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Synthesis of tetramic acids with a benzo[*f*]indolizine skeleton. Transannular rearrangements in pyrazino[1,2-*b*]isoquinolin-4-ones

Irene Ortín, Juan Francisco González, Elena de la Cuesta, Carmen Avendaño *

Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain

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ABSTRACT

Pyrazino[1,2-*b*]isoquinoline-1,4-diones (**3**) having a bulky activating group at the N(2)-position were rearranged to tetramic acids with a benzo[*f*]indolizine skeleton (**8**) in the presence of K^{t}BuO or LHMDS as bases. This rearrangement was diasteroselective for the 6,11a-*trans*-isomers of the starting compounds. 1-Hydroxy-pyrazino[1,2-*b*]isoquinolin-4-one (**7**) afforded a 1-trichloroacetamido derivative (**14**) after treatment with trichloroacetonitrile and a catalytic amount of sodium hydride as a base, through two subsequent base-promoted transannular rearrangements. In summary, the combination of functions in the piperazine ring of the starting tricyclic compounds conferred to them new reactivities that imply different base-promoted transannular rearrangements and led to unexpected transformations.

1. Introduction

Tetramic acid represents the enolic tautomer of 2,4-pyrrolidinedione. This ring system is contained in several natural products that have shown a broad spectrum of biological activity, more often incorporating a 3-acyl substituent.[1] Very few of these compounds contain a tetramic acid portion fused to other rings, being one exception the mycotoxin α-cyclopiazonic acid **1** (Fig. 1), that contains a pyrrolo[1′,2′:2,3]isoindolo[4,5,6-*cd*]indole skeleton. Compound **1** is a secondary metabolite produced by *Penicillium cyclopeum* and other fungal organisms whose biological activities have attracted much attention.[2] In contrast to simpler benzo[*f*]indolizidine compounds **2**, for which several synthetic approaches have been reported,[3–5] we do not know any synthesis of tetramic acid derivatives containing the benzo[*f*]indolizine skeleton. In the last years, we have developed a simple and efficient method to achieve pyrazino[1,2-*b*]isoquinoline-1,4-diones (**3a**), used as building blocks in the synthesis of saframycin, reineiramycin, quinocarcin, and ecteinascidin analogues.[6–12] N-Acetylation (**3b**) and N-carboxylation (**3e**) were key-steps in the subsequent derivatization because of the enhancement of two properties in the diketopiperazine (DKP) portion: the acidity of the C–H protons and the electrophilicity of the C(1)-carbonyl group.[7–12]

The combination of two activated lactam functions in simple DKP derivatives confers to them new reactivity patterns, as it was recently reported for bis-Boc and bis-Bz-DKPs **4** (Scheme 1). These compounds exhibit a base-promoted transannular rearrangement that led to ring contraction, allowing access to tetramic acid

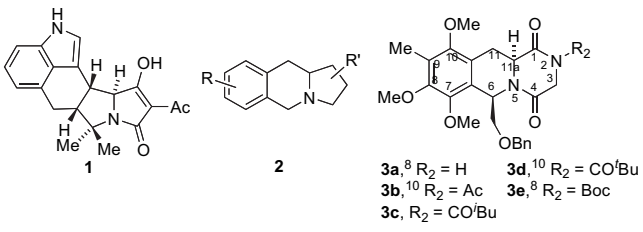
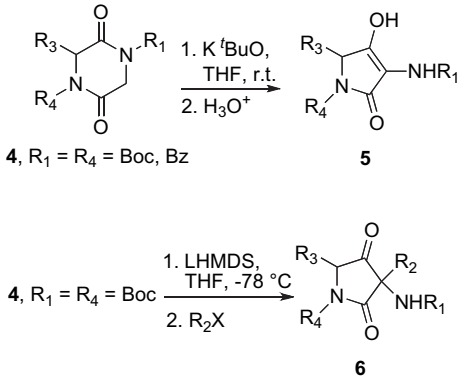


Fig. 1. Tetramic acid (**1**), benzo[*f*]indolizidine skeleton (**2**) as target molecules from pyrazino[1,2-*b*]isoquinoline-1,4-diones (**3**).



Scheme 1. Recently reported results for bis-Boc and bis-Bz-DKPs.

* Corresponding author. Tel.: +34 913941821; fax: +34 913941822; e-mail address: avendano@farm.ucm.es (C. Avendaño).

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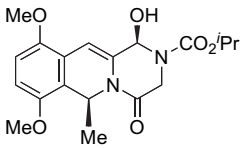
derivatives **5**. The tandem rearrangement/alkylation reaction occurred regioselectively (on the Gly portion) and diasteroselectively (with the two side chains on the same face of the heterocycle).[13,14] Compounds **6** were derived to α,γ-diamino-β-hydroxyacid esters.[15–17]

These precedents moved us to study the reactivity of compounds **3b**–**e** in base, in order to analyze the steric effects of the *N*-substituent besides the influence of the electronic factors. Additionally, the ready access to 1-hydroxy-11,11a-dehydro derivatives, such as **7** (Fig. 2), moved us to study its base-catalyzed reaction with Cl_3CCN, since the expected trichloroacetimidate at the C(1)-position could be a possible substrate for a concerted suprafacial [3,3]-sigmatropic rearrangement to give trichloroacetamides at the C(11)-position through an Overman-type reaction.[18–20]



7

Fig. 2. Compound **7**.

2. Results and discussion

2.1. Base-promoted transannular rearrangement of compounds 3

The optimal substrate for this rearrangement was compound **3d**, which afforded the fused aminotetramate **8d** as the only product after 12 h of treatment with K^{t}BuO (1.2 equiv) at room temperature, or LHMDS (1.2 equiv) at −78 °C, 2 h, and subsequent quenching with acid. The *N*-Boc derivative **3e** showed a reactivity very similar to **3d**, affording **8e** after treatment with K^{t}BuO or LHMDS, although the last base required to increase the reaction temperature up to 0 °C (Scheme 2). The epimerization of the 10a-proton found in compounds **8** was not surprising by considering that the 11a-proton in compounds **3** is labile, giving in basic media the more stable 6,11a-*trans*-isomers.[21] In fact, after 30 min of basic treatment, **3d** was recovered as a mixture with its 11a-epimer **3f** and a small amount of **8d**. The epimeric mixture was resolved by column chromatography of derivatives **3h** and **3i**, which were originated by hydrogenolysis and methanolysis of C(6)- and N(2)-protecting groups, respectively.[22] The rearrangement is diasteroselective for the 6,11a-*trans*-isomers **3f** and **3g**, since no traces of tetramic acid derivatives with a 5,10a-*cis* relationship were observed.

Compounds **8d** and **8e** were totally enolized in solution (^{1}H NMR) and in the solid state (IR) and their structure assignments were mainly based on ^{1}H NMR and ^{13}C NMR correlations as well as NOESY experiments, which showed the epimerization of the 10a-proton. Data for compound **8d** are given in Fig. 3 and Table 1.

