Ru(II)-Catalysis in preparation of sterically congested and stereochemically homogeneous heterospiranes

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Sterically highly crowded dienes may undergo RCM reactions to furnish heterocyclic bispiranes in high yields. The diene substrates were C_1-bridged bis[(2*R*)-5-alkenyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazines]. The carbonyl or hydroxymethyl bridges were prepared in stereoselective reactions. A free hydroxy group in the present series was incompatible with the RCM reaction. The ring closure proceeded readily after *O*-methylation. The course of the stereochemical transformations has been verified by X-ray analyses.

Introduction

Recent reviews highlight the importance and wide applicability of ring closing metathesis (RCM) in the construction of cyclic structures.[1–4] In work to further elucidate the chemistry of such cyclization reactions we herein report on the use of Ru(II)-catalysis in RCM reactions in sterically highly congested substrates. The course of the stereochemical transformations has been ascertained by single crystal X-ray analyses. Ruthenium alkylidene catalysts are compatible with a wide variety of functional groups in the substrates undergoing ring closure.[1,4] $PhCH{=}RuCl_2(PCy_3)_2$ is a widely used Ru catalyst complex that is tolerant to a variety of functional groups. The RCM reaction is normally recommended for terminal diene substrates, but this can be extended to non-terminal double bonds. Thus we have recently reported that the RCM reaction proceeded well for dienes where the terminal olefin carbon was substituted by a hydroxymethyl or a formyl group.[5] The substrate with the formyl group is a β-substituted acrolein, and the double bond is therefore electrophilic. The RCM reaction also proceeded readily when the double bond was polarized with the electron-withdrawing group facing the tethering moiety, but the rate was lower than without electronic deactivation.[6] This finding is not in full accord with a recent publication where reactions were reported to have failed for dienes substituted by an electron-withdrawing group.[7]

Our diene substrates were unsubstituted dialkenes that were highly sterically congested at the tethering moiety. The substrates for the RCM reactions were available from previous synthetic studies of conformationally rigidified cyclic amino acid analogues.[8,9]

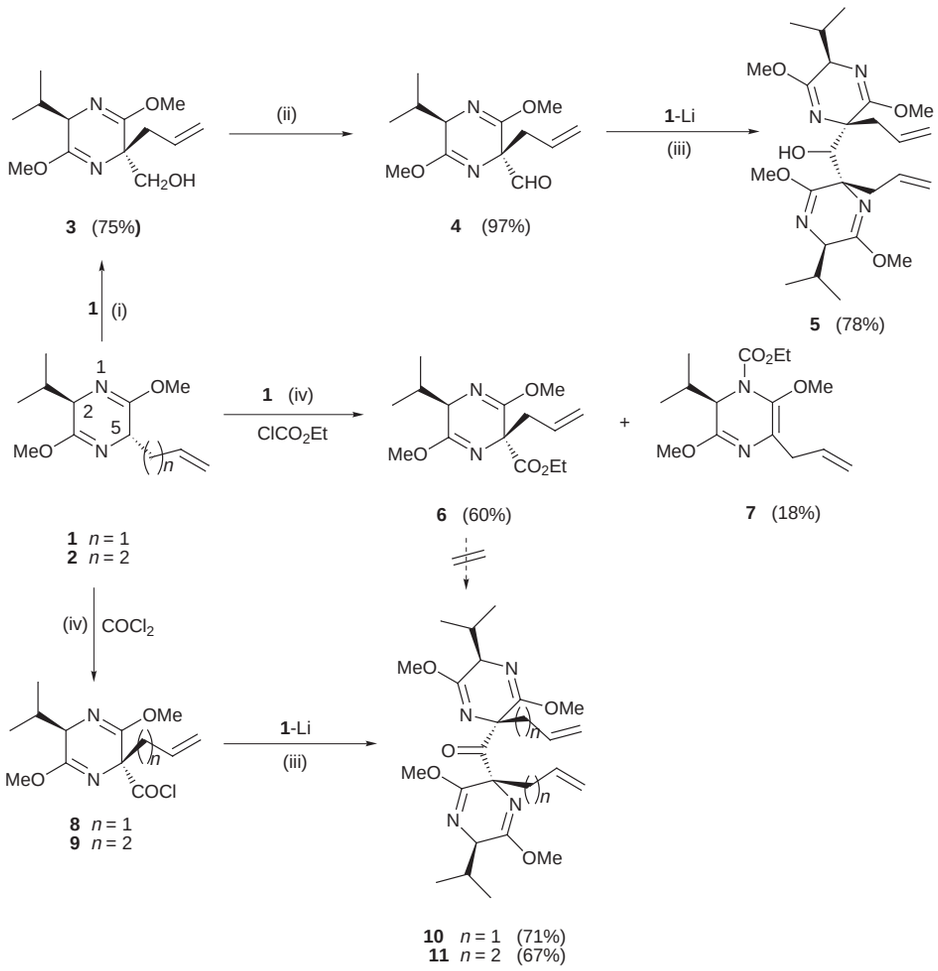
Results and discussion

The desired substrates were prepared as shown in Scheme 1. The one-carbon unit that is eventually to become the chain between two bislactim ethers was introduced as a hydroxymethyl substituent at C-5 in a reaction between the lithiated species of the 5-alkenyl substrate **1** and paraformaldehyde. In dialkylation reactions of the parent bislactim ether, (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine, introduction of the second alkyl group at C-5 has been found to be *trans* to the isopropyl group.[8,9] The *trans*-isomer **3** was also formed in this case. Swern oxidation at low temperature proceeded readily to furnish the aldehyde **4**. Addition of lithiated bislactim ether **1** onto the carbonyl group gave the sterically congested alcohol **5** in 75% yield.

In our first attempt to prepare the ketones **10** and **11** the lithiated derivative of the bislactim ether **1** was treated with ethyl chloroformate. The desired C-5 carboxylic ester derivative **6** was formed in 60% yield. The product has the carboxylic ester group *trans* to the isopropyl group and was the only stereoisomer seen. The chemoselectivity, however, was low in that a second product was obtained and identified as the *N*-acylated derivative **7**. An attempt to convert the ester **6** into the ketone **10** by treatment with the lithiated bislactim ether **1** at low temperature, by analogy to the above reaction of the formyl derivative **4** which yielded the alcohol **5**, gave essentially no reaction. The carbonyl reactivity is low because of steric shielding. Therefore the electrophilicity of the carbonyl group was increased by preparing the acid chlorides **8** and **9** from the propenyl and butenyl substrates **1** and **2**. The chlorocarbonylations were effected by allowing lithiated bislactim ether to react with phosgene at −78 °C in THF. The acid chlorides generated *in situ* were reacted further with a lithiated bislactim ether, either **1** or **2**, to furnish the ketone bridged structures **10** and **11** in good yields.

The ketone **10** and the alcohol **5** were interconverted by lithium aluminium hydride (LAH) reduction of the ketone **10** (93%) and by Swern oxidation of the alcohol **5** (46%) (Scheme 2). The ^1H and ^{13}C NMR spectra of the ketone are consistent with C_2-symmetry. The spectra of the alcohol **5** and the derived methyl ether **12** are characterized by a double set of signals of equal intensity. Single crystal X-ray structure analyses confirmed the structures **5** and **10** that were assigned to the products (Figs. 1 and 2).

