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Synthesis and Crystal Structure of Hydrogenated Pyrazino[2,1-*a*]isoquinoline Derivatives

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Racemic amino acids (Ala and Val) were used in order to optimize the procedures and to check the stereochemical outcome of the synthesis of tetrahydroisoquinoline derivatives. The key step introduced the Pictet-Spengler condensation on ketoamides **4a** and **4b** under very mild conditions that gave predominantly (3*S**,11b*R**)-diastereomers **6a** and **6b**. These results were confirmed by X-ray crystallography.

Key words: isoquinoline alkaloids, *rac*-amino acids, pyrazino[2,1-*a*]isoquinoline

We have already used certain derivatives of amino acids as chiral inductors in stereoselective synthesis of 1-substituted tetrahydroisoquinoline derivatives [1]. We would like to present here our detailed results obtained when selected amino acids were used as starting materials in the synthesis of more complex benzyltetrahydroisoquinolines. Our initial target was to verify the concept of Lawton [2], who first pointed out the role of the peptide chain in the biosynthesis of isoquinoline alkaloids.

RESULTS AND DISCUSSION

In order to optimize the conditions of all transformations and to determine the diastereoselectivity of the cyclization process, we utilized racemic alanine and valine as readily available starting materials. We found that amide **3a** (Scheme 1) could be efficiently prepared from 2-(3,4-dimethoxyphenyl)ethylamine, when blocked *rac*-alanine **1a** was used as the starting compound in a BOP (benzotriazol-1-yl-oxy-tris(dimethylamino)-phosphoniumhexafluorophosphate)-mediated coupling [3]. Treatment of **3a** with 1 equivalent of 2-oxo-3-phenylpropanoic acid, again in the presence of BOP reagent, gave directly ketoamide **4a** in 59% yield together with hydroxylactam derivative **5a** in 11% yield. Compound **4a** was subjected to the Pictet-Spengler-type condensation with methanolic hydrogen chloride at 0°C, that efficiently afforded a diketopiperazine derivative **6a**. In the chemistry of isoquinolines such an easy cyclization of non-

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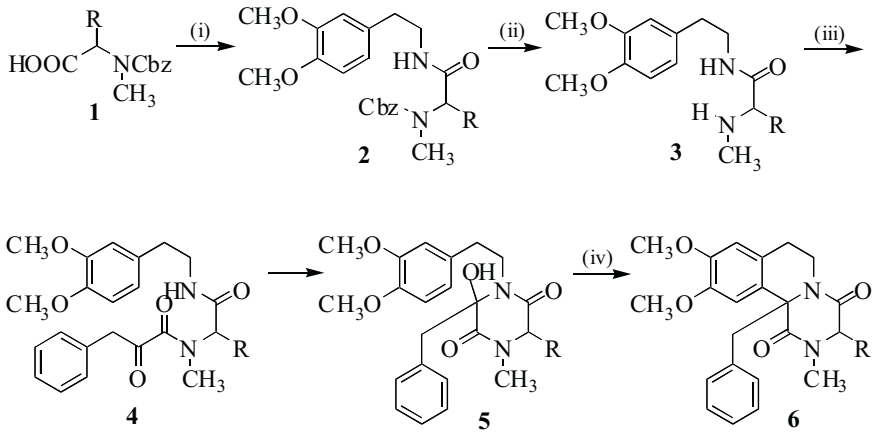
Scheme 1



Cbz = Benzyloxycarbonyl

(i) 2-(3,4-dimethoxyphenyl)ethylamine, Et_3N, BOP; (ii) H_2, Pd/C; (iii) phenylpyruvic acid, Et_3N, BOP; (iv) HCl, MeOH

1–6	R
a	CH_3
b	$CH(CH_3)_2$

phenolic derivatives is quite rare, which provided a further evidence for a significant influence of the peptide-like moiety in the processes involved.

Thus, the analogous reaction sequence was applied for protected *N*-methyl-*rac*-valine **1b**. Amide **3b** was obtained in a good yield in a two-step procedure consisted of the condensation of **1b** with 2-(3,4-dimethoxyphenyl)ethylamine immediately followed by hydrogenolytic (H_2, Pd/C) removal of the blocking Cbz-group. Further treatment of the amide **3b** with arylpyruvic acid in the presence of BOP reagent [3] gave ketoamide **4b**. Hydrogen chloride in dry methanol at 0°C promoted a facile Pictet-Spengler cyclization of **4b**, which brought the formation of *rac*-**6b** in 91% yield. Our initial attempts to determine the structure of final products **6a** and **6b** on the basis of spectral methods gave non-conclusive results. Therefore, we decided to apply an X-ray study for this purpose.

Crystal and molecular structures: The molecular structure and the numbering scheme of *rac*-**6a** is shown in Fig. 1, whereas Fig. 2 presents a respective drawing for *rac*-**6b**. Both structures crystallize in centrosymmetric space groups with one molecule in an asymmetric unit. The molecular dimensions of *rac*-**6a** and *rac*-**6b** are shown in Tab. 2 and 3, respectively. In *rac*-**6a** two almost equivalent orientations for the methyl group at the nitrogen atom were observed. Structure of *rac*-**6b** is partly disordered in the isopropyl and one of the methoxy groups regions. The respective occu-

pancy factors for C13 and C20 methyl groups are 0.67(1) and 0.60(2). For both structures the overall conformation of molecules is very similar, as shown by the selected torsion angles values (Tab. 4 and 5, respectively). The alternative description of the conformation of the molecules could be given by the dihedral angles between approximately planar fragments: the common planes of rings I and II, and the ring III and IV planes (see Fig. 1 and 2). That values are of 51.1(8) and 60.5(1)° for *rac*-**6a** and *rac*-**6b** rings III, respectively. Similarly, defined dihedral angles for benzyl groups (rings IV) are of 18.8(2) and 9.6(1)°, respectively. The methoxy groups O4–C13 are slightly rotated from C7A–C11A aromatic planes (the rotation angle around C10–O4 bonds from –11.8(4) through –20(7)° for *rac*-**6a** and *rac*-**6b**, respectively).
The above-presented results prompt us to extend our study on chiral, non-racemic amino acids. The work is currently under way.

