2.27 (dsp, J = 7 Hz, J = 3.5 Hz; 1H, $C\underline{H}(CH_3)_2$), 2.44 (d, J = 8 Hz; 1H, OH), 3.28 (dd, J = 3.5 Hz, J = 8 Hz; 1H, H-1'), 3.71 (s; 6H, 3- and 6-OCH_3), 3.97 (dd, ${}^{5}J$ = J = 3.5 Hz; 1H, H-5), 4.17 (dd, ${}^{5}J$ = J = 3.5 Hz; 1H, H-2).- ${}^{13}C$-NMR: 10.50 and 13.08 (CH_2, cyclopropyl), 16.74, 19.11 and 19.29 ($CH(\underline{C}H_3)_2$ and 2'-CH_3), 19.25 (C-2'), 31.66 ($\underline{C}H(CH_3)_2$), 52.52 and 52.70 (3- and 6-OCH_3), 58.77 (C-5), 60.58 (C-2), 77.61 (C-1'), 162.20 and 165.66 (C-3 and -6).
$C_{14}H_{24}N_2O_3$ (268.3): Calcd. C 62.66 H 9.01 Found C 62.55 H 9.13

Hydrolysis of Compounds 20; Methyl 2-amino-3-hydroxy-4,5-methylene-alcanoates of type 20

O-Acetyl-19; General procedure: See above for O-acetyl-10; the crude O-acetyl-19 was not distilled but purified by chromatography with ether/ petrolether 1:1.- IR (film): 1740 (CO_2Me), 1695 cm^{-1} (C=N).

(2R,5S,1'R,2'R,3'R)-2-(1'-Acetoxy-2',3'-methylene-but-1'-yl)-2,5-dihydro-5-isopropyl-3,6-dimetoxy-pyrazine (O-acetyl-19a): With 0.54 g of 19a; yield 0.53 g (86 %) of O-acetyl-19a.- ${}^{1}H$-NMR: 0.2-0.4 (m; 1H, cyclopropyl), 0.68 and 1.06 (2d, J = 7 Hz; 6H, $CH(C\underline{H}_3)_2$), 1.06 (d, covered; 3H, H-4'), 0.6-1.3 (m; 3H, cyclopropyl), 1.99 (s; 3H, O-Ac), 2.32 (dsp, J = 7 Hz, J = 3.5 Hz; 1H, $C\underline{H}(CH_3)_2$), 3.68 and 3.78 (2s; 6H, 3- and 6-OCH_3), 3.93 (dd, J = ${}^{5}J$ = 3.5 Hz; 1H, H-5), 4.23 (dd, J = 3 Hz, ${}^{5}J$ = 3.5 Hz; 1H, H-2), 4.62 (dd, J = 3 Hz, J = 9.5 Hz; 1H, H-1').- ${}^{13}C$-NMR: 11.71 (C-4'), 12.34 (CH_2, cyclopropyl), 16.39, 18.36, 19.19, 20.59 and 21.09 ($CH(\underline{C}H_3)_2$, $O_2C\underline{C}H_3$, C-2' and -3'), 31.29 ($\underline{C}H(CH_3)_2$), 52.38 and 52.49 (3- and 6-OCH_3), 59.00 and 60.49 (C-2 and -5), 78.56 (C-1'), 161.24 and 164.53 (C-3 and -6), 170.18 ($O_2\underline{C}CH_3$).
High resolution MS (70 eV): Found M^+ 310.189258 Calcd. M^+ 310.189258 for $C_{16}H_{26}N_2O_4$

(2R,5S,1'R,2'R,3'R)-2-(1'-Acetoxy-2',3'-methylene-3'-phenyl-prop-1'-yl)-2,5-dihydro-5-isopropyl-3,6-dimetoxy-pyrazine (O-acetyl-19b): With 0.66 g of 19b; yield 0.61 g (82%) of O-acetyl-19b.- ${}^{1}H$-NMR: 0.66 and 1.03 (2d, J = 7 Hz; 6H, $CH(C\underline{H}_3)_2$), 0.8-1.3 (m; 2H, cyclopropyl), 1.7-2.1 (m; 2H, H-2' and -3'), 2.02 (s; 3H, O-Ac), 2.27 (dsp, J = 7 Hz, J = 3.5 Hz; 1H, $C\underline{H}(CH_3)_2$), 3.66 and 3.73 (2s; 6H, 3- and 6-OCH_3), 3.88 (dd, J = ^5J = 3.5 Hz; 1H, H-5), 4.28 (dd, J = 3 Hz, ^5J = 3.5 Hz; 1H, H-2), 4.86 (dd, J = 3 Hz, J = 9 Hz; 1H, H-1'), 7.1-7.4 (m; 5H, phenyl).- ^{13}C-NMR: 14.88 (CH_2, cyclopropyl), 16.45 and 19.13 ($CH(\underline{C}H_3)_2$), 21.06, 21.73 and 22.77 ($O_2C\underline{C}H_3$, C-2' and -3'), 31.40 ($\underline{C}H(CH_3)_2$), 52.41 and 52.52 (3- and 6-OCH_3), 58.78 and 60.55 (C-2 and -5), 77.90 (C-1'), 125.79, 126.48, 128.29 and 142.03 (phenyl), 160.94 and 164.61 (C-3 and -6), 170.22 ($O_2\underline{C}CH_3$).