The RCM reaction of the alcohol **5** failed (Scheme 3). Therefore the hydroxy group was protected as the methyl ether **12**. Methylation of the sodium alkoxide derived from the alcohol **5** was effected by methyl iodide in almost quantitative yield. An attempt to prepare a selenocarbonyl derivative of the alcohol for radical deoxygenation by treatment of the alcohol **5** with phosgene at low temperature followed by benzeneselenol, furnished instead the urethane **13**. Therefore the intermediate chlorocarbonate undergoes a faster intramolecular *N*-acylation reaction than the wished for intermolecular reaction with selenol. The same product was formed using phosgene alone. In the product **13** the stereochemistry of the isopropyl group in one of the rings has been lost. A new stereogenic center has been introduced at the carbon of the hydroxy group. Both epimers at the alcoholic carbon were formed in almost equimolar amounts and could be separated by flash chromatography. One of the isomers was a crystalline compound, the other an oily material. A single crystal X-ray analysis showed the crystalline product to have been formed by acylation of N-4 in either of the two pyrazine rings. The hydrogen at *C*-(2) in the initially formed



Scheme 1 *Reagents and conditions*: (i) (a) BuLi, THF, −78 °C, (b) $(CH_2O)_n$; (ii) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −50 °C; (iii) THF, −78 °C; (iv) BuLi, THF, −78 °C.

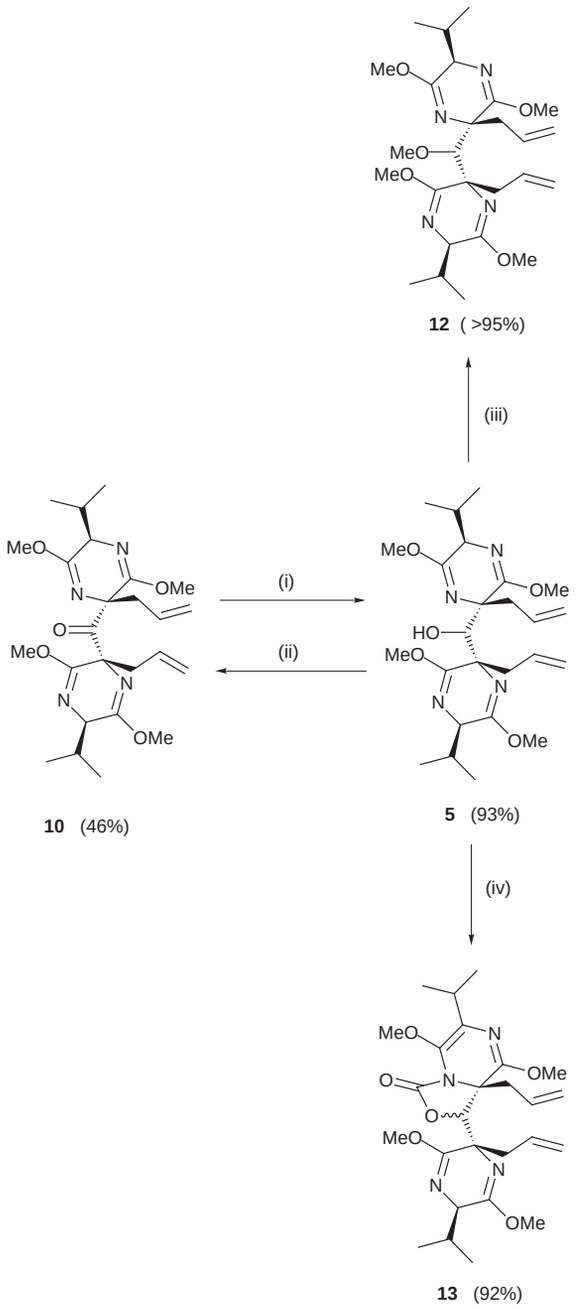
N-acylazinium ring becomes acidic and is lost in a process leading to the observed neutral molecules. The crystalline isomer was found by X-ray analysis to be the one with the (*S*)-configuration at the alcoholic carbon (**13b**, Scheme 4).

The RCM reactions were run under reflux conditions in benzene using the Grubbs catalyst system, *viz*. bis(tricyclohexylphosphine)benzylidenedichlororuthenium as the Ru(II)-catalyst precursor.[1] The alcohol **5** failed to yield any cyclic product **14** (Scheme 3). For the RCM reactions to take place it is essential that conformations biased towards closeness of the two ene groups are accessible. It was thought that hydrogen bonding in some form might be responsible for the failure of the alcohol to react. Therefore the methyl ether **12** was prepared. A very good RCM reaction resulted; the cyclic product **15** was obtained in 87% yield.

The Ru(II)-catalysts are normally compatible with hydroxy groups. We have synthesized constrained six- and seven-membered cyclic serine analogues by related RCM without hydroxy protection.[8] Thus in the preparation of cyclic hydroxy structures as analogues to homoserine, the RCM reaction proceeded readily for six-membered ring formation but failed in the seven-membered ring series. Protection by acetylation, however, resulted in very high yielding RCM processes (>90%) also for the seven-membered ring series.[9,10] RCM reactions require that the dienes are conformationally predisposed for ring formation. When hydrogen bonding in the substrate strongly favours unreactive conformers, breakage of the hydrogen bonding may drastically affect the metathetic conversion. Coordination of polar functional groups to the metal of the catalyst complex 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.[3] The two alkene groups in the ketone **10** or **11** would be expected to be able to assume conformations where the two alkene chains become almost parallel. Presumably this would facilitate the ring closing operation by the catalyst. The RCM reaction for the propenyl ketone **10** proceeded readily to furnish the cycloheptenone **16** in 75% yield. The butenyl substrate **11**, however, failed to yield any of the nine-membered ring structure **17**. This finding falls into the established pattern observed in RCM reactions; the ring closure usually proceeds well for the formation of five-, six- and seven-membered rings whereas the formation of larger ring structures is limited to conformationally favourable cases.[3]

The X-ray structures of the unreactive hydroxy compound **5** in the RCM reaction and the highly reactive ketone **10** showed no marked differences in the crystalline state that could be used to suggest conformational differences of importance for the reactivity in solution. In the crystalline state both the heterocyclic rings were pseudoparallel with the alkenyl groups pointing in opposite directions (Figs. 1 and 2). In solution the molecules must assume different conformations closer to alignment of the alkene groups for the RCM reaction to occur.

In the tricyclic stereoisomer **13b**, the propenyl groups in the crystalline isomer are widely separated (Fig. 3). Molecular models show it is difficult to align closely the propenyl groups because of steric interferences between the two heterocyclic ring systems and their substituents. In the non-crystalline stereoisomer, however, molecular models show conformational preferences for close alignment of the reactive allyl groups. Accordingly, the (*R*)-isomer **13a** gave close to quantitative yield of cyclic product **18a**, whereas no cyclization could be effected for the (*S*)-isomer **13b** (Scheme 4).



Scheme 2 *Reagents and conditions*: (i) $LiAlH_4$, THF, 0–20 °C; (ii) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; (iii) NaH, THF, MeI, 20 °C; (iv) NaH, THF, $COCl_2$, −20 °C.

The RCM reaction of the hydroxy derivative **5** had failed to yield the cycloheptenol **14** (Scheme 3). The latter, as a target compound, was therefore to be prepared from the corresponding cyclic ketone **16** by LAH reduction. The desired hydroxy compound **14** was readily obtained when the reduction was run at 0 °C (Scheme 5). At higher temperature the reduction proceeded further resulting in hydrogenolysis at the vicinal iminoether function with formation of a tetrahydropyrazine **19**. At ambient temperature 87% of the reduction product **19** was obtained. In this process a new stereogenic center has been created. Spectra and chromatographic behaviour suggest the formation of a single stereoisomer. Unfortunately we have failed to crystallize the product for X-ray analysis.

In conclusion we have found that sterically highly crowded dienes may undergo RCM reactions to furnish cyclic bispiranes in high yields. A free hydroxy group was incompatible with the RCM in the present system. After *O*-methyl protection, however, the ring formation proceeded in exceptionally high yield.

