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Synthesis of a novel tetrahydroisoquinoline pentacyclic framework

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ABSTRACT

N-Acyliminium cyclization of 6-substituted (3*R**,6*R**,11a*S**)-3-arylmethyl-pyrazino[1,2-*b*]isoquinoline-1,4-diones gave with very good yields a novel tetrahydroisoquinoline pentacyclic core framework (**29**), while this reaction failed in all-cis-isomers to give instead conjugated enamines by deprotonation. Electronic and steric factors that govern the approach to both diastereomers from 6-substituted pyrazino[1,2-*b*]isoquinoline-1,4-diones have been studied.

1. Introduction

We are developing a project directed to the synthesis of analogs of antitumor alkaloids belonging to the tetrahydroisoquinoline family, whose common structural features are a core ring fragment containing five condensed six-membered rings, four of which are two tetrahydroisoquinoline moieties (either as quinones or hydroquinones) and a pyrazine subunit as shown in Figure 1 for representative compounds.

Although compounds bearing a 7-cyano or a 7-hydroxy group have a DNA-damaging activity involving the formation of an iminium ion,[1] such mechanism is unlikely to account for the antiproliferative activity of other analogs. Recent data are extending the notion that active tetrahydroisoquinolines possess important protein targets and that their cellular activities may not be confined to DNA targeting.[2] Therefore, the synthesis of analogs of tetrahydroisoquinoline antitumor compounds may afford potent lead structures. In this context, we have obtained 14,14a-dehydro-6,15-imino-isoquino[3,2-*b*]-3-benzazocine-7-one compounds such as **1** (Pth=phthalimido), or more complex octacyclic structures such as **2**, through a simple and versatile approach (Scheme 1).[3]

Our strategy relies on the ready access to 2-acetyl-6-substituted pyrazino[1,2-*b*]isoquinoline-1,4-diones, that contain rings *CDE* of the target molecules, through Pictet–Spengler reactions on activated 3-arylmethylpiperazine-2,5-diones, and we have shown that the 11,11a-dehydro derivatives of these tricyclic compounds afford the pentacyclic core, containing rings *A*–*E*, through a four-step sequential process involving an aldol-type condensation at the C(3)-position, catalytic hydrogenation of the exocyclic double bond thus formed, activation of the *C*(1)-carbonyl group, and partial reduction/cyclization at this position through *N*-acyliminium ions as intermediates. Similar reductive cyclizations have been previously applied to 6-unsubstituted pyrazino[1,2-*b*]isoquinoline-1,4-diones[4] and to 3-arylmethylen-6-arylmethyl-piperazine-2,5-diones,[5,6] to get in this case 2,6-bridged 3-arylmethylene-piperazine-3-ones that contain *ABC* rings of these alkaloids.

Although the unsaturated compounds **1** are interesting by themselves[7] and could be finally reduced, their catalytic hydrogenation requires unusual high pressures of hydrogen.[8] This limitation moved us to study the extension of our synthetic approach to 6-substituted (6,11a)-*cis*-pyrazino[1,2-*b*]isoquinoline-1,4-diones, although we were concerned about the efficacy and the stereochemical control of the process. First of all, the basic conditions required for the anchimerically assisted aldol-type condensation[9] could promote the lability of the H-11a proton, a fact that was previously observed in a similar reaction with enantiomerically pure piperazine-2,5-diones.[10] Furthermore, although stereoselective catalytic hydrogenations of (*Z*)-3-arylidene-2,5-piperazinediones have been used effectively in the synthesis of 3-arylmethyl-2,5-piperazinediones,[11] the diastereoselective hydrogenation of the exocyclic double bond previously found in the 3-arylmethylene-11,11a-dehydro-pyrazino[1,2-*b*]isoquinoline-1,4-dione derivatives is favored by the planarity imposed by the 11,11a-double bond, and was expected to be more difficult in the more flexible saturated analogs. Finally, there are no precedents of reductive cyclizations mediated by *N*-acyliminium ions with 6-substituted pyrazino[1,2-*b*]isoquinoline-1,4-diones.[12] After a study about the scope of π-nucleophiles and the influence of