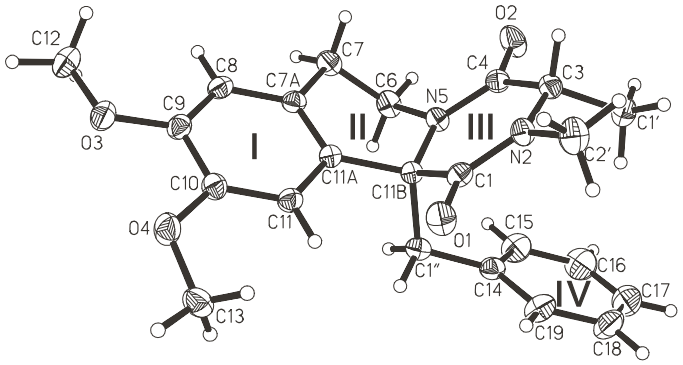


Figure 1. The molecular structure and the numbering scheme for (3*S**,11b*R**)-**6a**. The non-hydrogen atoms are shown as the 20% probability ellipsoids. Only one orientation of the disordered methyl group at N2 is depicted.

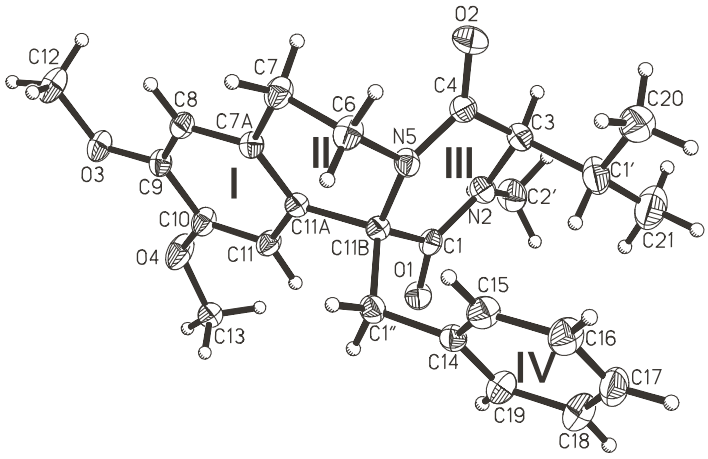


Figure 2. The molecular structure and the numbering scheme for (3*S**,11b*R**)-**6b**. The non-hydrogen atoms are shown as the 20% probability ellipsoids. Only one position of either of the disordered fragments is shown.

Table 1. Crystal data and structure refinement.

Identification code	(3*S**,11b*R**)-**6a**	(3*S**,11b*R**)-**6b**
Empirical formula	$C_{23}H_{26}N_2O_4$	$C_{25}H_{30}N_2O_4$
Formula weight	394.46	422.51
Temperature	293(2) K	293(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/c$	P-1
Unit cell dimensions	a = 16.495(3) Å	a = 8.754(2) Å, α = 64.67(3)°
	b = 14.423(3) Å, β = 98.71(3)°	b = 11.712(2) Å, β = 84.41(3)°
	c = 8.6920(17) Å	c = 12.453(2) Å, γ = 72.07(3)°
Volume	2044.0(7) Å^3	1097.1(4) Å^3
Z	4	2
Density (calculated)	1.282 Mg/m^3	1.279 Mg/m^3
Absorption coefficient	0.088 mm^{-1}	0.087 mm^{-1}
F(000)	840	452
Theta range for data collection	3.69 to 24.00°	3.32 to 22.50°
Index ranges	–18≤ h≤18, –16≤k ≤15, –6≤l≤9	–9 ≤h≤9, –12≤ k≤12, –13≤l≤13
Reflections collected	9340	13390
Independent reflections	3168 [R(int) = 0.0308]	2859 [R(int) = 0.0566]
Completeness	99.2%	99.6%
Absorption correction	Not applied	Not applied
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	3168/0/254	2859/2/275
Goodness-of-fit on F^2	1.041	1.138
Final R indices [I>2sigma(I)]	R1 = 0.0652, wR2 = 0.1765	R1 = 0.0845, wR2 = 0.1676
R indices (all data)	R1 = 0.0770, wR2 = 0.1922	R1 = 0.1067, wR2 = 0.1808
Extinction coefficient	0.003(3)	0.003(3)
Largest diff. peak and hole	0.244 and -0.207 e.Å^{-3}	0.317 and -0.269 e.Å^{-3}

Table 2. Bond lengths [Å] and angles [°] for (3*S**,11b*R**)-**6a**.

bond lengths		bond angles	
O(1)–C(1)	1.225(3)	C(9)–O(3)–C(12)	117.6(2)
O(2)–C(4)	1.229(3)	C(10)–O(4)–C(13)	117.3(2)
O(3)–C(9)	1.366(3)	O(1)–C(1)–N(2)	121.2(2)
O(3)–C(12)	1.422(4)	O(1)–C(1)–C(11B)	118.9(2)
O(4)–C(10)	1.370(3)	N(2)–C(1)–C(11B)	119.9(2)
O(4)–C(13)	1.410(4)	C(1)–N(2)–C(3)	126.3(2)
C(1)–N(2)	1.330(3)	C(1)–N(2)–C(2′)	117.2(2)

Table 2 (continuation)