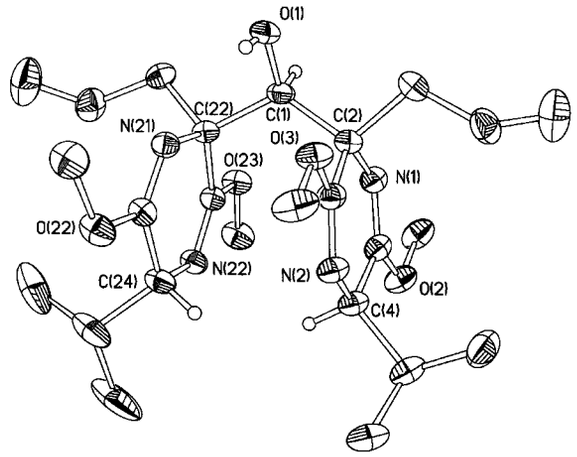


Fig. 1 ORTEP plot of the X-ray structure of **5**. Ellipsoids are shown at 50% probability. For clarity only the pertinent H-atoms are shown. The absolute configuration at C(2) and C(22) was established relative to the known chirality of C(4)(*R*) and C(24)(*R*).

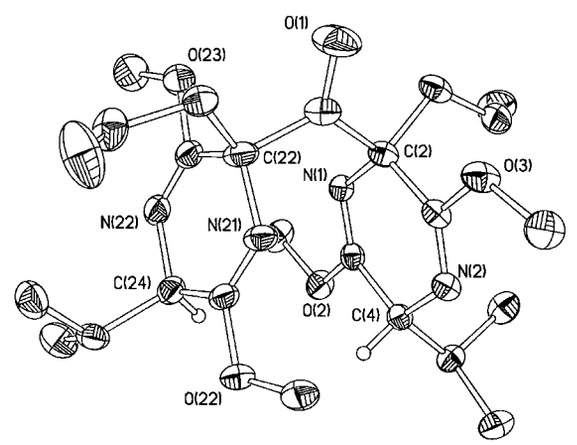


Fig. 2 ORTEP plot of the X-ray structure of **10**. Ellipsoids are shown at 50% probability. Only one of the two crystallographically independent molecules is shown. For clarity H-atoms are omitted except those of the chiral atoms. The absolute configuration is established as above.

Experimental

^1H NMR spectra were recorded in $CDCl_3$ at 500, 300 or 200 MHz with Bruker DPX 500, DPX 300 or DPX 200 spectrometers. The ^{13}C spectra were recorded in $CDCl_3$ at 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 was distilled from sodium and benzophenone under argon. Solvents were degassed by bubbling argon through. Bis(tricyclohexylphosphine)benzylidenedichlororuthenium was purchased from Strem Chemicals Inc., 7 Mulliken Way, Newburyport, MA.

X-Ray crystallographic analysis data for compounds 5, 10, and 13†

X-Ray data were collected on a Siemens SMART CCD diffractometer[11] using graphite monochromated MoKα 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.[11] Absorption corrections were applied by the use of

† CCDC reference number 207/325. See http://www.rsc.org/suppdata/p1/1999/1677 for crystallographic files in .cif format.

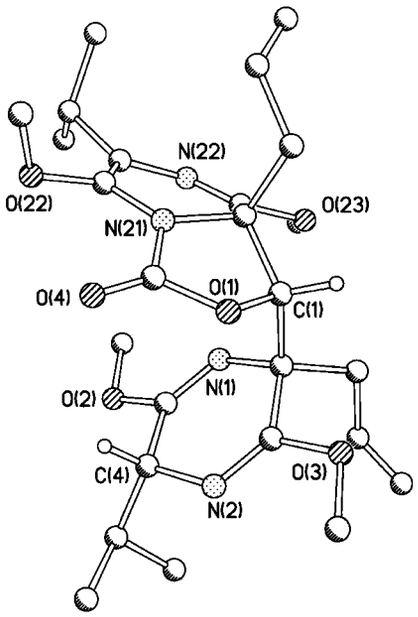
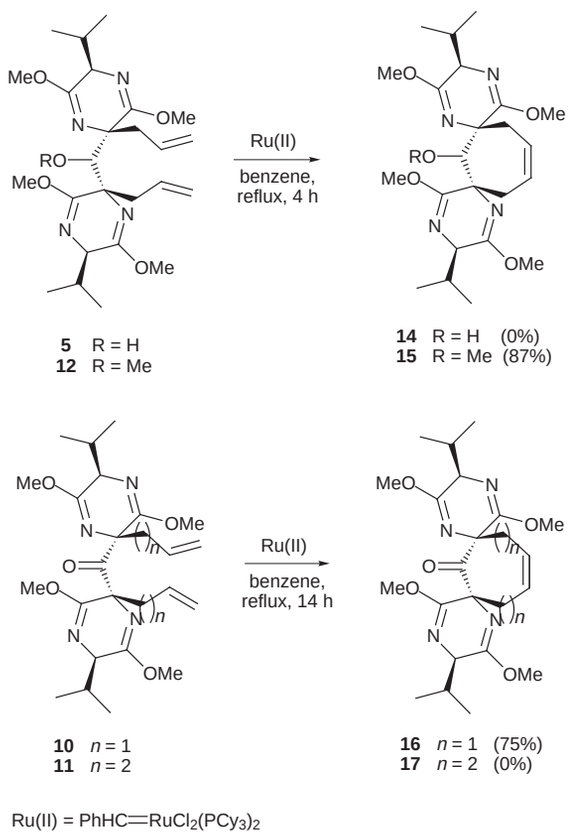


Fig. 3 PLUTO plot of the X-ray structure of **13b**. The quality of the crystals was poor, and the data did not allow for satisfactory refinement. The structure is shown here only as a proof of the connectivity and the relative configuration of C(4)(*R*) and C(1)(*S*).

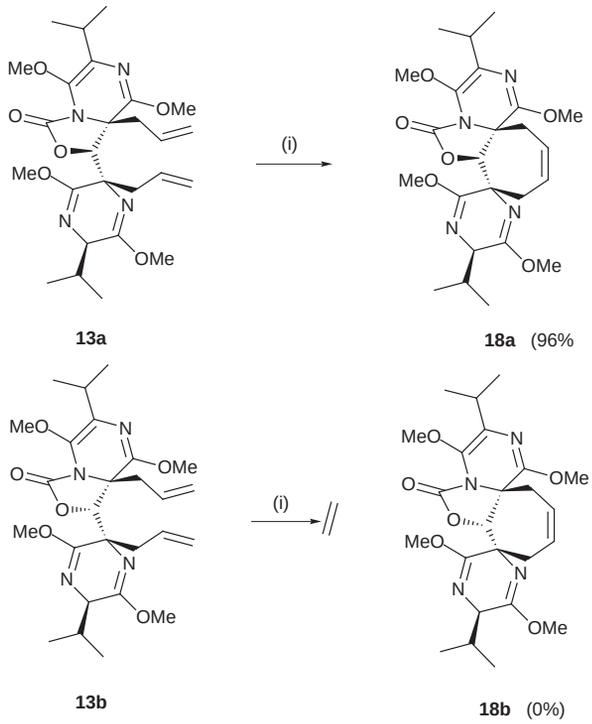


Scheme 3

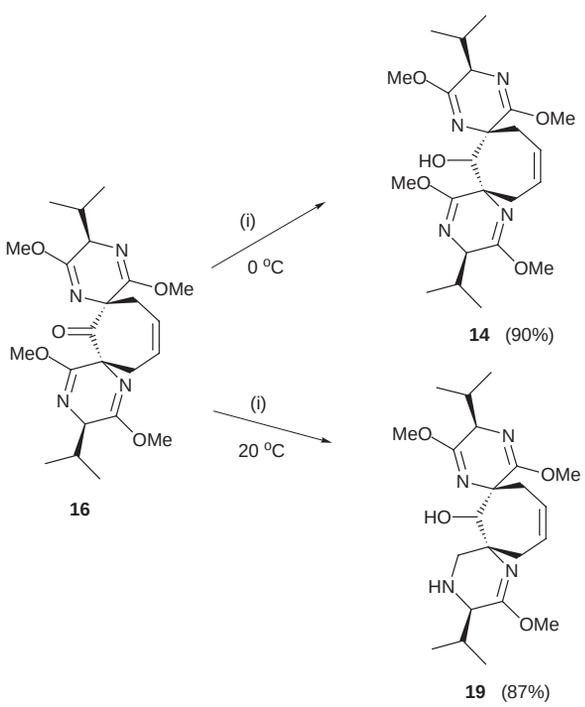
the SADABS program.[12] The structure was determined and refined using the SHELXTL program package.[13] The non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen positions were calculated from geometrical criteria and for **5** and **10** refined with isotropic thermal parameters. Crystal data for **5** and **10** are given in Table 1. Disorders were observed in several of the propene side chains in both structures, and the hydrogen atom and the hydroxy group at C(1) were disorderly interchanged in compound **5**.