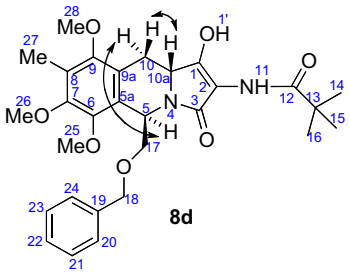
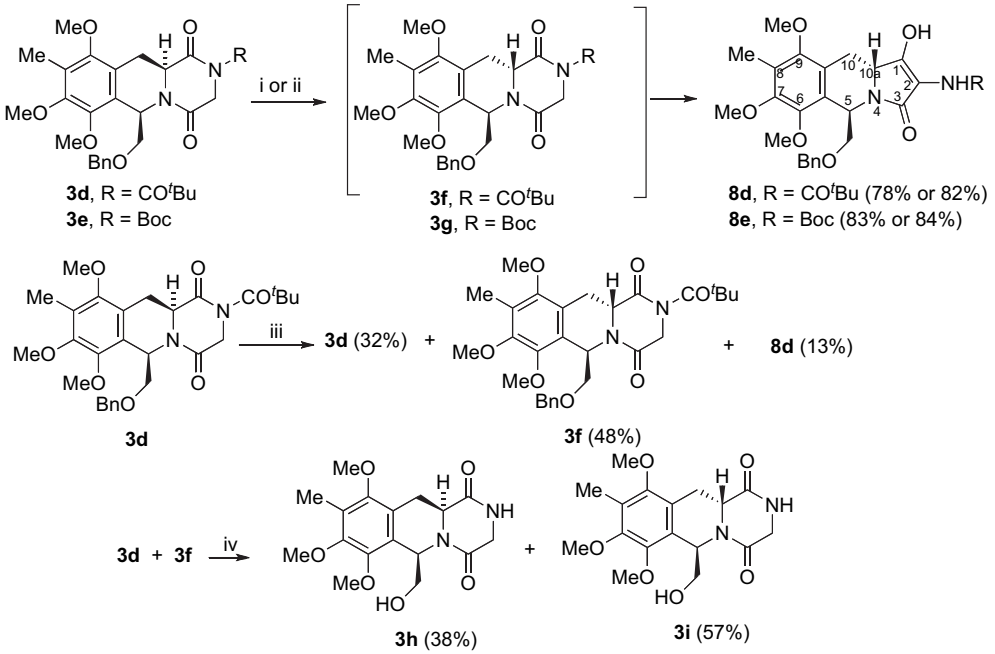


Fig. 3. Representative NOEs and structure assignments for compound **8d**.

Tetramic acid derivatives **8d** and **8e** must be formed through a first transannular attack of enolate **A** to the less hindered face of the C(1)-carbonyl group to provide the oxyanion **B**, in which the aziridine moiety must be located on the α-face. The opening of the aziridine ring may take place before or after protonation through the amide anion **C** or the aziridinium cation **D** (Scheme 3). To get further insight into both mechanisms, we studied the tandem rearrangement/alkylation reaction in which, instead of the expected 2-methyl derivative of **8d**, we obtained the *N*-methyl compound **9**. This result implies the N-methylation of the aziridine to



Scheme 2. (i) (1) K^{t}BuO, THF, rt, 12 h. (2) H_3O^+. (ii) (1) LHMDS, THF, −78 °C (0 °C for **3e**), 2 h. (2) H_3O^+. (iii) (1) LHMDS, THF, −78 °C, 30 min. (2) H_3O^+. (iv) H_2, Pd/C (30%), MeOH, rt 16 h.

Table 1
^{1}H and ^{13}C NMR data for compound **8d** in $CDCl_3$

Position	^{13}C	^{1}H, m, *J* (Hz)	HMBC
1	155.7		10a, 1′,11,10
1′ (OH)		11.53, s	10a, 1
2	103.1		
3	165.1		10a, 11
5	47.3	5.29, dd, *J*=6.4 and 2.9	25, 5a, 6
5a	124.6		5, 17
6	146.1		25, 5
7	150.0		26, 27
8	124.7		27
9	152.2		28, 27, 10
9a	122.2		10, 5
10	26.2	3.26, dd, *J*=16.7 and 5.6 2.30, dd, *J*=16.7 and 11.1	9, 9a, 1, 10a,
10a	51.0	4.10, dd, *J*=11.1 and 5.6	1, 3, 1′, 10
11 (NH)		7.42, s	3, 1, 12
12	178.9		11, 14, 15, 16
13	38.9		14, 15, 16
14, 15, and 16	27.5	1.23, s	13, 12
17	72.2	4.46, d, *J*=12.3 and 4.21, d, *J*=12.3	5a
18	72.7	3.50, m, and 3.61, m,	20, 21, 24
19	138.2		20, 21, 22, 23, 24
20–24	128.3 and 127.5	7.06, m	18, 19
25	60.2	3.63, s	6
26	60.0	3.59, s	7
27	9.4	2.00, s	7, 8, 9
28	59.9	3.48, s	9

give intermediates **E** and **F**, and a final protonation and supports intermediate **D** as a precursor of **8d**. Finally, the base-promoted methylation of **8d** afforded compound **10**, whose selective configuration was determined by NOESY experiments (see Fig. 4). We think that the 10,10a-dehydrogenation found in **10** comes from the radical oxidation with oxygen at the 10a-position of a *C*-methyl intermediate followed by dehydration.[23,24]