C(1)–C(11B)	1.535(3)	C(3)–N(2)–C(2′)	116.3(2)
N(2)–C(3)	1.456(3)	N(2)–C(3)–C(4)	113.8(2)
N(2)–C(2′)	1.466(3)	N(2)–C(3)–C(1′)	113.1(2)
C(3)–C(4)	1.497(4)	C(4)–C(3)–C(1′)	110.1(2)
C(3)–C(1′)	1.509(4)	O(2)–C(4)–N(5)	122.3(2)
C(4)–N(5)	1.336(3)	O(2)–C(4)–C(3)	117.5(2)
N(5)–C(6)	1.466(3)	N(5)–C(4)–C(3)	120.2(2)
N(5)–C(11B)	1.467(3)	C(4)–N(5)–C(6)	117.7(2)
C(6)–C(7)	1.496(4)	C(4)–N(5)–C(11B)	126.5(2)
C(7)–C(7A)	1.501(4)	C(6)–N(5)–C(11B)	115.5(2)
C(7A)–C(11A)	1.387(3)	N(5)–C(6)–C(7)	107.1(2)
C(7A)–C(8)	1.398(4)	C(6)–C(7)–C(7A)	110.0(2)
C(8)–C(9)	1.377(4)	C(11A)–C(7A)–C(8)	119.4(2)
C(9)–C(10)	1.399(4)	C(11A)–C(7A)–C(7)	121.5(2)
C(10)–C(11)	1.370(4)	C(8)–C(7A)–C(7)	119.0(2)
C(11)–C(11A)	1.402(3)	C(9)–C(8)–C(7A)	121.4(2)
C(11A)–C(11B)	1.539(3)	O(3)–C(9)–C(8)	125.1(2)
C(11B)–C(1′′)	1.564(4)	O(3)–C(9)–C(10)	115.7(2)
C(1′′)–C(14)	1.498(4)	C(8)–C(9)–C(10)	119.2(2)
C(14)–C(19)	1.382(4)	C(11)–C(10)–O(4)	124.5(2)
C(14)–C(15)	1.383(4)	C(11)–C(10)–C(9)	119.4(2)
C(15)–C(16)	1.377(5)	O(4)–C(10)–C(9)	116.0(2)
C(16)–C(17)	1.348(6)	C(10)–C(11)–C(11A)	121.9(2)
C(17)–C(18)	1.344(6)	C(7A)–C(11A)–C(11)	118.5(2)
C(18)–C(19)	1.389(5)	C(7A)–C(11A)–C(11B)	122.2(2)
		C(11)–C(11A)–C(11B)	119.3(2)
		N(5)–C(11B)–C(1)	112.4(2)
		N(5)–C(11B)–C(11A)	108.63(19)
		C(1)–C(11B)–C(11A)	110.65(19)
		N(5)–C(11B)–C(1′′)	109.36(19)
		C(1)–C(11B)–C(1′′)	106.0(2)
		C(11A)–C(11B)–C(1′′)	109.8(2)
		C(14)–C(1′′)–C(11B)	114.4(2)
		C(19)–C(14)–C(15)	116.7(3)
		C(19)–C(14)–C(1′′)	121.7(3)
		C(15)–C(14)–C(1′′)	121.6(3)

Table 2 (continuation)

	C(16)–C(15)–C(14)	121.6(4)
	C(17)–C(16)–C(15)	120.6(4)
	C(18)–C(17)–C(16)	119.5(4)
	C(17)–C(18)–C(19)	121.1(4)
	C(14)–C(19)–C(18)	120.6(4)

Table 3. Bond lengths [Å] and angles [°] for (3*S**,11b*R**)-**6b**.

bond lengths		bond angles	
O(1)–C(1)	1.224(5)	C(9)–O(3)–C(12)	117.6(3)
O(2)–C(4)	1.219(5)	C(10)–O(4)–C(13)	118.7(6)
O(3)–C(9)	1.365(5)	C(10)–O(4)–C(13′)	117.3(4)
O(3)–C(12)	1.412(5)	C(13)–O(4)–C(13′)	30.0(6)
O(4)–C(10)	1.357(5)	O(1)–C(1)–N(2)	121.5(4)
O(4)–C(13)	1.397(11)	O(1)–C(1)–C(11B)	119.6(4)
O(4)–(13’)	1.462(7)	N(2)–C(1)–C(11B)	118.5(4)
C(1)–N(2)	1.346(5)	C(1)–N(2)–C(3)	123.4(3)
C(1)–C(11B)	1.539(5)	C(1)–N(2)–C(2′)	116.7(4)
N(2)–C(3)	1.448(5)	C(3)–N(2)–C(2′)	119.0(3)
N(2)–C(2′)	1.464(5)	N(2)–C(3)–C(4)	111.1(3)
C(3)–C(4)	1.497(6)	N(2)–C(3)–C(1′)	111.8(4)
C(3)–C(1′)	1.588(7)	C(4)–C(3)–C(1′)	108.7(4)
C(4)–N(5)	1.359(5)	O(2)–C(4)–N(5)	122.3(4)
N(5)–C(6)	1.455(5)	O(2)–C(4)–C(3)	119.8(4)
N(5)–C(11B)	1.463(5)	N(5)–C(4)–C(3)	117.7(4)
C(6)–C(7)	1.494(6)	C(4)–N(5)–C(6)	115.9(4)
C(7)–C(7A)	1.505(5)	C(4)–N(5)–C(11B)	124.2(3)
C(7A)–C(11A)	1.382(5)	C(6)–N(5)–C(11B)	114.9(3)
C(7A)–C(8)	1.397(5)	N(5)–C(6)–C(7)	109.3(3)
C(8)–C(9)	1.361(5)	C(6)–C(7)–C(7A)	111.4(4)
C(9)–C(10)	1.391(6)	C(11A)–C(7A)–C(8)	119.9(4)
C(10)–C(11)	1.377(5)	C(11A)–C(7A)–C(7)	121.9(4)
C(11)–C(11A)	1.401(5)	C(8)–C(7A)–C(7)	118.0(3)
C(11A)–C(11B)	1.553(5)	C(9)–C(8)–C(7A)	121.7(4)
C(11B)–C(1′′)	1.549(5)	C(8)–C(9)–O(3)	125.2(4)
C(1′)–C(21)	1.455(7)	C(8)–C(9)–C(10)	118.9(4)
C(1′)–C(20)	1.507(9)	O(3)–C(9)–C(10)	115.9(4)