The crystals of structure **13** were of poor quality. Therefore we do not fully report the structure. Only the basic connectivity could be satisfactorily determined. The data for this system are therefore reduced to the crystal system, space group, unit cell dimensions and final *R* value.

Crystal data for **13b**, $C_{26}H_{38}N_4O_6$, monoclinic, $P2_1$, a = 8.259(1), b = 13.688(1), c = 24.171(2) Å, β = 96.55(1)°, V = 2714.6(1) Å^3, Z = 4, R = 0.080 for $I_o > 2\sigma(I_o)$ and 0.131 for all data. Severe disorder was observed in the propene side chains.



Scheme 4 *Reagents and conditions*: (i) Ru(II), benzene, reflux 3 h. Ru(II) = $(PCy_3)_2Cl_2Ru$=CHPh.



Scheme 5 *Reagents and conditions*: (i) $LiAlH_4$, THF, 2 h.

(2*R*,5*S*)-5-Allyl-2,5-dihydro-3,6-dimethoxy-5-hydroxymethyl-2-isopropylpyrazine 3

BuLi in hexane (1.55 M, 3.39 ml, 5.28 mmol) was added to a

Table 1 Crystal data and structure refinement for compounds **5** and **10**

Identification code	**5**	**10**
Empirical formula	$C_{25}H_{40}N_4O_5$	$C_{25}H_{38}N_4O_5$
Formula weight	476.61	474.59
Temperature	150(2) K	150(2) K
Crystal system	Monoclinic	Triclinic
Space group	$P2_1$	$P1$
Unit cell dimensions	a = 11.276(1) Å	a = 8.460(1) Å
	b = 8.485(1) Å	b = 11.499(1) Å
	c = 14.447(1) Å	c = 14.532(1) Å
	β = 104.10(1)°	α = 70.56(1)°
		β = 85.31(1)°
		γ = 85.31(1)°
Volume, Z	1340.56(6) Å^3, 2	1326.32(6) Å^3, 2
Absorption coefficient	0.083 mm^{-1}	0.083 mm^{-1}
Reflections collected	15768	15603
Independent reflections	8658 [R_{int} = 0.033]	11732 [R_{int} = 0.033]
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.048,	R_1 = 0.060,
	wR_2 = 0.015	wR_2 = 0.135
R indices (all data)	R_1 = 0.056,	R_1 = 0.078,
	wR_2 = 0.125	wR_2 = 0.150

solution of (2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine [14] (1.07 g, 4.77 mmol) in anhydrous THF (10 ml) at −78 °C. The solution was stirred at −78 °C for 30 min before it was transferred through Teflon tubing to a precooled (−78 °C) suspension of paraformaldehyde (0.72 g, 23.86 mmol) in THF (22 ml). The reaction mixture was stirred at this temperature for 3 h before it was allowed to reach ambient temperature overnight. The reaction was quenched by addition of phosphate buffer (pH 7) and water. The aqueous phase was extracted with dichloromethane, the combined organic solutions dried ($MgSO_4$), evaporated at reduced pressure and the residual material subjected to flash chromatography on silica gel using CH_2Cl_2–MeOH (95:5) to give **3** (0.90 g, 75%) as a colourless viscous oil (Found: C, 61.05; H, 8.62. $C_{13}H_{22}N_2O_2$ requires C, 61.39; H, 8.72%). HRMS: M 254.1612. Calc. for $C_{13}H_{22}N_2O_2$: 254.1613; δ_H 0.63/1.03 (6 H, d, 2 × CH*Me*$_2$), 2.07–2.14 (1 H, m, CH_2OH), 2.21–2.51 (3 H, m, CH_2, C*H*Me$_2$), 3.47 (1 H, dd, *J* 5.4, 10.6, C*H*HOH), 3.62–3.71 (1H, m, CH*H*OH), 3.63/3.65 (6 H, s, 2 × OMe), 3.90 (1 H, d, *J* 3.6, H-2), 4.90–5.04 (2 H, m, CH=C*H*$_2$), 5.48–5.65 (1 H, m, C*H*=CH$_2$); δ_C 17.26/19.52 (CH*Me*$_2$), 30.70 (*C*HMe$_2$), 40.38 (*C*H$_2$CH=CH$_2$), 52.27/52.43 (2 × OMe), 60.73 (C-2), 63.18 (C-5), 68.72 (CH_2OH), 117.76 (*C*H$_2$=CH), 133.58 (CH$_2$=*C*H), 162.21/164.59 (C-3, C-6); *m*/*z* 254 (M$^+$, 3.4%), 224 (7), 223 (49), 213 (21), 182 (12), 181 (100), 166 (7), 153 (22).

(2*R*,5*S*)-5-Allyl-2,5-dihydro-3,6-dimethoxy-5-formyl-2-isopropylpyrazine 4

A solution of DMSO (0.62 ml, 8.66 mmol) in dichloromethane (1.8 ml) was added to a solution of oxalyl chloride (0.371 ml, 4.33 mmol) in dichloromethane (9 ml) under argon at −60 °C. The mixture was stirred for 2 min before a solution of (2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-5-hydroxymethyl-2-isopropylpyrazine (1.00 g, 3.94 mmol) in dichloromethane (4.5 ml) was added dropwise. The reaction mixture was stirred at −10 °C for 15 min, cooled to −60 °C and triethylamine (1.80 ml) added. The stirring was continued at this temperature for 5 min, and for 30 min at ambient temperature. The reaction was quenched by addition of water and the mixture extracted with dichloromethane. The dried ($MgSO_4$) organic solution was filtered and the filtrate evaporated. The residue was taken up into diethyl ether, the solution filtered and the filtrate evaporated to furnish the product **4** (0.90 g, 91%) as a viscous oil. HRMS: M 252.1472. Calc. for $C_{13}H_{20}N_2O_2C$: 252.1474; δ_H 0.65/1.06 (6 H, d, *J* 6.8, CH*Me*$_2$), 2.29–2.35 (1 H, m, C*H*Me$_2$), 2.65 (1 H, dd, *J* 7.2, 13.5, C*H*H), 2.80 (1 H, dd, *J* 7.3, 13.5, CH*H*), 3.68/3.72 (6 H, s, 2 × OMe), 3.94 (1 H, d, *J* 3.4, H-2), 5.01–5.12 (2 H, m, CH=C*H*$_2$), 5.57–5.66 (1 H, m, C*H*=CH$_2$), 9.33 (1 H, s, CHO); δ_C 17.02/19.49 (CH*Me*$_2$), 30.59 (*C*HMe$_2$), 38.66 (*C*H$_2$CH=CH$_2$), 52.81/52.91 (2 × OMe), 60.58 (C-2), 69.95 (C-5), 118.91 (*C*H$_2$=CH), 132.23 (CH$_2$=*C*H), 158.09/164.94 (C-3, C-6), 195.20 (CHO); *m*/*z* (CI) 253 (M$^+$ + 1, 43%), 224 (14), 223 (91), 192 (14), 182 (11), 181 (100), 169 (9).