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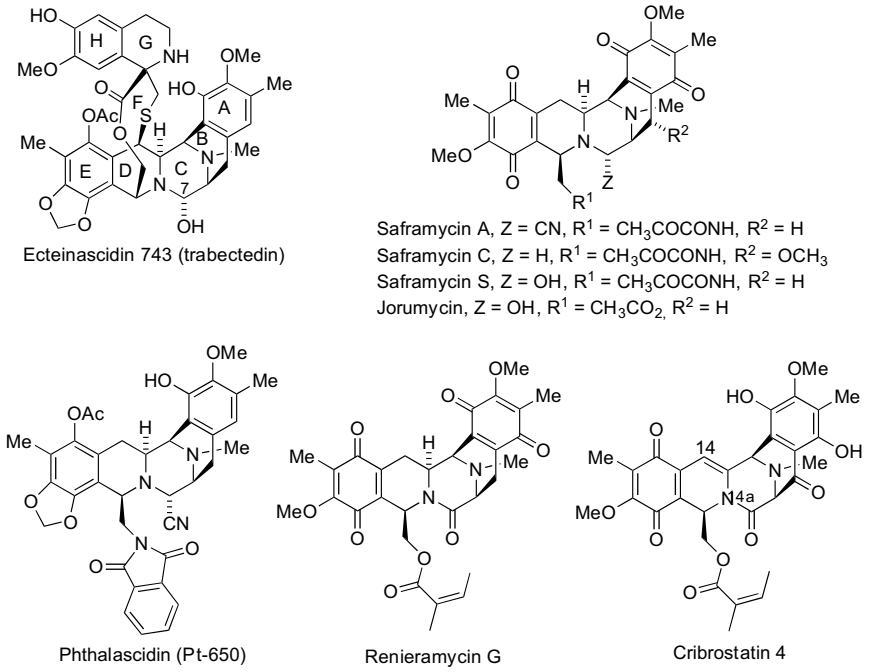


Figure 1.

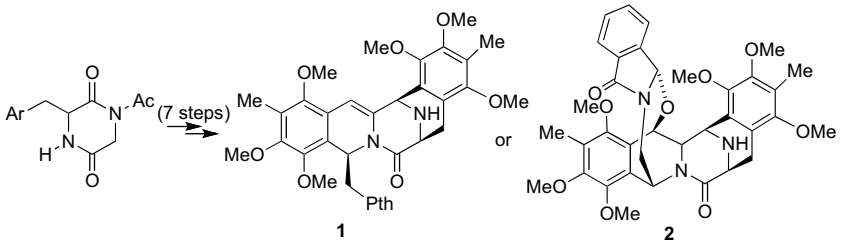
a *C*(3)-alkyl group on the stereochemical outcome of this reaction in simple 1-alkoxycarbonyl-6-arylmethyl-4-benzyl-piperazine-2,5-diones, it was postulated that cyclizations to give 2,6-bridged piperazine-3-one derivatives with an all-cis-stereochemistry require the presence of electron-rich arenes or heteroarenes in order to avoid alternative reactions and C(3)-epimerization.[13] However, this assumption has to be carefully considered since it is not predictive for all cis-3,6-substituted piperazine-2,5-diones,[14] being a close negative precedent the reported epimerization of the C(5)-stereocenter in the reductive cyclizations of *cis*-3,6-diarylmethyl-piperazine-2,5-diones to give 2,6-bridged piperazine-3-ones.[15]

We report here a systematic study about the factors that govern the four-step approach to 6,15-imino-isoquino[3,2-*b*]-3-benzazocine-7-one compounds from 6-substituted pyrazino[1,2-*b*]isoquinoline-1,4-diones.

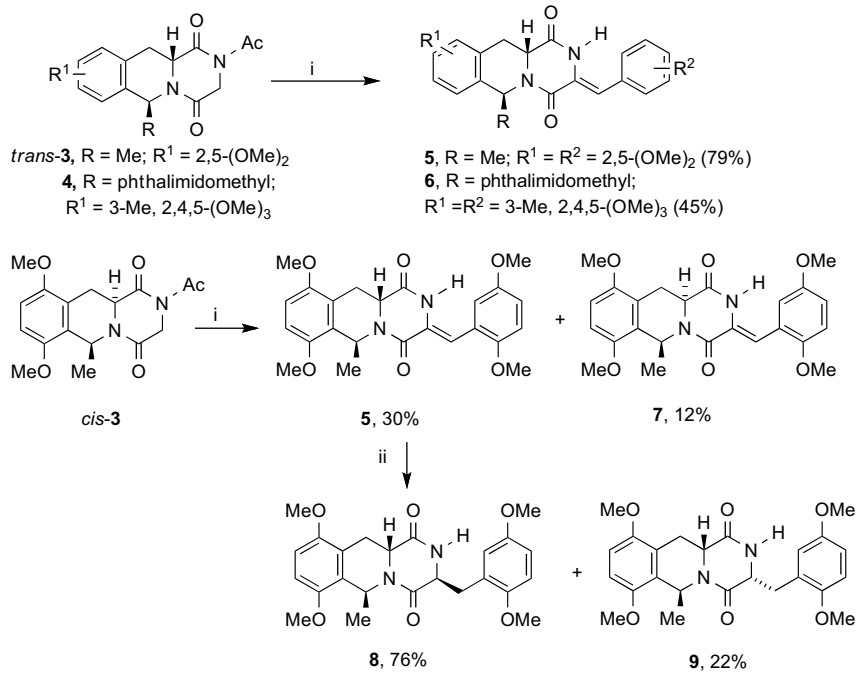
2. Results and discussion

In the first studied aldol-type condensations with model compounds and benzaldehyde derivatives, we found that these reactions were stereocontrolled in the 6/11a-trans-isomers, without affecting the C(11a)-stereocenter (see the conversion of compounds **3**[16] and **4**[3] to compounds **5** and **6**, respectively). However, the 6/11a-cis-isomer of compound **3** gave **7** together with its 11a-epimer **5** as the major product. The subsequent catalytic hydrogenation of the exocyclic double bond in compound **5** also showed a very poor diastereoselectivity, giving a 3.4:1 mixture of the trans-(3,11a) compound **8** and the cis-(3,11a)-isomer **9** (Scheme 2).