Table 3 (continuation)

C(1′)–C(20′)	1.604(13)	O(4)–C(10)–C(11)	124.2(4)
C(1′′)–C(14)	1.503(5)	O(4)–C(10)–C(9)	115.9(4)
C(14)–C(19)	1.371(6)	C(11)–C(10)–C(9)	119.9(4)
C(14)–C(15)	1.380(6)	C(10)–C(11)–C(11A)	121.5(4)
C(15)–C(16)	1.380(6)	C(7A)–C(11A)–C(11)	117.9(4)
C(16)–C(17)	1.366(7)	C(7A)–C(11A)–C(11B)	121.8(3)
C(17)–C(18)	1.377(7)	C(11)–C(11A)–C(11B)	120.3(3)
C(18)–C(19)	1.379(6)	N(5)–C(11B)–C(1)	112.6(3)
		N(5)–C(11B)–C(1′′)	111.2(3)
		C(1)–C(11B)–C(1′′)	107.2(3)
		N(5)–C(11B)–C(11A)	107.7(3)
		C(1)–C(11B)–C(11A)	107.7(3)
		C(1′′)–C(11B)–C(11A)	110.3(3)
		C(21)–C(1′)–C(20)	113.9(6)
		C(21)–C(1′)–C(3)	114.7(5)
		C(20)–C(1′)–C(3)	114.1(6)
		C(21)–C(1′)–C(20′)	99.3(8)
		C(20)–C(1′)–C(20′)	28.0(6)
		C(3)–C(1′)–C(20′)	103.1(7)
		C(14)–C(1′′)–C(11B)	113.7(3)
		C(19)–C(14)–C(15)	118.2(4)
		C(19)–C(14)–C(1′′)	120.7(4)
		C(15)–C(14)–C(1′′)	121.0(4)
		C(16)–C(15)–C(14)	121.3(5)
		C(17)–C(16)–C(15)	119.8(5)
		C(16)–C(17)–C(18)	119.6(5)
		C(17)–C(18)–C(19)	120.2(5)
		C(14)–C(19)–C(18)	120.8(5)

Table 4. Selected torsion angles [°] for (3*S**,11b*R**)-**6a**.

O(1)–C(1)–N(2)–C(3)	175.1(3)	C(10)–C(11)–C(11A)–C(7A)	–3.1(4)
C(11B)–C(1)–N(2)–C(3)	–3.6(4)	C(10)–C(11)–C(11A)–C(11B)	178.0(2)
O(1)–C(1)–N(2)–C(2′)	–0.5(4)	C(4)–N(5)–C(11B)–C(1)	7.8(3)
C(11B)–C(1)–N(2)–C(2′)	–179.2(2)	C(6)–N(5)–C(11B)–C(1)	–165.5(2)
C(1)–N(2)–C(3)–C(4)	10.1(4)	C(4)–N(5)–C(11B)–C(11A)	130.6(3)

Table 4 (continuation)

C(2′)–N(2)–C(3)–C(4)	–174.3(2)	C(6)–N(5)–C(11B)–C(11A)	–42.7(3)
C(1)–N(2)–C(3)–C(1′)	–116.4(3)	C(4)–N(5)–C(11B)–C(1′′)	–109.6(3)
C(2′)–N(2)–C(3)–C(1′)	59.1(3)	C(6)–N(5)–C(11B)–C(1′′)	77.1(3)
N(2)–C(3)–C(4)–O(2)	172.5(3)	O(1)–C(1)–C(11B)–N(5)	176.0(2)
C(1′)–C(3)–C(4)–O(2)	–59.4(4)	N(2)–C(1)–C(11B)–N(5)	–5.3(3)
N(2)–C(3)–C(4)–N(5)	–7.5(4)	O(1)–C(1)–C(11B)–C(11A)	54.4(3)
C(1′)–C(3)–C(4)–N(5)	120.6(3)	N(2)–C(1)–C(11B)–C(11A)	–126.9(2)
O(2)–C(4)–N(5)–C(6)	–8.2(4)	O(1)–C(1)–C(11B)–C(1′′)	–64.6(3)
C(3)–C(4)–N(5)–C(6)	171.8(2)	N(2)–C(1)–C(11B)–C(1′′)	114.1(3)
O(2)–C(4)–N(5)–C(11B)	178.7(3)	C(7A)–C(11A)–C(11B)–N(5)	4.4(3)
C(3)–C(4)–N(5)–C(11B)	–1.3(4)	C(11)–C(11A)–C(11B)–N(5)	–176.7(2)
C(4)–N(5)–C(6)–C(7)	–103.6(3)	C(7A)–C(11A)–C(11B)–C(1)	128.2(2)
C(11B)–N(5)–C(6)–C(7)	70.3(3)	C(11)–C(11A)–C(11B)–C(1)	–52.9(3)
N(5)–C(6)–C(7)–C(7A)	–54.2(3)	C(7A)–C(11A)–C(11B)–C(1′′)	–115.1(3)
C(6)–C(7)–C(7A)–C(11A)	20.2(3)	C(11)–C(11A)–C(11B)–C(1′′)	63.8(3)
C(6)–C(7)–C(7A)–C(8)	–156.1(2)	N(5)–C(11B)–C(1′′)–C(14)	59.4(3)
C(11A)–C(7A)–C(8)–C(9)	–0.4(4)	C(1)–C(11B)–C(1′′)–C(14)	–61.9(3)
C(7)–C(7A)–C(8)–C(9)	176.0(2)	C(11A)–C(11B)–C(1′′)–C(14)	178.6(2)
C(8)–C(7A)–C(11A)–C(11B)	–178.2(2)	C(11B)–C(1′′)–C(14)–C(19)	91.9(3)
C(7)–C(7A)–C(11A)–C(11B)	5.5(4)	C(11B)–C(1′′)–C(14)–C(15)	–86.9(3)

Table 5. Selected torsion angles [°] for (3*S**,11b*R**)-**6b**.