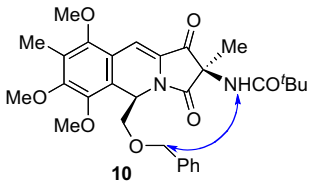
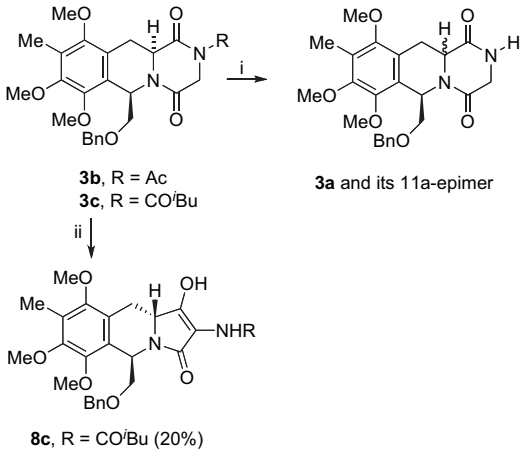
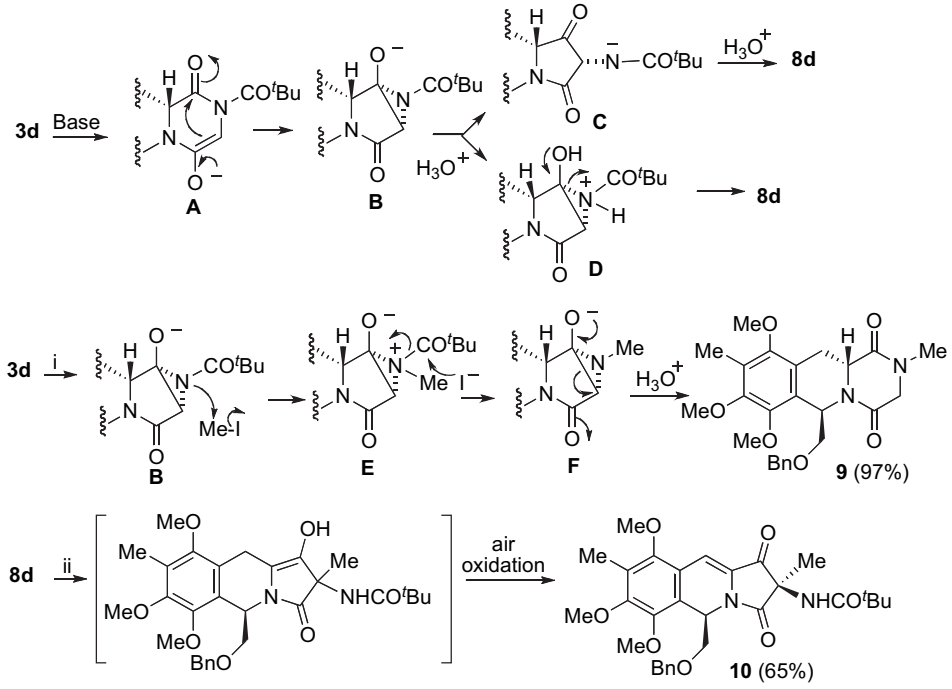


Fig. 4. Representative NOEs and structure assignments for compound **10**.

gave **3a** as inseparable epimeric mixture. Treatment with LHMDS gave very complex mixtures. In the case of **3c** the tetramic acid derivative **8c** was isolated in poor yield (Scheme 4).



Scheme 4. (i) (1) K^{t}BuO, THF, rt, 12 h. (2) H_3O^+. (ii): (1) LHMDS, THF, −78 °C, 2 h. (2) H_3O^+.

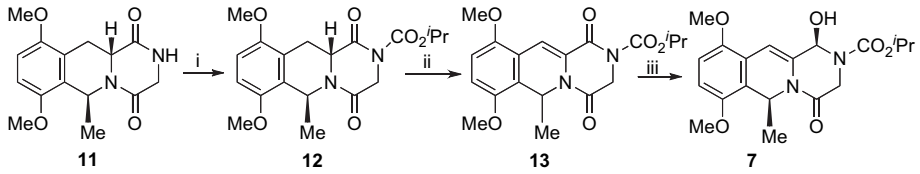


Scheme 3. (i) (1) LHMDS, THF, −78 °C, 2 h. (2) MeI, rt 16 h. (3) H_3O^+. (ii) (1) LHMDS, THF, −78 °C, 1 h. (2) MeI, rt 16 h.

The lower bulk of the acetyl and isopentanoyl groups in compounds **3b** and **3c** with respect to that of pivaloyl or Boc substituents, permits the nucleophilic attack at these exocyclic acyl groups. Accordingly, after treatment with K^{t}BuO **3b** and **3c** only

2.2. Base-catalyzed reaction of compound 7 with Cl_3CCN

The synthesis of compound **7** was carried out following previously described methodologies (Scheme 5).[8,25]



Scheme 5. (i) DMAP (3 equiv), Et_3N (6 equiv), $ClCO_2{}^iPr$ (6 equiv), rt, 24 h. (ii) NBS, AIBN, CCl_4, 100 °C, 1 h. (iii) $LiAlH(O^tBu)_3$ (5 equiv) in anhydrous THF, rt, 16 h.

The combination of the lactam and hemiaminal functions in this compound **7** showed an unexpected reactivity. Reaction with trichloroacetonitrile and a catalytic amount of sodium hydride as a base afforded compound **14** instead of the expected 1-trichloroacetamidate or the 11-trichloroacetamide derivative that would be the [3,3]-sigmatropic rearranged product formed through an Overman reaction-type. According to our proposed mechanism, compound **14** is formed through two subsequent base-promoted transannular rearrangements. First of all, the 'alkoxide' intermediate **I** obtained by deprotonation of the OH group of **7** by the base gives the 1,4-oxy-4-alkoxide **II** by transannular nucleophilic attack to the C(4)-carbonyl, and this cyclic hemiketal anion gives the corresponding trichloroacetimidate anion **III** after addition to trichloroacetonitrile. This new intermediate, through a second transannular nucleophilic attack rearranges to the anion **IV**, that gives **14** with regeneration of **I** from compound **7**. In this way the reaction may work with a catalytic amount of base (Scheme 6).

The structure of **14** was established according to elemental analysis, IR data and, especially, NMR experiments. Its ^1H NMR spectrum showed an NH amide signal at δ=7.58 ppm, and a doublet at δ=6.57 ppm corresponding to 1-proton coupled to it. After stirring the $CDCl_3$ solution with D_2O for 3 h, the first signal disappeared and the second one was converted into a singlet. This experiment indicated the presence of a −CH−NH− group that could be attributed to a compound formed through an Overman's-type rearrangement. However, H−C correlation NMR experiments clearly showed that this CH proton of **14** was located at the C(1)-position of the tricyclic system, since it shows three-bonds correlations with the C(3)-carbon atom and the carbonyl of the ^{i}PrOCO group. Furthermore, NOESY experiments showed NOE between the H-1 and the methyl group at C-6, which indicates that the H(1) and H(6)-protons were in an *anti*-relationship, which is incompatible with a concerted rearrangement (Fig. 5).