Bis[(2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl]methanol 5

BuLi in hexane (2.2 M, 1.48 ml, 3.26 mmol) was added to a solution of (2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (0.664 g, 2.96 mmol) in anhydrous THF (10 ml) at −78 °C. The solution was stirred at −78 °C for 30 min before a precooled (−78 °C) solution of (2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-5-formyl-2-isopropylpyrazine (0.750 g, 2.96 mmol) in anhydrous THF (3 ml) was added dropwise through Teflon tubing. The reaction mixture was stirred in the cold for 3 h and allowed to reach ambient temperature overnight. The reaction was quenched by addition of phosphate buffer (pH 7) and water, the mixture extracted with diethyl ether and the dried ($MgSO_4$) ether solutions evaporated. The product **5** (0.714 g, 78%) was isolated as a white solid after flash chromatography on silica gel using EtO_2–CH_2Cl_2 (1:19); mp 115 °C (from MeCN) (Found: C, 62.69; H, 8.19. $C_{25}H_{40}N_4O_5$ requires C, 63.00; H, 8.46%); δ_H 0.57/0.60/1.00/1.02 (12 H, d, *J* 6.8, 4 × CH*Me*$_2$), 2.20–2.30 (2 H, m, 2 × CHMe$_2$), 2.41 (1 H, dd, *J* 7.3, 13.2, CHH), 2.58–2.77 (3 H, m, 2 × CH_2), 3.54/3.55/3.60/3.63 (12 H, s, 4 × OMe), 3.70–3.76 (2 H, m, H-2′ and CHO*H*), 3.71 (1 H, d, *J* 3.7, H-2), 3.99 (1 H, d, *J* 11.5, C*H*OH), 4.86–5.00 (4H, m, 2 × CH=C*H*$_2$), 5.28–5.54 (2 H, m, 2 × C*H*=CH$_2$); δ_C 17.43/17.66/19.69/19.79 (4 × CH*Me*$_2$), 29.94/30.04 (2 × *C*HMe$_2$), 43.18/44.36 (2 × *C*H$_2$), 51.89/51.95/52.06/52.20 (4 × O*Me*), 60.13/60.75 (C-5, C-5′), 63.69/64.87 (C-2, C-2′), 81.90 (*C*HOH), 117.89/118.14 (2 × CH=*C*H$_2$), 134.20/134.31 (2 × *C*H=CH$_2$), 161.74/162.41/162.61/163.45 (C-3, C-3′, C-6, C-6′); *m*/*z* (CI) 477 (M$^+$ + 1, 18%), 254 (15), 253 (100), 224 (29.9), 223 (24.0), 193 (7.9), 181 (53.3).

Bis[(2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl]methanol 5 from the reduction of ketone 10

Lithium aluminium hydride (68 mg, 2.10 mmol) was added to a solution of bis[(2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl] ketone (0.498 g, 1.05 mmol) in THF (5 ml) at 0 °C and the reaction mixture stirred at ambient temperature overnight. The reaction was quenched with aqueous EtOAc and the aluminium salts removed by filtration. Evaporation of the filtrate left the product **5** (0.447 g, 89%).

(2*R*,5*S*)-5-Allyl-2,5-dihydro-3,6-dimethoxy-5-ethoxycarbonyl-2-isopropylpyrazine 6

BuLi (1.55 M in hexane, 0.70 ml, 1.12 mmol) was added to a solution of (2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (0.228 g, 1.02 mmol) in THF (2 ml) under argon at −78 °C and the mixture stirred for 30 min before ethyl chloroformate (0.112 g, 1.12 mmol) in THF (1 ml) was added. The reaction mixture was stirred at ambient temperature overnight before the reaction was quenched by addition of phosphate buffer (pH 7). The mixture was extracted with diethyl ether, the ether solution dried ($MgSO_4$), evaporated and the residual material subjected to flash chromatography using Et_2O–CH_2Cl_2 (1:19) which gave **6** (0.177 g, 60%) as a yellow oil. The second product eluted from the column (0.054 g, 18%) was *(2R)-5-allyl-1,2-dihydro-3,6-dimethoxy-1-ethoxycarbonyl-2-isopropylpyrazine* **7**.

Compound 6. HRMS: M$^+$ 296.1746. Calc. for $C_{15}H_{24}N_2O_4$: 296.1736; δ_H 0.63/1.07 (6 H, d, *J* 6.8, CH*Me*$_2$), 1.18 (3 H, t, *J* 7.1, CH_3CH_2-O), 2.33 (1 H, dsept, *J* 3.4, 6.8, CHMe$_2$), 2.65

(2 H, m, CH_2), 3.64/3.65 (6 H, s, 2 × OMe), 3.96 (1 H, d, *J* 3.4, H-2), 4.12 (2 H, q, *J* 7.1, CH_3CH_2-O), 4.94–5.08 (2 H, m, CH=CH_2), 5.47–5.58 (1 H, m, CH=CH_2); δ_C 13.97 (CH_3CH_2-O), 17.10/19.58 ($CHMe_2$), 30.30 ($CHMe_2$), 40.06 (CH_2CH=CH_2), 52.61/52.78 (2 × OMe), 60.37 (CH_3CH_2-O), 61.52 (C-2), 66.29 (C-5), 118.36 (CH_2=CH), 133.29 (CH_2=CH), 159.44/164.67 (C-3, C-6), 169.62 (CO_2Et); *m*/*z* (EI) 296 (M^+, 17%), 267 (12), 253 (34), 237 (7), 223 (6), 209 (27), 195 (9), 166 (19), 165 (26), 150 (13), 149 (20).

(2*R*)-5-Allyl-1,2-dihydro-3,6-dimethoxy-1-ethoxycarbonyl-2-isopropylpyrazine 7. HRMS: M^+ 296.1746. Calc. for $C_{15}H_{24}N_2O_4$: 296.1736; δ_H 0.91/0.94 (6 H, d, *J* 6.8, CHMe_2), 1.27 (3 H, t, *J* 7.1, CH_3CH_2–O), 1.82–1.97 (1 H, m, C*H*Me_2), 2.92–3.12 (2 H, m, CH_2), 3.60/3.72 (6 H, s, 2 × OMe), 4,14–4.33 (3 H, d, H-2, CH_3CH_2-O), 4.96–5.11 (2 H, m, CH=CH_2), 5.79–5.90 (1 H, m, C*H*=CH_2); δ_C 14.43 (CH_3CH_2–O), 18.61/19.19 (CHMe_2), 33.48 ($CHMe_2$), 53.41 (CH_2CH=CH_2), 59.26/59.88 (2 × OMe), 60.37 (CH_3CH_2-O), 61.52 (C-2), 66.29 (C-5), 118.36 (CH_2=CH), 133.29 (CH_2=CH), 159.44/164.67 (C-3, C-6), 169.62 (CO_2Et); *m*/*z* (EI) 296 (M^+, 11%), 223 (45), 182 (11), 181 (100), 167 (17).

Bis[(2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl] ketone 10

BuLi in hexane (1.55 M, 9.00 ml, 13.95 mmol) was added to a solution of (2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (3.00 g, 13.28 mmol) in anhydrous THF (26 ml) at −50 °C. The mixture was stirred at this temperature for 1 h, cooled to −78 °C and a precooled (−78 °C) solution of phosgene in toluene (1.93 M, 3.44 ml, 6.64 mmol) added dropwise through Teflon tubing. The reaction mixture was allowed to reach ambient temperature overnight and the reaction quenched by addition of phosphate buffer (pH 7). The mixture was extracted with dichloromethane, the organic extracts dried ($MgSO_4$) and the solvent distilled off. The product was either purified by flash chromatography using 10% ethyl acetate in hexane or by recrystallization from acetonitrile to give **10** (2.24 g, 71%), mp 98 °C (from MeCN) (Found: C, 62.94; H, 7.81. $C_{25}H_{38}N_4O_5$ requires C, 63.27; H, 8.07%); δ_H 0.68/1.02 (12 H, d, *J* 6.8, 2 × CHMe_2), 2.19–2.26 (2 H, m, 2 × C*H*Me_2), 2.32 (2 H, dd, *J* 7.6, 13.8, 2 × C*H*H), 2.93 (2H, dd, *J* 6.6, 13.8, 2 × CH*H*), 3.63 (12 H, s, 4 × OMe), 3.71 (2 H, d, *J* 3.9, H-2, H-2′), 4.91–4.97 (4 H, m, 2 × CH=CH_2), 5.53–5.64 (2H, m, 2 × C*H*=CH_2); δ_C 18.06/19.74 (2 × CHMe_2), 30.95 (2 × $CHMe_2$), 43.31 (2 × CH_2CH=CH_2), 52.66 (4 × OMe), 60.30 (C-2, C-2′), 69.73 (C-5, C-5′), 117.39 (2 × CH_2=CH), 133.89 (2 × CH_2=CH), 160.44/163.97 (C-3, C-3′, C-6, C-6′), 197.27 (C=O); *m*/*z* (CI) 475 (M^+ + 1, 37%), 224 (42), 223 (100), 181 (81).