O(1)–C(1)–N(2)–C(3)	–159.3(4)	C(4)–N(5)–C(11B)–C(1)	14.9(5)
C(11B)–C(1)–N(2)–C(3)	27.0(5)	C(6)–N(5)–C(11B)–C(1)	168.9(3)
O(1)–C(1)–N(2)–C(2′)	9.7(6)	C(4)–N(5)–C(11B)–C(1′′)	135.3(4)
C(11B)–C(1)–N(2)–C(2′)	–164.0(4)	C(6)–N(5)–C(11B)–C(1′′)	–70.7(4)
C(1)–N(2)–C(3)–C(4)	–36.9(5)	C(4)–N(5)–C(11B)–C(11A)	–103.7(4)
C(2′)–N(2)–C(3)–C(4)	154.3(4)	C(6)–N(5)–C(11B)–C(11A)	50.3(4)
C(1)–N(2)–C(3)–C(1′)	84.7(5)	O(1)–C(1)–C(11B)–N(5)	172.9(3)
C(2′)–N(2)–C(3)–C(1′)	–84.1(5)	N(2)–C(1)–C(11B)–N(5)	–13.2(5)
N(2)–C(3)–C(4)–O(2)	–149.5(4)	O(1)–C(1)–C(11B)–C(1′′)	50.2(5)
C(1′)–C(3)–C(4)–O(2)	87.1(5)	N(2)–C(1)–C(11B)–C(1′′)	–135.9(3)
N(2)–C(3)–C(4)–N(5)	35.4(5)	O(1)–C(1)–C(11B)–C(11A)	–68.5(4)
C(1′)–C(3)–C(4)–N(5)	–88.0(5)	N(2)–C(1)–C(11B)–C(11A)	105.4(4)
O(2)–C(4)–N(5)–C(6)	3.7(6)	C(7A)–C(11A)–C(11B)–N(5)	–16.9(5)

Table 5 (continuation)

C(3)–C(4)–N(5)–C(6)	178.6(3)	C(11)–C(11A)–C(11B)–N(5)	163.4(3)
O(2)–C(4)–N(5)–C(11B)	157.4(4)	C(7A)–C(11A)–C(11B)–C(1)	–138.6(4)
C(3)–C(4)–N(5)–C(11B)	–27.6(6)	C(11)–C(11A)–C(11B)–C(1)	41.7(5)
C(4)–N(5)–C(6)–C(7)	87.4(4)	C(7A)–C(11A)–C(11B)–C(1′′)	104.7(4)
C(11B)–N(5)–C(6)–C(7)	–68.9(5)	C(11)–C(11A)–C(11B)–C(1′′)	–75.0(4)
N(5)–C(6)–C(7)–C(7A)	47.5(5)	N(2)–C(3)–C(1′)–C(21)	53.6(6)
C(6)–C(7)–C(7A)–C(11A)	–17.5(6)	C(4)–C(3)–C(1′)–C(21)	176.6(5)
C(6)–C(7)–C(7A)–C(8)	166.8(4)	N(2)–C(3)–C(1′)–C(20)	–172.3(8)
C(7)–C(7A)–C(8)–C(9)	175.3(4)	C(4)–C(3)–C(1′)–C(20)	–49.3(9)
C(12)–O(3)–C(9)–C(8)	0.6(6)	N(2)–C(3)–C(1′)–C(20′)	160.4(9)
C(12)–O(3)–C(9)–C(10)	–179.4(4)	C(4)–C(3)–C(1′)–C(20′)	–76.6(9)
C(13)–O(4)–C(10)–C(11)	13.3(12)	N(5)–C(11B)–C(1′′)–C(14)	–59.1(4)
C(13)–O(4)–C(10)–C(9)	–168.0(10)	C(1)–C(11B)–C(1′′)–C(14)	64.5(4)
C(7)–C(7A)–C(11A)–C(11)	–178.1(4)	C(11A)–C(11B)–C(1′′)–C(14)	–178.6(3)
C(8)–C(7A)–C(11A)–C(11B)	177.9(3)	C(11B)–C(1′′)–C(14)–C(19)	–93.2(5)
C(7)–C(7A)–C(11A)–C(11B)	2.2(6)	C(11B)–C(1′′)–C(14)–C(15)	84.9(5)
C(10)–C(11)–C(11A)–C(11B)	–176.5(4)		

Crystallographic data (excluding structural factors) for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 206547 Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EW, UK (Fax: Int code + (1223)336-033; E-mail:deposit@ccdc.cam.ac.uk).