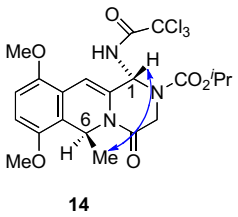
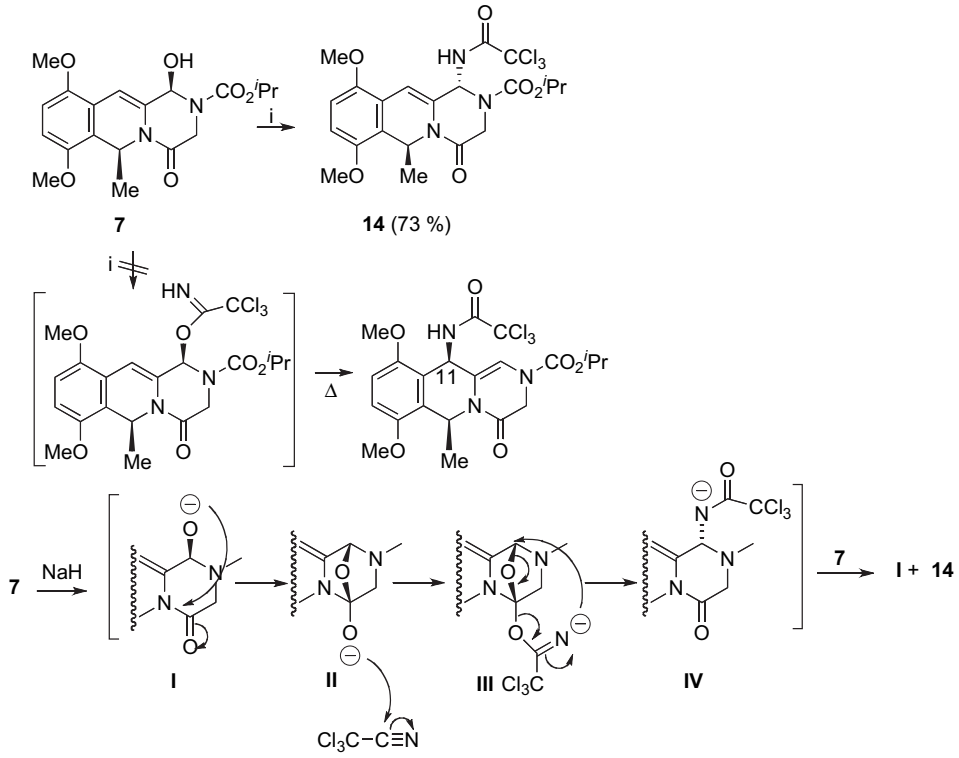


Fig. 5. Representative NOEs and structure assignments for compound **14**.

In conclusion, the combination of two functional groups at the C-1 and C-4 position in pyrazino[1,2-*b*]isoquinoline-1,4-diones, such as **3c**−**e** and in 1-hydroxy-pyrazino[1,2-*b*]isoquinolin-4-ones, such as **7**, conferred a new reactivity to these compounds that led to unexpected transformations that imply different base-promoted transannular rearrangements. Under basic conditions the first type of compounds afforded pyrrolo[1,2-*b*]isoquinoline-1,3-diones (**8**), which are tetramic acids with a benzo[*f*]indolizine skeleton whose structures have not literature precedents.



Scheme 6. (i) NaH (0.2 equiv), anhydrous THF, −10 °C, Cl_3CCN (2 equiv.), rt, 1 h.

3. Experimental

3.1. General

The reagents used were of commercial origin (Aldrich, Fluka) and were employed without further purification. Solvents (SDS, Scharlau) were purified and dried by standard procedures.[26] Reactions were monitored by thin-layer chromatography, using Macherey–Nagel or Merck plates with fluorescent indicator. Separations by flash liquid chromatography were performed using silica gel from SDS 60 ACC (230–400 mesh) or Merck (60, 40–63 μm) and aluminum oxide from Merck (90, 70–230 mesh).[27]

Melting points are uncorrected, and were determined using a Koffler hot stage microscope. Spectroscopic data were obtained with the following instruments: IR, Perkin–Elmer Paragon 1000 FT-IR; NMR spectra, Bruker AC-250 at 250 MHz for ^{1}H and at 63 MHz for ^{13}C (Servicio de Resonancia Magnética Nuclear, Universidad Complutense). When necessary, assignments were aided by DEPT, COSY, NOESY, and ^{13}C–^{1}H HMBC and HMQC correlation experiments. Combustion elemental analyses were obtained by the Servicio de Microanálisis Elemental, Universidad Complutense, using a Perkin–Elmer 2400 CHN and a Leco CHNS 932 microanalyzer.

3.1.1. (6R,11aS*)-6-Benzyloxymethyl-2-isopentanoyl-7,8,10-trimethoxy-9-methyl-2,3,11,11a-tetrahydro-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**3c**).* To a solution of **3a**[8] (0.64 mmol) in dry DCM (50 mL), was added triethylamine (3.84 mmol), 4-dimethylaminepyridine (DMAP) (3.84 mmol), and isopentanoyl chloride (3.84 mmol). The mixture was stirred under argon atmosphere and at room temperature for 16 h. Then, was diluted in water/ice and was extracted with DCM (100 mL×3). The combined extracts were washed with an aqueous solution of HCl 0.1 N (50 mL), with a saturated aqueous solution of $NaHCO_3$ (50 mL), with H_2O (30 mL), and with a saturated aqueous solution of NaCl (30 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude was purified by flash chromatography hexane/ethyl acetate (1:1) as eluent to give **3c** as a yellow oil (84% yield). IR (NaCl) $\nu_{máx}$ 2942, 1687, 1654 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.20 (m, 5H), 5.94 (dd, *J*=6.9 and 3.6 Hz, 1H), 4.61 (dd, *J*=10.5 and 5.2 Hz, 1H), 4.59 (d, *J*=9.8 Hz, 1H), 4.42 (d, *J*=16.8 Hz, 1H), 4.36 (d, *J*=9.8 Hz, 1H), 4.24 (d, *J*=16.8 Hz, 1H), 3.76 (s, 3H), 3.74 (m, 2H), 3.70 (s, 3H), 3.67 (s, 2H), 3.64 (m, 1H), 3.63 (s, 3H), 3.30 (dd, *J*=16.5 and 5.2 Hz, 1H), 2.91 (dd, *J*=16.5 and 10.5 Hz, 1H), 2.13 (s, 3H), 1.10 (m, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 179.7, 167.9, 163.1, 152.1, 150.3, 145.9, 137.8, 128.4, 127.8, 125.1, 123.9, 121.5, 72.8, 70.3, 63.7, 60.3, 60.1, 60.0, 54.4, 48.5, 46.2, 36.1, 26.6, 19.2, 9.4. Anal. Calcd for $C_{29}H_{36}N_2O_7$: C, 66.4; H, 6.9; N, 5.3. Found: C, 66.2; H, 6.8; N, 5.2.

3.2. Base-promoted transannular rearrangement of compounds 3. General procedures

Method A. To a solution of compounds **3** (2.50 mmol) in dry THF (10 mL) was added K^{t}BuO (2.75 mmol). The solution was stirred for 12 h under argon atmosphere at room temperature. Then, an aqueous solution of HCl 0.1 N (5 mL) was added. The organic extracts were washed with water (20 mL), with a saturated aqueous solution of NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude residue was purified by column chromatography to obtain compounds **8**.

Method B. To a solution of compounds **3** (2.50 mmol) in dry THF (10 mL) at −78 °C was added LHMDS (2.75 mmol) in THF. The solution was stirred at −78 °C (or 0 °C for compound **3e**) for 2 h under argon atmosphere. Then, an aqueous solution of HCl 0.1 N (5 mL) was added, and the organic extracts were washed with water (20 mL), with a saturated aqueous solution of NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude residue was purified by column chromatography to obtain compounds **8**.