We decided to study more stable (6,11a-cis)-compounds, such as *N*-acetyl and *N*-pivaloyl derivatives *cis*-**10**[17] and *cis*-**11**, for which the greater stability of the C(11a)-stereocenter is associated to the higher conformational freedom of the 6-benzyloxymethyl side chain as compared to compounds **3** and **4**. As expected, aldol-type reactions promoted by potassium *tert*-butoxide between *cis*-**10** and benzaldehyde derivatives especially chosen to get regioselective cyclizations and precursors of quinones gave compounds **13a** and **13b** as *Z*-isomers in 60% and 76% yield based on 50% and 64% conversion, respectively (Scheme 3). When this reaction was promoted by the less bulky base potassium fluoride[18] an inseparable 1:1 mixture of the starting material *cis*-**10** and its 11a-epimer *trans*-**10** was obtained. The steric bulk of the *N*-pivaloyl group in *cis*-**11** explains why its condensation with 3-methyl-2,4,5-trimethoxybenzaldehyde required a longer reaction time to give **13b** in lower yield. We could isolate and identify from a mixture of products compound **14**,[19] a stable hydrate carbonyl derivative formed by air-oxidation of enolate **I**.[20] All these results show that the 11a-proton is more acidic than the 3-proton due to the greater stabilization of enolate **II** as compared to **I**. This electronic effect, which is due to the greater electrophilicity of the *N*-acyl-*C*(1)-amide as compared to the unactivated *C*(4)-amide group, is in part counteracted by steric effects with the bulky base potassium *tert*-butoxide,



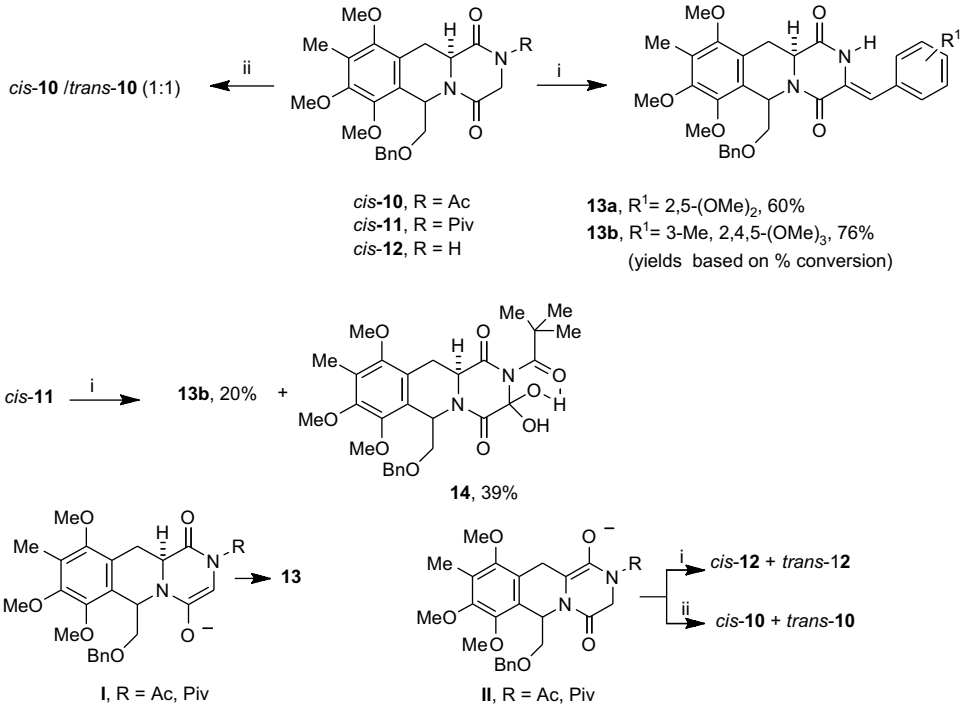
Scheme 1.