EXPERIMENTAL

NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR. Tetramethylsilane (TMS) or solvents were used as internal standards. Chemical shifts are reported in ppm. Coupling constants (*J*) are reported in hertz and multiplicity was represented as s = singlet, d = doublet, t = triplet and q = quartet. Mass spectra were collected on an AMD 604 apparatus; high resolution mass spectra were acquired using LSIMS (positive ion mode). TLC analyses were performed on Merck 60 silica gel plates and visualized using UV lamp and iodine vapor. Column chromatography was carried out at atmospheric pressure using silica gel (230–400 or under 400 mesh, Merck). X-ray intensity data for *rac*-**6a** and *rac*-**6b** were measured at T = 293 K on Kuma KM4CCD κ-axis diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073 Å). Crystal data together with the refinement details are given in Table 1. The crystals were positioned at 65 mm from the KM4CCD camera. 656 and 1416 frames were measured at 0.7 and 0.9° intervals for *rac*-**6a** and *rac*-**6b**, respectively. 30 and 15 seconds counting time were applied, respectively. The data were corrected for Lorentz and polarization effects. No absorption correction was applied. Data reduction and analysis were carried out using the Kuma Diffraction (Wrocław) programs. The structures were solved by direct methods from *SHELXS97* [4] and refined using *SHELXL97* software [5]. The relatively small dimensions of crystals used for data collections resulted in not very high quality data and in consequence in not very good agreement factors, although very sensitive method of radiation detection (CCD) and long exposure time were applied.

Benzyl 2-{[2-(3,4-dimethoxyphenyl)ethyl]amino}-1-methyl-2-oxoethyl(methyl)carbamate (2a): To a solution of *N*-Me-Cbz-alanine **1a** [6] (2.00 g, 8.44 mmol) in dry THF (50 mL), 2-(3,4-dimethoxyphenyl)ethylamine (1.53 g, 8.44 mmol) and triethylamine (1.87 mL, 16.9 mmol) were added. To the resultant mixture BOP reagent (4.10 g, 9.30 mmol) was introduced at one portion, stirring was continued for 2 h and the mixture was left at room temperature overnight. After evaporation of the solvent, the residue was dissolved in chloroform (50 mL), washed with saturated sodium chloride solution (2× 10 mL) and water (10 mL). The organic phase was then dried ($MgSO_4$) and evaporated to give a crude product, which was then purified by chromatography on silica gel. Elution with 2% (v/v) methanol in chloroform gave 3.24 g of compound **2a** in 96% yield: IR (KBr, cm^{-1}): 3350, 3090–2825, 1675, 1520, 1330, 1260, 1230, 1170. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (m, 5H, H_{arom}), 6.79–6.64 (m, 3H, H_{arom}), 5.17 (q, 1H, J = 4.5 Hz, H-1), 5.12 (q_{AB}, 2H, J = 12.0 Hz, PhC$\underline{H}_2$), 4.74 (br s, 1H, NH), 3.86 and 3.82 (two s, 3H each, 2×OCH_3), 3.46 (m, 2H, NHC$\underline{H}_2CH_2$), 2.77 (s, 3H, NCH_3), 2.71 (m, 2H, $NHCH_2C\underline{H}_2$), 1.33 (d, 3H, J = 7.0 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 157.4, 149.0, 147.7, 136.3, 131.2, 128.8, 128.6, 128.5, 120.6, 111.7, 111.3, 67.7, 55.9, 55.8, 55.8, 40.7, 35.2, 27.4, 19.0.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(methylamino)propanamide (3a):** To a solution of compound **2a** (3.38 g, 8.44 mmol) in ethanol (150 mL) a concentrated HCl (2 mL) was added. The resulted solution was stirred under hydrogen blanket over palladium-on-charcoal catalyst (0.1 g) at 50°C for 2 h. The completion of the reaction was monitored by TLC. The catalyst was removed by filtration through Celite, the solvent was evaporated, the residue was taken up into saturated sodium bicarbonate solution and extracted with chloroform. Drying ($MgSO_4$) and evaporation afforded compound **3a** as an oil in quantitative yield: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (br t, 1H, NH), 6.82–6.72 (m, 3H, H_{arom}), 3.87 and 3.86 (two s, 3H each, 2×OCH_3), 3.51 (m, 2H, NHC$\underline{H}_2CH_2$), 3.08 (q, 1H, J = 7.0 Hz, H-2), 2.78 (app t, 2H, $NHCH_2C\underline{H}_2$), 2.30 (s, 3H, NCH_3), 1.25 (d, 3H, J = 7.0 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.8, 148.9, 147.6, 131.5, 120.7, 111.9, 111.3, 60.4, 55.9, 55.8, 40.1, 35.4, 35.2, 19.7.

***N*-(2-{[2-(3,4-Dimethoxyphenyl)ethyl]amino}-1-methyl-2-oxoethyl)-*N*-methyl-2-oxo-3-phenylpropanamide (4a):** To a stirred solution of phenylpyruvic acid (0.55 g, 3.38 mmol) in dry THF (20 mL) compound **3a** (0.91 g, 3.38 mmol) was introduced followed by Et_3N (0.75 mL, 6.76 mmol) and BOP reagent (1.65 g, 3.72 mmol) at room temperature. After 2 h of stirring the mixture was left overnight. The solvent was evaporated in *vacuo* and the residue was dissolved in methylene chloride (30 mL) and washed with a solution of saturated sodium chloride and water. The organic phase was dried ($MgSO_4$) and the solvent was evaporated giving a yellow oil which was purified by chromatography on silica gel using 2% (v/v) methanol in chloroform. Compound **4a** was obtained in a yield of 59% as an oil: IR (film, cm^{-1}): 3350, 3100–2850, 1650, 1520, 1450, 1270, 1230, 1050. ^{1}H NMR (500 MHz, $CDCl_3$), two stable conformers present (I:II = 4:3): δ = 7.20–7.40 (m, 10H, H_{arom}), 6.80 (m, 2H, H_{arom}), 6.70 (m, 4H, H_{arom}), 6.37 (br t, 1H, NH) (I), 5.85 (br.t, 1H, NH) (II), 4.27 and 4.04 (q_{AB}, 2H, J= 14.5 Hz, PhC$\underline{H}_2$) (I), 4.02 and 3.92 (q_{AB}, 2H, J = 14.5 Hz, PhC$\underline{H}_2$) (II), 3.82 (q, 1H, J = 6.5 Hz, H-1) (I), 4.93 (q, 1H, J = 6.5 Hz, H-1) (II), 3.86 and 3.85, 3.88 and 3.84 (four s, 3H each, 4×OCH_3), 3.30–3.56 (m, 4H, NHC$\underline{H}_2CH_2$), 2.71 (m, 4H, $NHCH_2C\underline{H}_2$), 2.63 (s, 3H, NCH_3) (I), 2.51 (s, 3H, NCH_3) (II), 0.83 (d, 3H, J= 7.0 Hz, CH_3) (I), 1.22 (d, 3H, J = 7.0 Hz, CH_3) (II). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.6, 196.7, 169.4, 168.7, 167.2, 166.7, 149.0, 149.0, 147.7, 147.7, 131.1, 131.1, 131.0, 130.5, 130.0, 130.0, 129.9, 129.9, 129.4, 129.4, 129.0, 129.0, 128.0, 127.8, 120.7, 120.6, 111.8, 111.7, 111.4, 111.3, 55.9, 55.9, 55.9, 55.8, 47.2, 47.0, 41.0, 40.9, 35.2, 35.2, 30.2, 27.4, 13.6, 12.8. LSIMS (+) 8 kV (%): 435 $[M+Na]^+$(100), 413 [M+H]+(2).