3.2.1. (5R,10aR*)-5-Benzyloxymethyl-1-hydroxy-3-isobutylcarbonylamino-6,7,9-trimethoxy-8-methyl-10,10a-dihydro-5H-pyrrolo[1,2-b]isoquinolin-3-one (**8c**).* When the general procedure B was applied to compound **3c**, the obtained residue was purified by column chromatography with hexane/ethyl acetate (4:6) as eluent to give compound **8c** (20% yield) as an orange solid; mp: 83–84 °C; IR (NaCl) $\nu_{max,}$ 3254, 2935, 2348, 1669, 1540 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.68 (s, 1H), 7.59 (s, 1H), 7.24 (m, 5H), 6.08 (s, 1H), 5.49 (dd, *J*=6.6 and 3.0 Hz, 1H), 4.66 (d, *J*=12.2 Hz, 1H), 4.41 (d, *J*=12.2 Hz, 1H), 4.30 (dd, *J*=11.1 and 5.6 Hz, 1H), 3.85 (s, 3H), 3.81 (m, 2H), 3.80 (s, 3H), 3.69 (s, 3H), 3.51 (m, 2H), 3.46 (dd, *J*=16.7 and 5.7 Hz, 1H), 2.67 (m, 1H), 2.50 (dd, *J*=16.7 and 11.1 Hz, 1H), 2.22 (s, 3H), 1.29 (m, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.4, 165.0, 155.9, 152.2, 150.1, 146.1, 138.2, 128.3, 127.5, 124.8, 124.6, 122.2, 103.3, 72.7, 72.2, 60.3, 60.0, 59.9, 51.1, 47.4, 35.1, 26.3, 19.5, 17.4, 9.4. Anal. Calcd for $C_{29}H_{36}N_2O_7$: C, 66.4; H, 6.9; N, 5.3. Found: C, 66.1; H, 6.6; N, 5.1.

3.2.2. (5R,10aR*)-5-Benzyloxymethyl-1-hydroxy-6,7,9-trimethoxy-8-methyl-3-pivaloylamino-10,10a-dihydro-5H-pyrrolo[1,2-b]isoquinolin-3-one (**8d**).* According to the general procedures the crude residue was purified by column chromatography hexane/ethyl acetate (1:1) as eluent to obtain compound **8d** (78% yield, method A and 82% yield method B) as a yellow solid; mp: 68–69 °C; IR (NaCl) ν_{max} 2939, 1680, 1630 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.53 (s, 1H), 7.42 (s, 1H), 7.06 (m, 5H), 5.29 (dd, *J*=6.4 and 2.9 Hz, 1H), 4.46 (d, *J*=12.3 Hz, 1H), 4.21 (d, *J*=12.3 Hz, 1H), 4.10 (dd, *J*=11.1 and 5.6 Hz, 2H), 3.63 (s, 3H), 3.61 (m, 1H), 3.59 (s, 3H), 3.50 (m, 1H), 3.48 (s, 3H), 3.26 (dd, *J*=16.7 and 5.6 Hz, 1H), 2.30 (dd, *J*=16.7 and 11.1 Hz, 1H), 2.00 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 178.9, 165.1, 155.7, 152.2, 150.0, 146.1, 138.2, 128.3, 127.5, 124.7, 124.6, 122.2, 103.1, 72.7, 72.2, 60.2, 60.0, 59.9, 51.0, 47.3, 38.9, 27.5, 26.2, 9.4. Anal. Calcd for $C_{29}H_{36}N_2O_7$: C, 66.4; H, 6.9; N, 5.3. Found: C, 66.1; H, 6.6; N, 5.2.

3.2.3. (5R,10aR*)-5-Benzyloxymethyl-3-tert-butyloxycarbonylamino-1-hydroxy-6,7,9-trimethoxy-8-methyl-10,10a-dihydro-5H-pyrrolo[1,2-b]isoquinolin-3-one (**8e**).* According to the general procedures the crude residue was purified by column chromatography hexane/ethyl acetate (1:1) as eluent to obtain compound **8e** (83% yield, method A and 84% yield method B) as a yellow solid; mp: 78–79 °C; IR (NaCl) ν_{max} 3248, 2938, 1660 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.70 (s, 1H), 7.27 (m, 5H), 6.66 (s, 1H), 5.49 (dd, *J*=6.5 and 2.9 Hz, 1H), 4.66 (d, *J*=12.2 Hz, 1H), 4.40 (d, *J*=12.2 Hz, 1H), 4.27 (dd, *J*=11.1 and 5.5 Hz, 1H), 3.88 (dd, *J*=10.1 and 2.9 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.68 (s, 3H), 3.67 (dd, *J*=10.1 and 6.5 Hz, 1H), 3.45 (dd, *J*=16.6 and 5.5 Hz, 1H), 2.49 (dd, *J*=16.6 and 11.1 Hz, 1H), 2.22 (s, 3H), 1.53 (s, 9H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.9, 155.6, 152.3, 152.2, 150.0, 146.2, 138.3, 128.3, 127.5, 127.4, 124.6, 122.3, 102.9, 82.6, 72.7, 72.3, 60.3, 60.0, 59.9, 50.9, 47.3, 28.1, 26.4, 9.4. Anal. Calcd for $C_{29}H_{36}N_2O_8$: C, 64.4; H, 6.7; N, 5.2. Found: C, 64.6; H, 6.6; N, 5.2.

3.2.4. (6R,11aS*)-6-Benzyloxymethyl-2-pivaloyl-7,8,10-trimethoxy-9-methyl-2,3,11,11a-tetrahydro-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**3d**) and its epimer (6R*,11aR*)-6-benzyloxymethyl-2-pivaloyl-7,8,10-trimethoxy-9-methyl-2,3,11,11a-tetrahydro-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**3f**).* To a solution of compound **3d** (2.50 mmol) in dry THF (10 mL) at −78 °C was added LHMDS (2.75 mmol) in THF. The solution was stirred at −78 °C for 30 min under argon atmosphere. Then, an aqueous solution of HCl 0.1 N (5 mL) was added. The organic extracts were washed with water (20 mL), with a saturated aqueous solution of NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude residue was purified by