Synthesis of bis[(2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl] ketone 10 by Swern oxidation of the alcohol 5

A solution of DMSO (0.178 g, 2.26 mmol) in dichloromethane (0.5 ml) was added to a solution of oxalyl chloride (0.098 ml, 1.13 mmol) in dichloromethane (2.3 ml) under argon at −60 °C. The mixture was stirred for 2 min before a solution of bis[(2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl]methanol (0.492 g, 1.03 mmol) in dichloromethane (1.0 ml) was added dropwise. The stirring was continued for 15 min at −10 °C, the mixture cooled to −60 °C and triethylamine (0.45 ml) added. The stirring was continued for 5 min at this temperature before the mixture was allowed to warm up to ambient temperature. The product 10 (0.215 g, 46%) was isolated as a white crystalline material after recrystallization from MeCN.

Bis[(2*R*,5*S*)-5-(but-3-enyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl] ketone 11

BuLi in hexane (1.50 M, 2.94 ml, 4.44 mmol) was added to a solution of (2*R*,5*S*)-5-(but-3-enyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine[9a] (1.00 g, 4.20 mmol) in anhydrous THF (8.0 ml) at −50 °C. The mixture was stirred at this temperature for 1 h, cooled to −78 °C and a precooled (−78 °C) solution of phosgene in toluene (1.93 M, 1.09 ml, 2.10 mmol) added dropwise through Teflon tubing. The reaction mixture was allowed to reach ambient temperature overnight and the reaction quenched by addition of phosphate buffer (pH 7). The mixture was extracted with dichloromethane, the organic extracts dried ($MgSO_4$) and the solvent distilled off. The product was either purified by flash chromatography using 10% ethyl acetate in hexane or by recrystallization from acetonitrile to give **11** (0.71 g, 67%), mp 99–100 °C (from MeCN) (Found: C, 65.00; H, 8.48. $C_{27}H_{42}N_4O_5$ requires C, 64.52; H, 8.42%); δ_H 0.68/1.02 (12 H, d, *J* 6.9, 2 × CHMe_2), 1.30–1.42 (2 H, m, 2 × C*H*H), 1.91–2.07 (2 H, m, 2 × C*H*H), 2.17–2.32 (2 H, m, 2 × C*H*Me_2), 2.37–2.56 (2 H, m, 2 × C*H*H), 3.63/3.67 (12 H, s, 4 × OMe), 3.82 (2 H, d, *J* 3.9, H-2, H-2′), 4.85–5.07 (4 H, m, 2 × CH=CH_2), 5.66–5.88 (2 H, m, 2 × C*H*=CH_2); δ_C 17.84/19.66 (2 × CHMe_2), 27.88 (2 × CH_2), 31.10 (2 × $CHMe_2$), 38.59 (2 × CH_2CH=CH_2), 52.59/52.65 (4 × OMe), 60.44 (C-2, C-2′), 69.46 (C-5, C-5′), 114.12 (2 × CH_2=CH), 138.95 (2 × CH_2=CH), 161.24/163.87 (C-3, C-3′, C-6, C-6′), 197.56 (C=O); *m*/*z* (CI) 503 (M^+ + 1, 75%), 239 (11), 238 (37), 237 (100), 195 (50), 153 (11).

Bis[(2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl](methoxy)methane 12

Sodium hydride (71 mg, 1.878 mmol) was added to a precooled solution of bis[(2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl]methanol (0.447 g, 0.939 mmol) in THF (1 ml) under argon at 0 °C. The mixture was stirred at this temperature for 30 min before a solution of methyl iodide (0.200 g, 1.40 mmol) in THF (1 ml) was added. The reaction mixture was stirred at ambient temperature for 5 h. The reaction was stopped by the addition of saturated aqueous NH_4Cl, the mixture extracted with diethyl ether and the dried ($MgSO_4$) solution evaporated. The residual product 12 was a colourless viscous oil (0.460 g, >95%) (Found: C, 63.72; H, 8.64. $C_{26}H_{42}N_4O_5$ requires C, 63.65; H, 8.63%); δ_H 0.57/0.64 (6 H, d, *J* 6.8, 2 × CHMe_2), 1.02/1.04 (6H, d, *J* 7.1, 2 × CHMe_2), 2.21–2.38 (2 H, m, 2 × C*H*Me_2), 2.50 (1 H, dd, *J* 6.8, 12.8, C*H*H), 2.58–2.65 (2 H, m, CH_2), 2.80 (1 H, dd, *J* 6.9 , 12.8, C*H*H), 3.45/3.58/3.59/3.61/3.65 (15 H, s, 5 × OMe), 3.67 (1 H, s, C*H*OMe), 3.76/3.79 (1 H, d, *J* 3.2, H-2 and H-2′), 4.86–5.00 (4 H, m, 2 × CH=CH_2), 5.30–5.50 (2 H, m, 2 × C*H*=CH_2); δ_C 17.24/17.48/19.66/19.78 (4 × CHMe_2), 29.97/30.05 (2 × $CHMe_2$), 41.33/42.69 (2 × CH_2), 51.82/51.95/52.06/52.45 (4 × O*Me*), 59.82/60.21 (C-2, C-2′), 63.13 (O*Me*), 66.89/66.92 (C-5, C-5′), 90.88 (*C*HOMe), 117.44/117.71 (2 × CH=CH_2), 134.71 (2 × *C*H=CH_2), 162.05/162.32/162.38/162.68 (C-3, C-3′, C-6, C-6′); *m*/*z* (CI): 491 (M^+ + 1, 69%), 267 (100), 227 (116), 223 (24), 193 (19), 181 (29).

1-(5-Allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl)-8a-allyl-6-isopropyl-5,8-dimethoxy-1,8a-dihydro[1,3]oxazolo-[3,4-*a*]pyrazin-3-one 13

DMAP (11 mg) was added to a precooled (0 °C) solution of bis[(2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl]methanol (0.312 g, 0.655 mmol) in anhydrous THF (10 ml). The solution was stirred for 30 min before a solution of a phosgene (2.25 ml, 1.93 M, 4.39 mmol) was added. The resultant solution was allowed to reach ambient temperature and stirred for 1 h. Excess phosgene and the solvent were removed at reduced pressure. Anhydrous THF (4 ml) was added followed by pyridine (0.29 ml). The reaction mixture was stirred for 2 h before being quenched with phosphate buffer (pH 7). The product was a 1 : 1 mixture of the two stereoisomers **13a** and **13b**. The stereoisomers were separated

by flash chromatograpy using EtOAc–hexane (1 : 4) (total yield 0.321 g, 92%).