3-Benzyl-4-[2-(3,4-dimethoxyphenyl)ethyl]-3-hydroxy-1,6-dimethylpiperazine-2,5-dione (5a): 5a was obtained with 11% chemical yield as an oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (m, 3H, H_{arom}), 6.95 (m, 2H, H_{arom}), 6.83 (m, 3H, H_{arom}), 4.10 (m, 1H, NC$\underline{H}_2CH_2$), 3.91 and 3.87 (two s, 3H each, 2×OCH_3), 3.48 (m, 1H, NC$\underline{H}_2CH_2$), 3.17 (q_{AB}, 2H, J= 13.5 Hz, PhC$\underline{H}_2$), 2.85 (m, 2H, $NCH_2C\underline{H}_2$), 2.77 (s, 3H, NCH_3), 2.30 (q, 1H, J = 6.5 Hz, $N(CH_3)C\underline{H}CH_3$), 1.71 (s, 1H, OH), 1.34 (d, 3H, J = 6.5 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.1, 165.7, 148.9, 147.6, 133.6, 131.9, 130.1, 128.5, 127.9, 121.0, 112.2, 111.3, 86.0, 55.9, 55.9, 55.7, 46.4, 44.5, 35.3, 31.5, 18.2.

(3*S,11b*R**)-11b-Benzyl-9,10-dimethoxy-2,3-dimethyl-7,11b-dihydro-2*H*-pyrazino[2,1-*a*]isoquinoline-1,4(3*H*,6*H*)-dione (6a):** Acetyl chloride (5 mL) was added to the ice-cooled dry methanol (150 mL) and after 15 min, compound **5a** (1.00 g, 2.40 mmol) was added in one portion. The mixture was left for two weeks in a refrigerator. The solvent was evaporated in *vacuo* and the residue was dissolved in chloroform (50 mL). The organic phase was washed with sodium bicarbonate solution (20

mL), water (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel. Elution with 1% (v/v) methanol in chloroform gave 828 mg of white crystalline compound **6a** (88%): m.p. 185–192°C. IR (KBr, cm^{-1}): 2830–3100, 1650, 1520, 1260. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (s, 1H, H_{arom}-11), 7.34–7.12 (m, 5H, H_{arom}), 6.58 (s, 1H, H_{arom}-8), 4.98 (ddd, 1H, J_1 = 12.5 Hz, J_2 = 5.5 Hz, J_3 = 1.5 Hz, NCH_2CH_2), 3.98 and 3.87 (two s, 3H each, 2×OCH_3), 3.73 (q, 1H, J = 7.0 Hz, H-3), 3.74 and 3.32 (q_{AB}, 2H, J = 14 Hz, $PhCH_2$), 3.26 (td, 1H, J_1 = 12.5 Hz, J_2 = 3.5 Hz, NCH_2CH_2), 3.08 (m, 1H, NCH_2CH_2), 2.75 (s, 3H, NCH_3), 2.67 (m, 1H, NCH_2CH_2), 0.44 (d, 3H, J = 7.0 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 165.9, 148.4, 147.2, 135.6, 130.6, 128.6, 128.5, 127.5, 127.2, 111.7, 111.2, 67.3, 57.3, 56.1, 55.8, 47.1, 37.2, 32.7, 28.7, 18.0. LSIMS (+) 8 kV (%): 395 (28) $[M+H]^+$, 303 (42), 95 (40), 81 (41).

Benzyl 1-({[2-(3,4-dimethoxyphenyl)ethyl]amino}carbonyl)-2-methylpropyl(methyl) carbamate (2b): The procedure described for the synthesis of **2a** was applied to **1b** [6] (2.50 g, 9.46 mmol). 3.92 g of **2f** (97%) was obtained as an oil: IR (film, cm^{-1}): 3360, 3050-2825, 1680, 1670, 1520, 1260, 1160. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (m, H, H_{arom}), 6.14 (br t, 1H, NH), 5.13 (s, 2H, $PhCH_2$), 3.86 and 3.82 (two s, 3H each, 2×OCH_3), 3.98 (d, 1H, J = 10.5 Hz, H-1), 3.47 (m, 2H, $NHCH_2CH_2$), 2.87 (s, 3H, NCH_3), 2.71 (t, 2H, J = 7.5 Hz, $NHCH_2CH_2$), 2.27 (m, 1H, $CH(CH_3)_2$), 0.91 and 0.85 (two d, 3H each, J = 6.5 Hz, 2×CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 157.4, 149.0, 147.6, 136.5, 131.2, 128.5, 128.1, 127.5, 120.6, 111.8, 111.3, 67.4, 65.4, 55.9, 55.8, 40.4, 35.4, 29.8, 26.0, 19.6, 18.6. LSIMS (+) 8 kV (%): 467 $[M+K]^+$(1), 451 $[M+Na]^+$(100), 429 $[M+H]^+$(4), 301 (5).