column chromatography (hexane/ethyl acetate 1:1) to obtain compound **8d** (13% yield) and compound **3d** (32% yield) and **3f** (48% yield) as a mixture of diastereoisomers. IR (NaCl) $\nu_{max,}$ 2938, 2348, 1682 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.13 (m, 5H), 7.00 (m, 2.5H), 5.92 (dd, *J*=6.5 and 3.8 Hz, 0.5H), 5.78 (t, *J*=3.8 Hz, 1H), 4.63 (dd, *J*=11.6 and 4.9 Hz), 4.55 (d, *J*=12.1 Hz, 0.5H), 4.55 (d, *J*=16.5 Hz, 0.5H), 4.38 (d, *J*=12.2 Hz, 1H), 4.35 (d, *J*=12.1 Hz, 0.5H), 4.28 (d, *J*=12.2 Hz, 1H), 4.21 (d, *J*=17.5 Hz, 1H), 4.10 (d, *J*=17.5 Hz, 1H), 3.96 (d, *J*=16.5 Hz, 0.5H), 3.92 (dd, *J*=12.2 and 4.6 Hz, 1H), 3.76 (m, 1.5H), 3.75 (s, 1.5H), 3.74 (s, 3H), 3.73 (m, 0.5H), 3.71 (s, 3H), 3.69 (s, 1.5H), 3.61 (s, 3H), 3.60 (s, 1.5H), 3.54 (dd, *J*=15.3 and 4.6 Hz, 1H), 3.43 (dd, *J*=9.8 and 3.8 Hz, 1H), 3.34 (dd, *J*=16.7 and 4.9 Hz, 0.5H), 3.00 (dd, *J*=15.3 and 12.2 Hz, 1H), 2.77 (dd, *J*=16.7 and 11.6 Hz, 0.5H), 2.15 (s, 3H), 2.11 (s, 1.5H), 1.27 (s, 4.5H), 1.26 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 185.7, 184.4, 169.1, 168.8, 166.4, 162.9, 152.2, 151.3, 150.3, 150.2, 145.9, 145.8, 137.9, 137.8, 128.3, 128.1, 127.7, 127.6, 127.4, 127.1, 125.3, 125.1, 124.9, 123.8, 122.8, 121.5, 72.5, 73.3, 73.0, 72.8, 60.9, 60.4, 60.2, 60.0, 59.9, 59.8, 56.4, 53.7, 49.9, 48.5, 48.8, 48.0, 43.7, 43.3, 27.4, 27.0, 27.3, 23.9, 9.3.

3.3. Hydrogenolysis and methanolysis

To the mixture of epimers **3d** and **3f** (200 mg) in methanol was added Pd/C (60 mg) and the reaction was stirred under hydrogen atmosphere for 16 h. Then, the reaction was filtered over Celite and the solvent was removed in vacuo. The crude residue was purified by column chromatography ethyl acetate/methanol (1:1) as eluent to obtain compounds **3h** (38% yield) and compound **3i** (57% yield) as white solids.

3.3.1. (6R,11aS*)-6-Hydroxymethyl-7,8,10-trimethoxy-9-methyl-2,3,11,11a-tetrahydro-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**3h**).* Mp: 204–205 °C; IR (NaCl) $\nu_{max,}$ 3744, 3673, 2939, 1683, 1651 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.56 (s, 1H), 5.95 (dd, *J*=8.8 and 3.4 Hz, 1H), 4.52 (dd, *J*=12.2 and 3.9 Hz, 1H), 4.25 (d, *J*=16.5 Hz, 1H), 4.08 (d, *J*=16.5 Hz, 1H), 4.07 (m, 1H), 3.93 (s, 3H), 3.81 (s, 3H), 3.73 (m, 1H), 3.69 (s, 3H), 3.46 (dd, *J*=16.8 and 3.9 Hz, 1H), 2.82 (dd, *J*=16.8 and 12.2 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.0, 163.3, 152.3, 150.3, 146.1, 125.0, 123.3, 121.6, 62.4, 60.4, 60.0, 59.9, 51.4, 51.3, 44.7, 28.0, 9.3. Anal. Calcd for $C_{17}H_{22}N_2O_6$: C, 58.3; H, 6.3; N, 8.0. Found: C, 58.0; H, 6.0; N, 7.8.

3.3.2. (6R,11aR*)-6-Hydroxymethyl-7,8,10-trimethoxy-9-methyl-2,3,11,11a-tetrahydro-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**3i**).* Mp: 210–211 °C; IR (NaCl) $\nu_{max,}$ 3734, 3674, 2942, 1682, 1652 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.43 (s, 1H), 5.83 (dd, *J*=6.4 and 4.6 Hz, 1H), 4.07 (s, 2H), 3.94 (dd, *J*=12.5 and 3.9 Hz, 1H), 3.93 (s, 3H), 3.85 (m, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 3.67 (dd, *J*=15.7 and 3.9 Hz, 1H), 3.61 (m, 1H), 2.87 (dd, *J*=15.7 and 12.5 Hz, 1H), 2.23 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.3, 167.9, 151.4, 150.3, 145.9, 125.4, 124.4, 122.7, 66.6, 61.1, 60.6, 59.9, 54.8, 52.6, 45.5, 23.4, 9.4. Anal. Calcd for $C_{17}H_{22}N_2O_6$: C, 58.3; H, 6.3; N, 8.0. Found: C, 57.9; H, 6.0; N, 7.8.

3.3.3. (6R,11aR*)-6-Benzyloxymethyl-2,9-dimethyl-7,8,10-trimethoxy-2,6,11,11a-tetrahydro-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**9**).* To a solution of compound **3d** (2.50 mmol) in dry THF (10 mL) at −78 °C was added LHMDS (2.75 mmol) in THF. The solution was stirred at −78 °C for 2 h under argon atmosphere. Then, ICH_3 (12.5 mmol) was added at −78 °C and continue stirring for 16 h at room temperature. Then, the reaction mixture was diluted with AcOEt (20 mL), washed with an aqueous solution of HCl 0.1 N, with water, with a saturated aqueous solution of NaCl, and dried over anhydrous Na_2SO_4. The solvent, was removed in vacuo and the crude residue was purified by column chromatography hexane/ethyl acetate (1:1) as eluent to obtain compound **9** (98% yield) as an orange oil. IR (NaCl) $\nu_{max,}$ 2938, 2348, 2245, 1667 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.19 (m, 5H), 5.99 (dd, *J*=7.6 and 3.6 Hz, 1H), 4.61 (d, *J*=11.9 Hz, 1H), 4.44 (dd, *J*=12.3 and 4.4 Hz, 1H), 4.36 (d, *J*=11.9 Hz, 1H), 3.96 (m, 2H), 3.74 (s, 3H), 3.72 (m, 2H), 3.67 (s, 3H), 3.58 (s, 3H), 3.40 (dd, *J*=16.9 and 4.4 Hz, 1H), 2.62 (dd, *J*=16.9 and 12.3 Hz, 1H), 2.94 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 165.3, 161.5, 152.1, 150.1, 145.8, 137.9, 128.3, 127.7, 127.6, 124.8, 123.4, 122.0, 72.6, 69.8, 60.1, 59.8, 51.8, 51.3, 48.3, 33.2, 28.4, 9.2. Anal. Calcd for $C_{25}H_{30}N_2O_6$: C, 66.1; H, 6.7; N, 6.2. Found: C, 59.8; H, 6.3; N, 5.9.