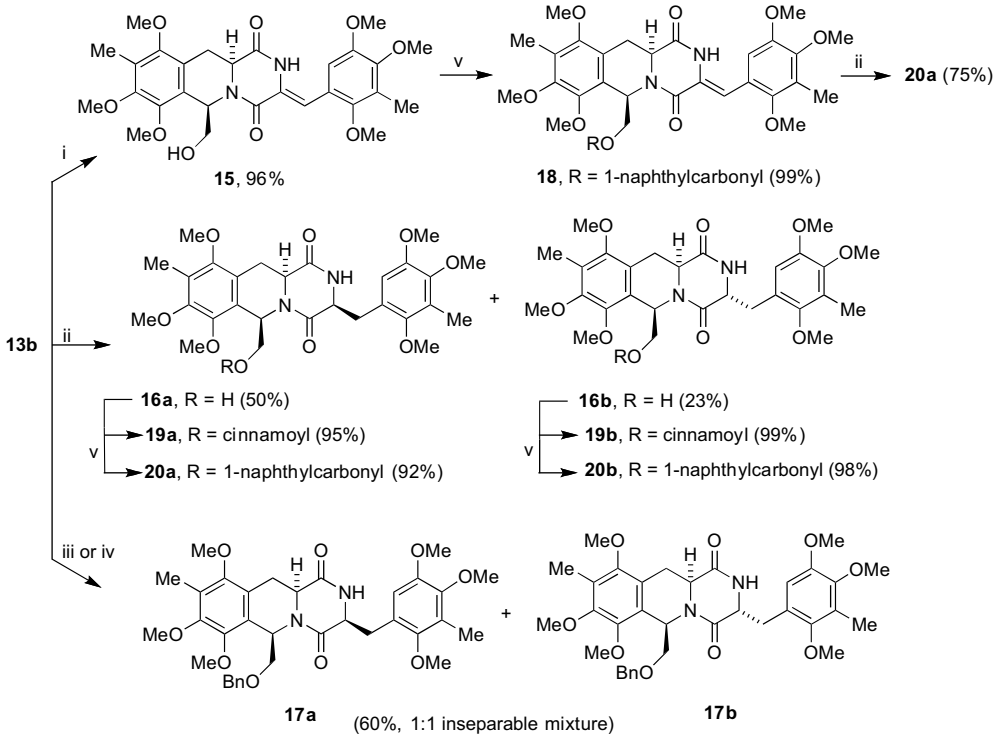
Scheme 2. (i) Substituted benzaldehyde, ^{t}BuOK/^{t}BuOH (1.2 equiv), CH_2Cl_2, rt, 6 h. (ii) H_2/C/Pd (10%), EtOAc, 2 atm, 14 h.

permitting the generation of the desired enolate **I** and its further aldol-type reaction.

We next studied the hydrogenation of **13b** catalyzed by Pd/C. This reaction could be stopped after the deprotection of the OBn group to obtain compound **15**, or to achieve the fully reduced product as a 2:1 mixture of diastereoisomers **16a** and **16b** (Scheme 4). In order to explore the steric induction of the benzyloxymethyl side chain without affecting the C–O linkage, the reduction of **13b** was also performed with zinc/acetic acid[21] or with the in situ generation of the unstable hydrogen donor diimide.[22,23] Both methods afforded with 60% yield after column chromatography a nearly equimolecular inseparable mixture of diastereoisomers **17a** and **17b**, which could be identified by there ^{1}H NMR spectra. Diimide results, in particular, show how the great conformational freedom of the C(6)-benzyloxymethyl side chain makes both faces of the exocyclic double bond equally accessible to the transfer of



Scheme 3. (i) Substituted benzaldehyde, ^{t}BuOK/^{t}BuOH (1.2 equiv), CH_2Cl_2 anhydrous, rt, 6 h for *cis*-**10** to **13a** or 12 h (or *cis*-**11** to **13b**). (ii) Substituted benzaldehyde, KF/Al_2O_3/DMF anhydrous, rt., 15 min.

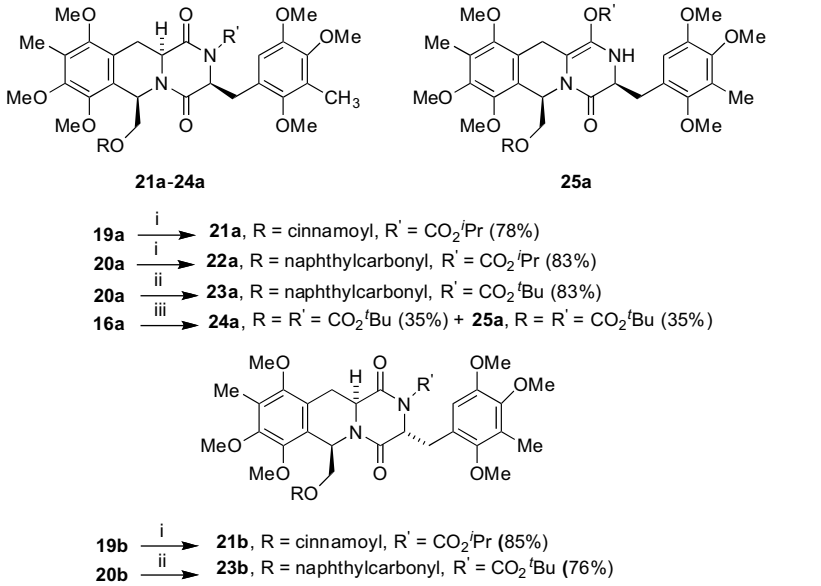


Scheme 4. (i) H_2 (1 atm), C/Pd (10%), EtOAc, rt, overnight. (ii) H_2 (4 atm), C/Pd (50%), MeOH, rt, overnight. (iii) Zn (17 equiv), HOAc, 125 °C, 24 h. (iv): H_2N–NH_2 hydrate (5 equiv), 33% H_2O_2 (1 mL), 1% aqueous $CuSO_4$ (0.5 mL), EtOH, rt, 24 h. (v) EDC (2 equiv), DMAP (1.1 equiv), RCO_2H (1 equiv), DCM anhydrous, rt, overnight.