Hydrolysis of O-acetyl-**19**; **20a**,**b**; General procedure: See above for the hydrolysis of O-acetyl-**10**; Dihydropyrazine **19** (2.0 mmol), THF (25 ml) and 0.2 N HCl (2.5 ml, 5.0 mmol) were used and **20** purified by cristallisation from ether/petrolether.

Methyl (2R,3S,4R,5R)-2-acetamino-3-hydroxy-4,5-methylene-hexanoate (**20a**): With 0.62 g of O-acetyl-**19a**; yield 0.33 g (76 %) of **20a**; m.p. 105°C.- IR (KBr): 3400-3100 (OH,NH), 3060 (cyclopropyl-H), 1760 (CO_2Me), 1650 cm^{-1} (NH-Ac).- ^1H-NMR: 0.37 (ddd, J = 4.5 Hz, J = 5 Hz, J = 8 Hz; 1H, CH_2/cyclopropyl), 0.5-0.65 (m; 1H, CH_2/cyclopropyl), 0.65-0.8 (m; 2H, H-4 and -5), 1.02 (d, J = 5 Hz; 1H, H-6), 2.11 (s; 3H, NH-Ac), 2.5 (b; 1H, OH), 3.38 (dd, J = 3 Hz, J = 8.5 Hz; 1H, H-3), 3.78 (s; 3H, CO_2Me), 4.80 (dd, J = 3 Hz, J = 9 Hz; 1H, H-2), 6.5 (bd, J = 9 Hz; 1H, NH).- ^{13}C-NMR: 10.92 (C-6), 12.06 (CH_2/cyclopropyl), 18.07 (C-5), 22.90 and 23.23 ($NHCH\underline{C}H_3$ and C-4), 52.42 ($CO_2\underline{C}H_3$), 57.22 (C-2), 75.79 (C-3), 171.09 and 171.46 ($\underline{C}O_2Me$ and $NH\underline{C}OMe$).

$C_{10}H_{17}NO_4$ (215.2): Calcd. C 55.80 H 7.96 Found C 55.92 H 7.92

Methyl (2R,3S,4R,5R)-2-acetamino-3-hydroxy-4,5-methylene-5-phenyl-pentanoate (**20b**): With 0.74 g of O-acetyl-**19b**; yield 0.36 g (65 %) of **20b**; m.p. 136°C.- IR (KBr): 3460 (OH), 3320 (NH), 3070 (cyclopropyl-H), 1715 (CO_2Me), 1645 cm^{-1} (NH-Ac).- ^1H-NMR: 1.03 (2ddd, J = 5 Hz, J = 5 Hz, J = 9 Hz; AB-part of ABCDX, 2H, CH_2/cyclopropyl), 1.37 (dddd, J = 5 Hz, J = 5 Hz, J = 9 Hz, ^2J = 8 Hz; C-part of ABCDX, 1H, H-4), 1.90 (ddd, J = 9 Hz, J = 5 Hz, J = 5 Hz; D-part of ABCDX, 1H, H-5), 2.05 (s; 3H, NH-Ac), 2.9 (b; 1H, OH), 3.64 (s; 3H, CO_2Me), 3.67 (dd, J = 3 Hz, J = 8 Hz; 1H, H-3), 4.82 (dd, J = 3 Hz, J = 8.5 Hz; 1H, H-2), 6.43 (bd, J = 8.5 Hz; 1H, NH), 7.0-7.3 (m; 5H, phenyl).- ^{13}C-NMR: 13.30 (CH_2/cyclopropyl), 20.78 and 25.32 (C-4 and -5), 22.98 ($NHCH\underline{C}H_3$), 52.51 ($CO_2\underline{C}H_3$), 57.40 (C-2), 74.82 (C-3), 125.91, 126.22, 128.34 and 141.35 (phenyl), 171.01 and 171.28 ($\underline{C}O_2Me$ and $NH\underline{C}OMe$).

$C_{15}H_{19}NO_4$ (277.3): Calcd. C 64.94 H 6.91 Found C 64.97 H 6.97

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