(1*R*)-Isomer 13a. The (1*R*)-isomer was first eluted from the flash column to give a viscous oil. HRMS: M 502.2751. Calc. for $C_{26}H_{38}N_4O_6$: 502.2791; δ_H 0.76/0.91/1.05/1.06 (12 H, d, 2 × CH*Me*$_2$, *J* 6.8), 1.98–2.10 (2 H, m, C*H*$_2$), 2.16–2.24 (1 H, m, C*H*Me$_2$), 2.56 (1 H, dd, C*H*H, *J* 7.0, 13.5), 2.74 (1 H, dd, C*H*H, *J* 8.0, 13.5), 2.87 (1 H, sept, C*H*Me$_2$, *J* 6.8), 3.61/3.67/3.72 (12 H, s, 4 × OMe), 3.75 (1 H, sept, H-2′, *J* 4.5), 4.78–5.09 (4 H, m, 2 × CH=C*H*$_2$), 5.33 (1 H, s, C*H*-O), 5.29–5.79 (2 H, m, 2 × C*H*=CH$_2$); δ_C 18.64/19.89/19.99/20.56 (2 × CH*Me*$_2$), 26.14/31.11 (2 × *C*Me$_2$), 32.60/44.85 (2 × *C*H$_2$), 52.35/52.74/53.88/57.61 (4 × O*Me*), 61.59 (C-2′), 63.06/65.07 (C-8a and C-5′), 80.93 (*C*-O-C=O), 119.13/119.26 (2 × CH=*C*H$_2$), 122.34 (C-6), 131.00 (*C*H=CH$_2$), 132.30 (C-5), 132.90 (*C*H=CH$_2$), 155.58/157.71/161.01/163.69 (C-3′, C-6′, C-8 and CO); *m*/*z* (EI): 502 (M$^+$, 9%), 418 (26), 417 (100), 385 (11), 375 (20), 334 (17), 333 (15), 223 (33), 195 (13), 181 (34).

(1*S*)-Isomer 13b. This was the last product eluted. The product **13b** was a solid that was recrystallized from acetonitrile for X-ray analysis; mp 123 °C (Found: C, 62.14; H, 8.48. $C_{26}H_{38}N_4O_6$ requires C, 62.13; H, 7.62%). HRMS: M 502.2746. Calc. for $C_{26}H_{38}N_4O_6$: 502.2791; δ_H 0.64/0.96/1.00/1.03 (12 H, d, 2 × CH*Me*$_2$, *J* 6.8), 2.19–2.31 (1H, m, C*H*Me$_2$), 2.43–2.62 (3 H, m, C*H*Me$_2$ and C*H*$_2$), 2.81–2.98 (2 H, m, C*H*$_2$), 3.51/3.64/3.65/3.75 (12 H, s, 4 × OMe), 3.90 (1 H, d, H-2′, *J* 3.7), 4.59 (1 H, s, -C*H*-O-C=O), 4.96–5.05 (2 H, m, CH=C*H*$_2$), 5.15–5.21 (2 H, m, CH=C*H*$_2$), 5.50–5.76 (2 H, m 2 × C*H*=CH$_2$); δ_C 17.57/19.48/20.17/20.41 (2 × CH*Me*$_2$), 25.74/30.40 (2 × *C*HMe$_2$), 44.02 (2 × *C*H$_2$), 52.35/52.68/52.73/60.38 (4 × O*Me*), 59.87/65.80 (C-5′ and C-8a), 86.39 (*C*-O-C=O), 118.30/120.89 (2 × CH=*C*H$_2$), 119.13/133.21 (C-5 and C-6), 129.86/133.44 (2 × CH=CH$_2$), 152.30/155.02/160.11/164.88 (C-3′, C-8, C-6′ and C=O); *m*/*z* (EI): 502 (M$^+$, 4%), 4.61 (5), 418 (26), 417 (100), 3.75 (20), 334 (17), 333 (14), 223 (28), 195 (13), 181 (31).

(2*R*,2″*R*,5*S*,5″*S*)-2,2″,5,5″-Tetrahydro-3,3″,6,6″-tetramethoxy-2,2″-diisopropylpyrazine-5-spiro-1′-cyclohept-5′-ene-3′-spiro-5″-pyrazin-2′-ol 14

Lithium aluminium hydride (20 mg, 0.527 mmol) was added to a solution of (2*R*,2″*R*,5*S*,5″*S*)-2,2″,5,5″-tetrahydro-3,3″,6,6″-tetramethoxy-2,2″-diisopropylpyrazine-5-spiro-1′-cyclohept-5′-ene-3′-spiro-5″-pyrazin-2″-one **16** (0.235 g, 0.527 mmol) in THF (3 ml) at 0 °C and the reaction mixture stirred for 2 h at 0 °C. The reaction was quenched by addition of aqueous ethyl acetate, the aluminium salts removed by filtration and the solution evaporated to give **14** as an oil that solidified (0.212 g, 90%), mp 119 °C (from MeCN) (Found: C, 61.73; H, 8.19. $C_{23}H_{36}N_4O_5$ requires C, 61.59; H, 8.09%); δ_H 0.61/0.69/1.04/1.06 (12 H, d, *J* 6.8, CH*Me*$_2$), 1.94–2.41 (4 H, m, 2 × C*H*H, 2 × C*H*Me$_2$), 2.76–2.92 (1 H, m, 2 × C*H*H), 3.31–3.46 (1 H, m, 2 × C*H*H), 3.62/3.63/3.66/3.68 (12 H, s, 4 × OMe), 3.85 (1 H, s, C*H*OH), 3.89–3.91 (2 H, m, H-2, H-2″), 5.50–5.78 (2 H, m, C*H*=C*H*); δ_C 16.28/17.36/19.37/19.44 (2 × CH*Me*$_2$), 30.03/31.28 (2 × *C*HMe$_2$), 35.62/37.75 (2 × *C*H$_2$CH=CH), 52.43/52.55/52.61 (4 × OMe), 60.22/60.29 (C-2, C-2″), 64.29/64.99 (C-5, C-5″), 80.88 (*C*HOH), 125.46/127.42 (*C*H=C*H*), 162.66/163.33/164.04/164.89 (C-3, C-3″, C-6, C-6″); *m*/*z* (CI) 449 (M$^+$ + 1, 54%), 448 (23), 434 (16), 433 (58), 417 (19), 406 (28), 405 (100), 377 (39), 236 (31), 213 (22), 193 (50), 169 (36).

(2*R*,2″*R*,5*S*,5″*S*)-2,2″,5,5″-Tetrahydro-2′,3,3″,6,6″-pentamethoxy-2,2″-diisopropylpyrazine-5-spiro-1′-cyclohept-5′-ene-3′-spiro-5″-pyrazine 15

Bis(tricyclohexylphosphine)benzylidenedichlororuthenium (40 mg, 0.049 mmol) was suspended in dry degassed benzene (15 ml) under argon, and the suspension stirred for 5 min before addition to a solution of bis[(2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl](methoxy)methane **12** (0.800 g, 1.63 mmol) in dry degassed benzene (14 ml). The reaction mixture was heated slowly to reflux and the heating continued for 4 h. The cold mixture was filtered, the filtrate evaporated and the product isolated after flash chromatograpy using EtOAc–CH_2Cl_2 (1 : 5) to give the product **15** as a viscous oil which solidified (0.660 g, 87%), mp 117–118 °C (from MeCN) (Found: C, 62.69; H, 8.21: $C_{24}H_{38}N_4O_5$ requires C, 62.38; H, 8.28%); δ_H 0.58/0.59 (6 H, d, *J* 6.8, CH*Me*$_2$), 1.00–1.05 (6 H, m, CH*Me*$_2$), 2.05 (1 H, dd, *J* 7.1, 14.7, C*H*H), 2.17–2.32 (2 H, m, 2 × C*H*Me$_2$), 2.39–2.51 (2 H, m, C*H*$_2$), 3.07 (1 H, s, O*Me*), 3.28 (1 H, dd, *J* 4.7, 14.7, C*H*H), 3.60/3.62/3.63/3.64 (12 H, s, 4 × OMe), 3.60–3.64 (1 H, s, C*H*OMe), 3.81 (1 H, d, *J* 3.0, H-2), 3.84 (1 H, d, *J* 3.2, H-2″), 5.66–5.82 (2 H, m, C*H*=C*H*); δ_C 16.22/16.56/19.27/19.39 (4 × CH*Me*$_2$), 29.99/30.37 (2 × *C*HMe$_2$), 36.07/38.32 (2 × *C*H$_2$CH=CH), 51.88/52.08/52.37/52.57 (4 × OMe), 59.88/60.29 (C-2, C-2″), 61.36 (CHO*Me*), 62.57/64.51 (C-5, C-5″), 91.80 (*C*HOMe), 126.93/127.69 (2 × *C*H=CH), 161.94/163.20/163.52/164.17 (C-3, C-3″, C-6, C-6″); *m*/*z* (CI): 463 (M$^+$ + 1, 100%), 462 (31), 461 (15), 447 (27), 431 (27), 420 (14), 419 (56), 387 (27), 236 (11), 235 (18), 227 (34),193 (32), 183 (12), 153 (11).