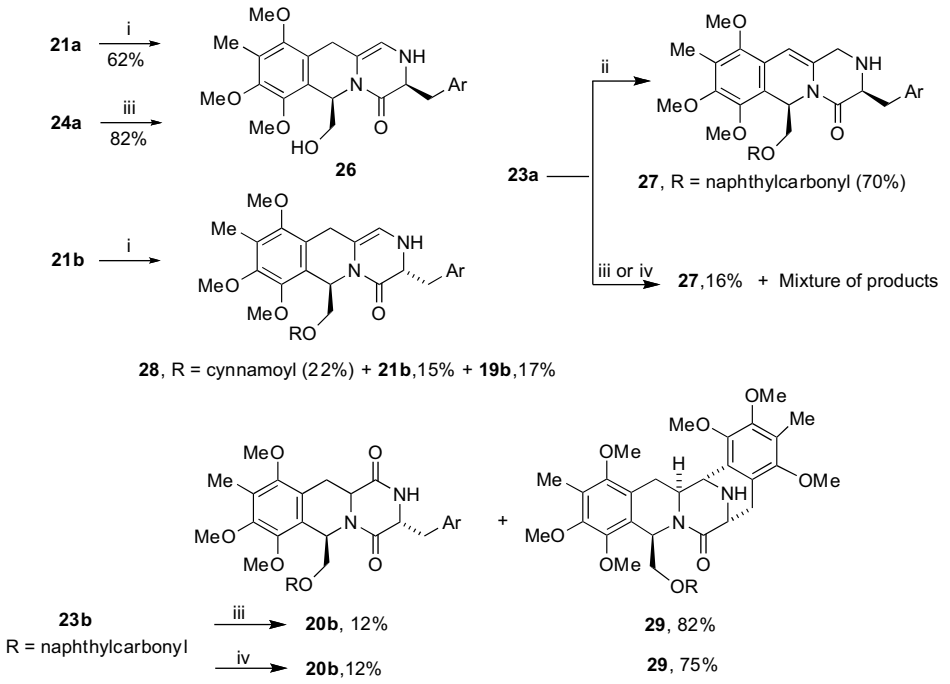
hydrogen. Esterification of the hydroxyl group in compounds **15**, **16a**, and **16b** gave compounds **18**, **19a**,**b**, and **20a**,**b**. The desired all-cis product **20a** was alternatively obtained by catalytic reduction of the 1-naphthylcarbonyl derivative **18** in which, as expected, the steric bulk of the C(6) side chain controls the addition of hydrogen to the α-face.

We next studied the construction of the piperazine bridge in the 3,11a-cis and 3,11a-trans-isomers **16a**, **19a**,**b**, and **20a**,**b** after activation of the *C*(1)-carbonyl by treatment with isopropyl chloroformate (compounds **21a**,**b** and **22a**) or Boc anhydride (compounds **23a**,**b** and **24a**). Only in the reaction of **16a** with Boc anhydride the N-acylation competed with the O-acylation of the lactam function (see **25a** in Scheme 5).

Four reaction conditions were studied to generate the intermediate *N*-acyliminium ions from the non-isolated 1-hydroxy derivatives obtained by partial reduction of the *N*-alkoxycarbonyl derivatives,[4] treatment with formic acid under reflux,[24] trifluoroacetic acid at room temperature[25] or under reflux, and methanesulfonic anhydride at room temperature.[26] All studied cis-isomers **21a**, **23a**, and **24a** gave unconjugated (**26**) or conjugated (**27**)



Scheme 5. (i) Isopropyl chloroformate (6 equiv), Et_3N (6 equiv), DMAP (3 equiv), anhyd DCM, rt, 48 h. (ii) Boc anhydride (2 equiv), DMAP (0.8 equiv), anhyd CH_3CN, rt, 18 h. (iii) Boc anhydride (4 equiv), DMAP (2 equiv), anhyd CH_3CN, rt, 18 h.



Scheme 6. Reaction conditions after treatment with $LiAlH(^tBuO)_3$ (6 equiv) in anhydrous THF, rt, 3 h. (i) concd HCO_2H, 80 °C, 30 min (in the case of **21a** the product was further treated with TFA/sulfuric acid, which hydrolyzed the ester side chain to give **26**). (ii) F_3CCO_2H, rt, 20 h. (iii) F_3CCO_2H, reflux, 2 h. (iv) $(CH_3SO_2)_2O$, anhydrous DCM, rt, 48 h.

enamines after different treatments. Similarly, (3*R**,6*R**,11a*S**)-isomer **21b** after treatment with formic acid gave unconjugated enamine **28** while **23b** was cyclized to **29** in very good yield under other conditions (Scheme 6).