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-3-methyl-2-(methylamino)butanamide (3b):** The procedure described for the synthesis of **3a** was applied to **2b** (3.92 g, 9.17 mmol). 2.34 g of **3b** (87%) was obtained as an oil: IR (KBr, cm^{-1}): 3340, 3320, 3100–810, 1620, 1520, 1270, 1050. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (br t, 1H, $NHCH_2CH_2$), 6.80 (d_{AB}, 1H, J = 8.5 Hz, H_{arom}-5), 6.75 (d_{AB}, 1H, J = 8.5 Hz, H_{arom}-6), 6.74 (d_{AB}, 1H, J = 2.0 Hz, H_{arom}-2), 3.87 and 3.86 (two s, 3H each, 2× OCH_3), 3.54 (m, 2H, $NHCH_2CH_2$), 2.78 (m, 2H, $NHCH_2CH_2$), 2.73(d, 1H, J = 4.5 Hz, H-2), 2.29 (s, 3H, NCH_3), 2.06 (m, 1H, $CH(CH_3)_2$), 0.96 and 0.84 (two d, 3H each, J = 7.0 Hz, 2×CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.4, 148.9, 147.6, 131.6, 120.6, 111.9, 111.3, 70.8, 55.9, 55.8, 40.0, 36.2, 35.6, 31.3, 19.6, 17.7. LSIMS (+) 8 kV (%): 295 $[M+H]^+$(100).

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-3-methyl-2-[methyl(2-oxo-3-phenylpropanoyl)amino]butanamide (4b):** The procedure described for the synthesis of **4a** was applied to **3b** (1.87 g, 6.36 mmol) and provided 1.48 g of **4b** (53%) as an oil: ^{1}H NMR (500 MHz, $CDCl_3$); two stable conformers present (I:II = 11:10): δ = 7.37–7.14 (m, 10H, H_{arom}), 6.82–6.65 (m, 6H, H_{arom}), 6.70 (m, 1H, NH) (I), 5.94 (br t, 1H, J = 5.5 Hz, NH) (II), 4.25 and 4.06 (q_{AB}, 2H, J = 15.0 Hz, $PhCH_2$) (I), 4.04 and 3.97 (q_{AB}, 2H, J = 15.0 Hz, $PhCH_2$) (II), 4.22 (d, 1H, J = 10.5 Hz, H-2) (II), 3.31 (d, 1H, J = 10.5 Hz, H-2) (I), 3.88 (s, 3H, OCH_3), 3.85 (s, 9H, 3×OCH_3), 3.52 (m, 2H, $NHCH_2CH_2$) (I), 3.38 (m, 2H, $NHCH_2CH_2$) (II), 2.79 (s, 3H, NCH_3) (I), 2.72 (m, 4H $NHCH_2CH_2$), 2.65 (s, 3H, NCH_3) (II), 2.22 (m, 2H, $CH(CH_3)_2$), 0.88 and 0.61 (two d, 3H each, J = 6.5 Hz, 2×CH_3) (I), 0.71 and 0.27 (two d, 3H each, J = 6.8 Hz, 2× CH_3) (II). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.9, 196.7, 168.4, 167.9, 167.4, 166.2, 149.0, 148.9, 147.7, 147.6, 131.0, 131.0, 131.0, 131.0, 130.1, 129.9, 129.1, 129.0, 128.0, 127.8, 120.7, 120.7, 111.8, 111.7, 111.4, 111.3, 66.2, 62.7, 55.9, 55.9, 55.8, 55.8, 47.1, 46.8, 40.7, 40.6, 35.3, 35.3, 30.6, 28.2, 25.4, 25.3, 19.5, 19.5, 18.1, 17.6. LSIMS (+) 8 kV (%): 441 $[M+H]^+$(30), 260 (47), 164 (68), 91 (41), 86 (56).

(3*S,11b*R**)-11b-Benzyl-3-isopropyl-9,10-dimethoxy-2-methyl-7,11b-dihydro-2*H*-pyrazino[2,1-*a*]isoquinoline-1,4(3*H*,6*H*)-dione (6b):** Following the procedure described for the synthesis of **6a**, compound **4b** (287 mg, 0.65 mmol) was converted into **6b** isolated in the form of white crystalline solid (200 mg, 91%): m.p. 160–170°C. IR (KBr, cm^{-1}): 3100–2820, 1670, 1650, 1510, 1250, 1220. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (s, 1H, H_{arom}-11), 7.2 (m, 5H, H_{arom}), 6.56 (s, 1H, H_{arom}-8), 4.78 (ddd, 1H, J_1 = 12.5, J_2 = 5.5 Hz, J_3 = 1.0 Hz, NCH_2CH_2), 3.94 and 3.86 (two s, 3H each, 2×OCH_3), 3.61 (d, 1H, J = 4.0 Hz, H-3), 3.85 and 3.37 (q_{AB}, 2H, J = 14 Hz, $PhCH_2$), 3.30 (m, 1H, NCH_2CH_2), 3.17 (m, 1H, NCH_2CH_2), 2.86 (s, 3H, NCH_3), 2.60 (m, 1H, NCH_2CH_2), 1.67 (m, 1H, $CH(CH_3)_2$), 0.83 and 0.21 (two d, 3H each, J = 7.0 Hz, 2× CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.3, 165.5, 148.5, 147.1, 135.9, 130.7, 129.4, 128.5, 127.3, 126.7, 111.4, 110.6, 68.0, 67.1, 56.0, 55.8, 46.3, 38.1,31.7, 27.4, 20.0, 16.4.

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