(2*R*,2″*R*,5*S*,5″*S*)-2,2″,5,5″-Tetrahydro-3,3″,6,6″-tetramethoxy-2,2″-diisopropylpyrazine-5-spiro-1′-cyclohept-5′-ene-3′-spiro-5″-pyrazin-2″-one 16

Bis(tricyclohexylphosphine)benzylidenedichlororuthenium (18.7 mg, 0.023 mmol) was suspended in dry degassed benzene (4 ml) under argon, and the suspension stirred for 5 min before addition to a solution of bis[(2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl] ketone (0.215 g, 0.45 mmol) in dry degassed benzene (5 ml). The reaction mixture was heated slowly to reflux and the heating continued overnight. The cold mixture was filtered, the filtrate evaporated and the residue subjected to flash chromatograpy using EtOAc–CH_2Cl_2 (1 : 19) to give **16** as a solid (0.150 g, 75%), mp 121 °C (from MeCN) (Found: C, 61.53; H, 7.50. $C_{23}H_{34}N_4O_5$ requires C, 61.86; H, 7.67%); δ_H 0.66/1.05 (12H, d, *J* 6.8, CH*Me*$_2$), 2.08–2.11 (2 H, m, 2 × C*H*H), 2.13–2.16 (2 H, m, 2 × CH*H*), 2.23–2.33 (2 H, m, *J* 3.2, 6.8, 2 × C*H*Me$_2$), 3.62/3.67 (12 H, s, 4 × OMe), 3.94 (2 H, d, H-2, H-2″), 5.55–5.57 (2 H, m, C*H*=C*H*); δ_C 16.79/19.32 (2 × CH*Me*$_2$), 30.66 (2 × *C*HMe$_2$), 36.90 (2 × *C*H$_2$CH=CH), 52.59/52.64 (4 × OMe), 60.30 (C-2, C-2″), 71,48 (C-5, C-5″), 124.86 (2 × *C*H=CH), 161.28/164.16 (C-3, C-3″, C-6, C-6″), 198.99 (C=O); *m*/*z* (EI): 447 (M$^+$, 30%), 403 (17), 376 (23), 375 (100), 333 (7), 235 (25), 193 (11), 179 (13).

(2′*R*,5′*S*,8*R*)-2′,3-Diisopropyl-1,3′,4,6′-tetramethoxy-2′,5′,7a,8,9,12-hexahydrocyclohepta[4,5][1,3]oxazolo[3,4-*a*]pyrazine-6-one-8-spiro-5′-pyrazine 18a

Bis(tricyclohexylphosphine)benzylidenedichlororuthenium (8.0 mg, 0.0091 mmol) was suspended in dry degassed benzene (2 ml) under argon, and the suspension stirred for 5 min before addition to a solution of (*S*)-1-(5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl)-8a-allyl-6-isopropyl-5,8-dimethoxy-1,8a-dihydro[1,3]oxazolo[3,4-*a*]pyrazin-3-one **13a** (0.092 g, 0.18 mmol) in dry degassed benzene (6 ml). The reaction mixture was heated at 70 °C for 3 h. The cold mixture was filtered, the filtrate evaporated and the residue subjected to flash chromatography using EtOAc–hexane (1 : 4) to give **18a** as a viscous oil (0.082, 96%). HRMS: M 474.2480. Calc. for $C_{24}H_{34}N_4O_6$: 474.2478; δ_H 0.67/0.95/1.08/1.09 (12 H, d, 2 × CH*Me*$_2$, *J* 6.8), 2.05–2.21 (2 H, m, C*H*$_2$), 2.34 (1 H, dsept, C*H*Me$_2$, *J* 3.3, 6.8), 2.94 (1 H, s, C*H*Me$_2$, *J* 6.8), 3.33–3.54 (2 H, m, C*H*$_2$), 3.66/3.70/3.72 (12 H, s, 4 × OMe), 3.92 (1 H, d, H-2, *J* 3.3), 4.58 (1 H, s, -C*H*-O-C=O), 5.27–5.36 (1 H, m, C*H*=CH), 5.52–5.60

(1 H, m, C*H*=CH); δ_C 16.51/19.41/20.59/20.68 (2 × CH*Me*$_2$), 26.11/28.24 (2 × *C*HMe$_2$), 30.49/36.81 (2 × *C*H$_2$), 53.00/53.18/54.04/59.79 (4 × O*Me*), 59.87 (C-2), 61.74 (C-5′ and C-13), 80.52 (*C*-O-C=O), 120.59/129.00 (2 × *C*H=CH), 121.82/131.55 (C-3 and C-4), 154.52/157.06/163.23/165.28 (C-3′, C-6′, C-7 and C=O); *m*/*z* (EI): 475 (M$'^+$ + 1, 15%), 474 (M$'^+$, 54%), 387 (13), 376 (14), 334 (19), 333 (100), 238 (6), 234 (22), 233 (5), 219 (7), 195 (11), 193 (22).

(*R* or *S*)-(2*R*,2″*R*,5*S*,5″*S*)-1″,2,2″,5,5″,6″-Hexahydro-3,3″,6-trimethoxy-2,2″-diisopropylpyrazine-5-spiro-1′-cyclohept-5′-ene-3′-spiro-5″-pyrazin-2′-ol 19

Lithium aluminium hydride (20 mg, 0.527 mmol) was added to a solution of (2*R*,2″*R*,5*S*,5″*S*)-2,2″,5,5″-tetrahydro-3,3″,6,6″-tetramethoxy-2,2″-diisopropylpyrazine-5-spiro-1′-cyclohept-5′-ene-3′-spiro-5″-pyrazin-2″-one (0.235 g, 0.527 mmol) in dry THF (3 ml) at 20 °C and the reaction mixture stirred at ambient temperature for 2 h. The reaction was stopped by addition of aqueous ethyl acetate, and the aluminium salts removed by filtration. Evaporation of the filtrate left the product **19** as a colorless oil (0.212 g, 90%); δ_H 0.61/0.80/0.93/1.03 (12 H, d, *J* 6.8, CH*Me*$_2$), 1.73–1.81/1.94–2.05/2.93–2.98/3.23–3.30 (4 H, m, 4 × C*H*H), 1.94–2.05/3.52–3.67 (2 H, m, -C*H*$_2$N-), 2.20–2.31 (2 H, m, 2 × C*H*Me$_2$), 2.90 (1 H, s, C*H*OH), 3.19/3.80 (2 H, d, *J* 3.0, H-2, H-2″), 3.49/3.62/3.69 (9H, s, 3 × OMe), 5.66–5.79 (2H, m, C*H*=C*H*); δ_C 16.03/16.50/18.95/19.52 (2 × CH*Me*$_2$), 28.88/29.49 (2 × *C*HMe$_2$), 30.47/30.77 (2 × *C*H$_2$CH=CH), 48.51 (C-6″), 51.86/52.67/53.05 (3 × OMe), 58.90/59.30 (C-2, C-2″), 59.51 (C-5″), 62.87 (C-5), 80.27 (*C*HOH), 126.91/131.38 (*C*H=C*H*), 162.37/164.29/166.42 (C-3, C-3″, C-6); *m*/*z* (CI) 449 (M$^+$ + 1, 54%), 421 (100), 420 (34), 419 (29), 405 (22), 389 (31), 378 (14), 377 (63), 345 (19).

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