3. Conclusions

We conclude that aldol-type reactions with aromatic aldehydes of (6,11a-trans)-isomers are effective and that the (6,11a-cis)-isomers may give rather good conversions without epimerization of the C(11a)-stereocenter with an adequate selection of the base and the C(6) side chain (*cis*-**10** to **13b**). This control is more difficult in analogs with a less flexible C(6) side chain. The subsequent hydrogenation of the exocyclic double bond gave mixtures of (3*S**,6*R**,11a*S**)-3-arylmethyl-pyrazino[1,2-*b*]isoquinoline-1,4-diones (all-cis compounds) and their (3*R**,6*R**,11a*S**)-diastereomers. However, certain C(6) chains control the addition of hydrogen to the α-face (see compound **19** to **20**). Finally, the *N*-acyliminium intermediates generated by acid treatment of the non-isolated 3-arylmethyl-1-hydroxy-pyrazino[1,2-*b*]isoquinoline-4-ones gave their corresponding enamines by deprotonation, but the (3*R**,6*R**,11a*S**)-diastereomers cyclized to (6*R**,9*R**,14a*S**,15*R**)-6,15-imino-7-oxo-isoquino[3,2-*b*]-3-benzazocine compound **29** with very good yield through a Pictect–Spengler type reaction. The cyclization failure in all cis-isomers is most probably due to steric interactions between the C(3) and C(6) side chains, both of which have to adopt nearly axial positions (Fig. 2).

4. Experimental

4.1. 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. 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).

Melting points are uncorrected, and were determined using a Hoffler 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 ^1H 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–^1H 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.

4.2. General procedure for condensation of tricyclic compounds with aromatic aldehydes

To a solution of the tricyclic compound (0.18 mmol) and the corresponding aromatic aldehyde (0.23 mmol) in dry DCM (2 mL), under an argon atmosphere, was added K^{t}BuO (0.27 mmol) in ^{t}BuOH. The mixture was stirred at room temperature for 12 h and then a saturated aqueous solution of NH_4Cl (5 mL) was added. The mixture was extracted with DCM (50 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 vacuum to give, after column chromatography, the pure compounds.

4.2.1. (6S,11aR*)-6-Methyl-7,10-dimethoxy-3-(2,5-dimethoxybenzylidene)-2,3,11,11a-tetrahydro-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**5**)*

After condensation of *trans*-**3** (212 mg, 0.64 mmol) with 2,5-dimethoxybenzaldehyde. The crude product was purified by flash chromatography on silica gel column with hexane/ethyl acetate (7:3) as eluant giving **5** (180 mg, 64% yield) and with hexane/ethyl acetate (8:2) as eluant to give **7** (75 mg, 27% yield). Data for

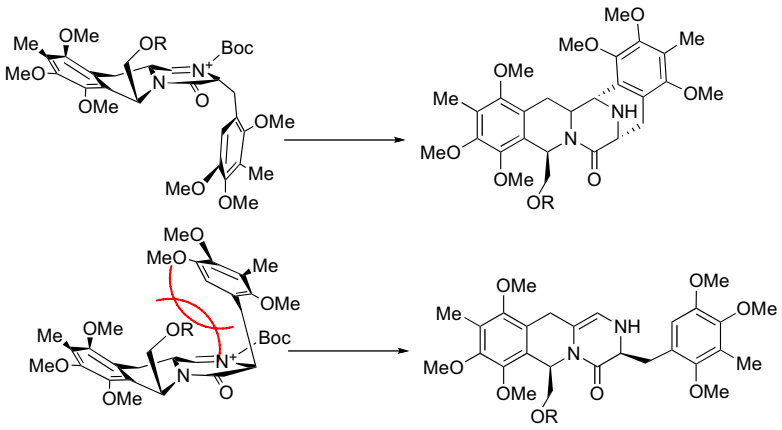


Figure 2.

5. Yellow solid, Mp: 95–96 °C; IR (NaCl) ν_{max} 3234, 2942, 2831, 1694, 1628, 1484 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 8.75 (s, 1H, NH), 6.82 (m, 2H), 6.90 (s, 1H), 6.73 (d, 1H, *J*=2.8 Hz), 6.62 (s, 2H), 5.99 (q, 1H, *J*=6.7 Hz), 4.46 (dd, 1H, *J*=12.5 and 4.6 Hz,), 3.80 (s, 3H), 3,75 (s, 3H), 3.70 (s, 3H), 3.69 (s, 3H), 3.44 (dd, 1H, *J*=17.3 and 4.6 Hz), 2.67 (dd, 1H, *J*=17.3 and 12.5 Hz), 1.43 (d, 3H, *J*=6.7 Hz). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.1, 156.2, 154.0, 150.8, 150.2, 149.8, 126.9, 125.7, 123.3, 121.5, 116.2, 115.2, 113.6, 113.1, 108.2, 107.9, 56.7, 55.7, 55.6, 55.5, 51.5, 45.4, 29.1, 18.6. Anal. Calcd for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.32; H, 5.43; N, 6.12.