3.3.4. (2R,5R*)-5-Benzyloxymethyl-1-hydroxy-6,7,9-trimethoxy-2,8-dimethyl-3-pivaloylamino-2,5-dihydro-pyrrolo[1,2-b]isoquinolin-3-one (**10**).* To a solution of compound **8d** (0.20 mmol) in dry THF (5 mL) at −78 °C was added LHMDS (0.23 mmol) in THF (5 mL). The solution was stirred at −78 °C for 1 h under argon atmosphere. Then, ICH_3 (12.5 mmol) was added at −78 °C and continue stirring for 16 h at room temperature. The solution was diluted with AcOEt (20 mL), washed with an aqueous solution of HCl 0.1 N, with water, with a saturated aqueous solution of NaCl, and dried over anhydrous Na_2SO_4. The solvent, was removed in vacuo and the crude residue was purified by column chromatography hexane/ethyl acetate (6:4) as eluent to obtain compound **10** (65% yield) as a yellow solid. Mp: 74–75 °C; IR (NaCl) $\nu_{max,}$ 3372, 2937, 2348, 2250, 1754, 1723, 1644 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.24 (m, 5H), 6.85 (s, 1H), 6.11 (s, 1H), 6.03 (dd, *J*=6.2 and 3.6 Hz, 1H), 4.65 (d, *J*=12.0 Hz, 1H), 4.41 (d, *J*=12.0 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.77 (m, 2H), 3.76 (s, 3H), 2.21 (s, 3H), 1.46 (s, 3H), 1.24 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 193.0, 178.4, 171.5, 153.1, 152.5, 146.1, 138.0, 131.4, 128.2, 127.4, 127.3, 125.8, 121.6, 120.1, 101.6, 72.6, 71.4, 62.0, 60.5, 59.9, 59.2, 48.8, 37.8, 27.2, 19.1, 9.3. Anal. Calcd for $C_{30}H_{36}N_2O_7$: C, 67.2; H, 6.8; N, 5.2. Found: C, 66.9; H, 6.6; N, 4.8.

3.3.5. (6S,11aR*)-7,10-Dimethoxy-6-methyl-2,3,11,11a-tetrahydro-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**11**).* A solution of TMSCl (0.54 mL, 4.9 mmol) and triethylamine (0.68 mL, 4.9 mmol) was added to a stirred solution of 1-acetyl-3-(2,5-dimethoxybenzyl)-piperazine-2,5-dione, (1.0 mg, 3.05 mmol) in dry DCM (20 mL). The mixture was stirred under argon atmosphere at room temperature for 1 h and a solution of acetaldehyde dimethyl acetal (0.68 mL, 6.52 mmol) in dry DCM (20 mL) and TMSOTf (1.6 mL, 9.78 mmol) was added. This mixture was stirred for other 12 h at room temperature and then, a 10% aqueous solution of $NaHCO_3$ (50 mL) was added. After extraction with DCM (30 mL×3), the combined extracts were washed with H_2O (20 mL) and a saturated aqueous solution of NaCl (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo, to give a residue that was purified by flash chromatography on silica gel with methanol/ethyl acetate (1:9) as eluent to give **11** (1.15 g, 81%). IR (NaCl) $\nu_{max,}$ 3233, 2942, 1668, 1651, 1489 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.71 (ws, 1H), 6.67 (s, 2H), 5.98 (q, *J*=6.6 Hz, 1H), 4.40 (dd, *J*=11.9 and 4.1 Hz, 1H), 3.65 (s, 3H), 3.63 (s, 3H), 3.60 (dd, *J*=15.4 and 4.1 Hz, 1H), 2.62 (dd, *J*=15.4 and 11.9 Hz, 1H), 1.27 (d, *J*=6.6 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.4, 165.4, 150.0, 149.1, 127.6, 122.8, 109.2, 108.8, 55.8, 55.6, 54.8, 46.3, 45.6, 22.6, 21.8. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.1; H, 6.3; N, 9.7. Found: C, 61.5; H, 6.5; N, 9.6.

3.3.6. (6S,11aR*)-2-Isopropyloxycarbonyl-7,10-dimethoxy-6-methyl-2,3,11,11a-tetrahydro-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**12**).* A solution of compound **11** (2.63 g, 9.1 mmol), triethylamine (7.58 mL, 54 mmol), and 4-dimethylaminopyridine (3.33 g, 27 mmol) in dry DCM (140 mL) was cooled in ice water, and isopropyl chloroformate (18 mL, 18 mmol) was added dropwise. The solution was stirred under argon atmosphere for 16 h at room temperature, and then, an aqueous solution of NH_4Cl (50 mL) was added. After extraction with DCM (20 mL×3), the extracts were washed with H_2O (30 mL) and a saturated aqueous solution of NaCl (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give

a residue that was purified by flash column chromatography on silica gel with hexane/ethyl acetate (7:3) as eluent to give **12** (2.34 g, 68% yield) as a yellow solid. Mp: 128–129 °C; IR (NaCl) ν_{max}, 2359, 1772, 1733, 1717 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 6.72 (s, 2H), 5.92 (q, J=6.8 Hz, 1H), 5.15 (sept, J=6.3 Hz, 1H), 5.06 (d, J=17.7 Hz, 1H), 4.31 (dd, J=12.1 and 4.7 Hz, 1H), 4.28 (d, J=17.7 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.45 (dd, J=17.2 and 4.7 Hz, 1H), 2.84 (dd, J=17.2 and 12.1 Hz, 1H), 1.44 (d, J=6.8 Hz, 3H), 1.30 (d, J=6.3 Hz, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.7, 161.8, 151.6, 151.3, 150.1, 127.2, 121.7, 108.7, 108.6, 72.8, 56.1, 55.9, 53.1, 48.1, 45.1, 28.1, 22.1, and 18.9. Anal. Calcd for $C_{19}H_{24}N_2O_6$: C, 60.6; H, 6.4; N, 7.4. Found: C, 60.5; H, 6.3; N, 7.4.

*3.3.7. 2-Isopropyloxycarbonyl-7,10-dimethoxy-6-methyl-2,3-dihydro-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**13**).* A solution of **12** (2.6 g, 6.9 mmol), AIBN (113 mg, 0.69 mmol), and NBS (1.47 g, 8.3 mmol) in CCl_4 (70 mL) was refluxed (100 °C) under argon atmosphere for 16 h. The unreacted NBS was filtered from the cooled reaction, the solvent was evaporated under reduced pressure and the residue was purified on silica gel with hexane/ethyl acetate (7:3) as eluent to give **13** (1.4 g, 54% yield) as a yellow oil. IR (NaCl) ν_{max} 2984, 1781, 1726, 1666, 1484 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.61 (s, 1H), 6.85 (d, J=8.4, 1H), 6.78 (d, J=8.4 Hz, 1H), 6.15 (m, 1H), 5.16 (m, 1H), 4.73 (d, J=16.9 Hz, 1H), 4.14 (d, J=16.9 Hz, 1H), 3.82 (s, 6H), 1.39 (m, 6H), 1.25 (d, J=7.1 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 161.7, 158.2, 151.7, 150.1, 148.6, 124.9, 118.2, 114.5, 112.9, 109.8, 72.3, 55.9, 55.7, 47.6, 44.7, 21.7, 18.9. Anal. Calcd for $C_{19}H_{22}N_2O_6$: C, 61.0; H, 5.9; N, 7.5. Found: C, 60.6; H, 5.7; N, 7.3.