4.2.2. (6S,11aS*)-6-Methyl-7,10-dimethoxy-3-(2,5-dimethoxybenzylidene)-2,3,11,11a-tetrahydro-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**7**)*

Yellow solid. Mp: 83 °C; IR (NaCl) ν_{max} 3234, 2942, 2831, 1694, 1628, 1484 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.80 (d, 1H, *J*=9.0 Hz), 6.71 (d, 1H, *J*=9.0 Hz,), 6.62 (d, 1H, *J*=2.7 Hz), 6.60 (s, 1H), 6.52 (d, 1H, *J*=2.7 Hz), 6.37 (d, 1H, *J*=2.8 Hz, NH), 6.08 (q, 1H, *J*=6.6 Hz), 4.40 (m, 1H), 3.82 (s, 6H), 3.68 (s, 3H), 3.50 (s, 3H), 3.25 (dd, 1H, *J*=13.3 and 4.7 Hz), 2.93 (dd, 1H, *J*=13.3 and 6.8 Hz), 1.21 (d, 3H, *J*=6.6 Hz). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.4, 161.2, 153.2, 151.9, 149.7, 148.6, 124.8, 124.4, 123.5, 118.7, 116.8, 113.7, 111.7, 111.0, 109.7, 109.6, 56.8, 55.9, 55.7, 55.4, 55.3, 44.7, 36.2, 18.8. Anal. Calcd for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.42; H, 5.64; N, 6.32.

4.2.3. (6R,11aR*)-9-Methyl-3-(3-methyl-2,4,5-trimethoxybenzylidene)-6-phthalimidomethyl-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**6**)*

After condensation of *trans*-**4** with 3-methyl-2,4,5-trimethoxybenzaldehyde. The crude product was purified by flash chromatography on silica gel column with hexane/ethyl acetate (6:4) as eluant, giving **6** (45% yield) as a yellow solid. Mp: 215–216 °C; IR (NaCl) ν_{max} 3249, 2940, 1773, 1715, 1694, 1626 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 9.24 (ws, 1H), 7.90–7.75 (m, 2H), 7.70–7.60 (m, 2H), 6.52 (s, 1H), 6.39 (s, 1H), 6.29 (dd, 1H, *J*=10.7 and 3.3 Hz), 4.89 (dd, 1H, *J*=12.6 and 4.3 Hz), 4.42 (dd, 1H, *J*=14.0 and 3.6 Hz), 4.20–3.60 (m, 2H), 4.07 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H), 3.67 (s, 3H), 3.56 (s, 3H), 2.80 (dd, 1H, *J*=16.8 and 12.6 Hz), 2.21 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.3, 164.6, 157.7, 152.3, 150.6, 149.5, 149.0, 148.5, 146.3, 133.8, 132.1, 126.5, 125.4, 124.5, 123.6, 123.2, 121.7, 121.5, 113.1, 111.6, 60.6, 60.5, 60.3, 60.1, 60.0, 55.8, 52.8, 49.0, 38.6, 28.8, 9.5, 9.4. Anal. Calcd for $C_{36}H_{37}N_3O_{10}$: C, 64.37; H, 5.55; N, 6.26. Found: C, 63.98; H, 5.32; N, 6.01.

4.2.4. (6R,11aS*)-6-Benzyloxymethyl-9-methyl-3-(2,5-dimethoxybenzylidene)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**13a**)*

After condensation of *cis*-**10** (680 mg, 1.6 mmol) with 2,4,5-trimethoxy-3-methyl-benzaldehyde. The crude product was purified by flash chromatography on silica gel column with hexane/ethyl acetate (1:1) as eluant, giving **13a** (326 mg, 60% yield based on conversion) as a yellow solid. Mp: 75–76 °C; IR (NaCl) ν_{max} 2940, 1694, 1633 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.06 (m, 5H), 6.81 (s, 1H), 6.72 (s, 1H), 6.69 (d, 1H, *J*=2.8 Hz), 6.61 (d, 1H, *J*=2.8 Hz), 6.00 (dd, 1H, *J*=6.5 and 3.8 Hz), 4.54 (dd, 1H, *J*=12.3 and 4.6 Hz), 4.50 (d, 1H, *J*=12.4 Hz), 4.23 (d, 1H, *J*=12.4 Hz), 3.69 (s, 3H), 3.63 (m, 2H), 3.63 (s, 3H), 3.57 (s, 6H), 3.45 (s, 3H), 3.28 (dd, 1H, *J*=16.9 and 4.6 Hz), 2.59 (dd, 1H, *J*=16.9 and 12.3 Hz), 1.98 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.0, 157.1,154.0, 152.1, 150.2, 150.1, 145.9, 138.0, 128.4, 127.7, 127.6, 125.5, 124.7, 123.8, 123.3, 121.8, 116.3, 115.2, 113.6, 113.4, 72.7, 70.3, 60.3, 60.0, 59.9, 56.8, 55.7, 52.9, 49.0, 28.8, 9.3. Anal. Calcd for $C_{33}H_{36}N_2O_8$: C, 67.33; H, 6.16; N, 4.76. Found: C, 66.97; H, 6.26; N, 4.53.