3.3.8. (1R,6S*)-2-Isopropyloxycarbonyl-1-hydroxy-7,10-dimethoxy-6-methyl-1,2,3,6-tetrahydro-pyrazino[1,2-b]isoquinolin-4-one (**7**).* To a stirred solution of lithium tri-*tert*-butoxy aluminum hydride (2.65 g, 8.12 mmol) in dry THF (50 mL) cooled in ice water was added a solution of compound **13** (1.01 g, 2.7 mmol) in dry THF (10 mL), and the mixture was stirred under argon atmosphere at room temperature for 16 h. The reaction mixture was quenched by addition of ice, filtered over Celite, and extracted with ethyl acetate. The extracts were washed with H_2O and with a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo, the residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (7:3) as eluent to give compound **7** (1 g, 98% yield) as a pale yellow solid. Mp: 94–95 °C; IR (NaCl) ν_{max} 3351, 2980, 1713, 1682 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.72 (s, 2H), 6.39 (s, 1H), 6.22 (ws, 1H), 6.07 (q, J=6.5 Hz, 1H), 4.96 (sept, J=6.1 Hz, 1H), 4.42 (d, J=18.3 Hz, 1H), 4.08 (d, J=18.3 Hz, 1H), 3.97 (s, 6H), 1.31 (m, 3H), 1.30 (d, J=6.1 Hz, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 162.7, 152.4, 148.7, 128.4, 123.8, 118.9, 110.2, 109.5, 103.1, 70.3, 55.8, 55.6, 44.9, 44.3, 22.0, 14.1. Anal. Calcd for $C_{19}H_{24}N_2O_6$: C, 60.6; H, 6.4; N, 7.4. Found: C, 60.4; H, 6.2; N, 7.2.

3.3.9. (1R,6S*)-Trichloroacetamido-2-isopropyloxycarbonyl-7,10-dimethoxy-6-methyl-3,6-dihydro-pyrazino[1,2-b]isoquinolin-4-one (**14**).* A solution of sodium hydride (32 mg, 1.35 mmol) and compound **7** (500 mg, 1.24 mmol) in anhydrous THF (20 mL) was cooled to −10 °C. Trichloroacetonitrile was then added (0.24 mL, 2.46 mmol) and the reaction was stirred at room temperature for 1 h. Then, hexane (20 mL) was added, the solution was filtered over Celite, and washed with DCM (10 mL). The solvent was removed in vacuo and the crude residue was purified by column chromatography hexane/ethyl acetate (1:1) as eluent to obtain compound **14** (73% yield) as a yellow oil. IR (NaCl) $\nu_{máx}$ 3271, 2937, 1715 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.78 (d, J=9.0 Hz, 1H), 6.73 (d, J=9.0 Hz, 1H), 6.69 (s, 1H), 6.58 (ws, 1H), 6.57 (d, J=6.7 Hz, 1H), 6.12 (d, J=6.5 Hz, 1H), 5.03 (sept, J=6.2 Hz, 1H), 4.36 (d, J=17.1 Hz, 1H); 4.20 (d, J=17.1 Hz, 1H), 3.83 (s, 6H), 1.30 (m, 6H), 1.24 (d, J=6.5 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 162.7, 160.8, 153.2, 149.0, 148.6, 123.8, 118.3, 111.0, 109.6, 106.6, 92.2, 70.8, 60.6, 55.9, 55.7, 45.8, 43.9, 22.0, 18.3. Anal. Calcd for $C_{21}H_{24}N_3O_6$: C, 48.4; H, 4.6; N, 8.1. Found: C, 48.0; H, 4.3; N, 7.9.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.09.011. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. Royles, B. J. L. *Chem. Rev.* **1995**, *95*, 1981–2001.
2. Burdock, G. A.; Flamm, W. G. *Int. J. Toxicol.* **2000**, *19*, 195–218.
3. Yamaguchi, R.; Hamasaki, T.; Utimoto, K. *Chem. Lett.* **1988**, 913–916.
4. Kadlecíková, K.; Dalla, V.; Marchalín, S.; Decroix, B.; Baran, P. *Tetrahedron* **2005**, *61*, 4743–4754.
5. Cui, M.; Wang, K.; Wang, Q.; Huang, R. *Lett. Org. Chem.* **2008**, *5*, 98–102.
6. González, J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2004**, *60*, 6319–6326.
7. González, J. F.; de la Cuesta, E.; Avendaño, C. *Bioorg. Med. Chem.* **2007**, *15*, 112–118.
8. Ortín, I.; González, J. F.; de la Cuesta, E.; Manguan-García, C.; Perona, R.; Avendaño, C. *Bioorg. Med. Chem.* **2008**, *16*, 9065–9078.
9. Ortín, I.; González, J. F.; de la Cuesta, E.; Manguan-García, C.; Perona, R.; Avendaño, C. *Bioorg. Med. Chem.* **2009**, *17*, 8040–8047.
10. Ortín, I.; González, J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2009**, *65*, 2201–2211.
11. Ortín, I.; González, J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2009**, *65*, 9944–9951.
12. Ortín, I.; González, J. F.; de la Cuesta, E.; Avendaño, C. *Bioorg. Med. Chem.* **2010**, *18*, 6813–6821.
13. Farran, D.; Parrot, I.; Martinez, J.; Dewynter, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 7488–7490.
14. Farran, D.; Parrot, I.; Toupet, L.; Martinez, J.; Dewynter, G. *Org. Biomol. Chem.* **2008**, *6*, 3989–3996.
15. Farran, D.; Toupet, L.; Martinez, J.; Dewynter, G. *Org. Lett.* **2007**, *9*, 4833–4836.
16. Coursindel, T.; Farran, D.; Martinez, J.; Dewynter, G. *Tetrahedron Lett.* **2008**, *49*, 906–909.
17. Farran, D.; Echalier, D.; Martinez, J.; Dewynter, G. *J. Pept. Sci.* **2009**, *15*, 474–478.
18. Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901–2910.
19. Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218–224.
20. Overman, L. E.; Carpenter, N. E. *Organic Reactions*; WILEY: New York, NY, 2005; Vol. 66, pp 1–107.
21. González, J. F.; Salazar, L.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2005**, *61*, 7447–7455.
22. González, J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron Lett.* **2006**, *47*, 6711–6714.
23. Sánchez, J. D.; Ramos, M. T.; Avendaño, C. *J. Org. Chem.* **2001**, *66*, 5731–5735.
24. Bourry, A.; Couturier, D.; Sanz, G.; Van Hijfte, L.; Hénichart, J.-P.; Rigo, B. *Tetrahedron* **2006**, *62*, 4400–4407.
25. González, J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron Lett.* **2003**, *44*, 4395–4398.
26. Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry*, 2 ed.; Stanley Thornes Ltd: London, 1998.
27. Still, W. C.; Khan, M.; Mitra, A. J. *Org. Chem.* **1978**, *43*, 2923–2925.