4.2.5. (6R,11aS*)-6-Benzyloxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzylidene)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**13b**)*

The crude product was purified by flash chromatography on silica gel column with hexane/ethyl acetate (6:4) as eluant, giving **13b** (76% yield based on conversion) as a yellow solid. Mp: 73–74 °C; IR (NaCl) ν_{max} 2936, 1693, 1629 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.20 (m, 5H), 6.90 (s, 1H), 6.58 (s, 1H), 6.16 (dd, 1H, *J*=6.9 and 3.6 Hz), 4.67 (dd, 1H, *J*=12.3 and 4.6 Hz), 4.64 (d, 1H, *J*=12.1 Hz), 4.38 (d, 1H, *J*=12.1 Hz), 3.78 (s, 3H), 3.77 (m, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 3.58 (s, 3H), 3.57 (s, 3H), 3.41 (dd, 1H, *J*=16.9 and 4.6 Hz), 2.70 (dd, 1H, *J*=16.9 and 12.3 Hz), 2.18 (s, 3H), 2.11(s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.1, 157.5, 152.2, 150.2, 149.6, 148.9, 148.6, 145.9, 138.0, 128.3, 127.6, 127.1, 126.5, 125.0, 124.8, 123.8, 121.8, 121.7, 113.7, 111.7, 72.7, 70.2, 61.1, 60.4, 60.3, 60.0, 59.9, 55.8, 52.9, 49.0, 28.8, 9.5, 9.3. Anal. Calcd for $C_{35}H_{40}N_2O_9$: C, 66.44; H, 6.37; N, 4.43. Found: C, 66.26; H, 6.32; N, 4.34.

4.2.6. (6R,11aS*)-6-Benzyloxymethyl-3,3-dihydroxy-9-methyl-2-(pivaloyl)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**14**)*

According to the general procedure, the crude product was purified by flash chromatography on silica gel column with hexane/ethyl acetate (1:1) as eluant, giving **13b** (20% yield) and **14** (39% yield) as a yellow solid. Mp: 68–69 °C; IR (NaCl) ν_{max} 2939, 1680, 1630 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 11.53 (s, 1H), 7.42 (s, 1H),

7.06 (m, 5H), 5.29 (dd, 1H, *J*=6.4 and 2.9 Hz), 4.46 (d, 1H, *J*=12.3 Hz), 4.21 (d, 1H, *J*=12.3 Hz), 4.10 (dd, 2H, *J*=11.1 and 5.6 Hz), 3.76 (s, 3H), 3.63 (s, 3H), 3.61 (m, 1H), 3.59 (s, 3H), 3.50 (m, 1H), 3.48 (s, 3H), 3.26 (dd, 1H, *J*=16.7 and 5.6 Hz), 2.30 (dd, 1H, *J*=16.7 and 11.1 Hz), 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 $C_{29}H_{36}N_2O_9$: C, 62.58; H, 6.52; N, 5.03. Found: C, 62.62; H, 6.59; N, 4.95.

4.2.7. (6R,11aS*)-6-Hydroxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzylidene)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**15**)*

A solution of **13b** (2.11 mmol) in ethyl acetate (40 mL) containing 10% palladium on carbon (150 mg) was vigorously stirred under 1.0 atm of hydrogen, at room temperature for 16 h. The reaction mixture was filtered through Celite and the solvent evaporated under reduced pressure to give a residue that was purified by flash column chromatography on silica gel column with hexane/ethyl acetate (3:7) as eluant giving **15** (1.0 g, 96% yield) as a yellow solid. Mp: 114–115 °C; IR (NaCl) ν_{max} 3411, 2934, 1694, 1624 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.38 (s, 1H), 6.89 (s, 1H), 6.87 (s, 1H), 6.04 (dd, 1H, *J*=8.2 and 3.4 Hz), 4.65 (dd, 1H, *J*=12.3 and 7.8 Hz), 4.08 (dd, 1H, *J*=11.6 and 3.4 Hz), 3.86 (s, 3H), 3.82 (m, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 3.59 (s, 3H), 3.58 (s, 3H), 3.46 (dd, 1H, *J*=17.0 and 4.6 Hz), 2.74 (dd, 1H, *J*=17.0 and 12.3 Hz), 2.18 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.9, 158.5, 152.3, 150.4, 149.6, 148.9, 148.7, 146.0, 126.6, 125.2, 124.8, 123.1, 121.6, 114.0, 111.8, 64.1, 61.0, 60.4, 60.3, 60.0, 59.9, 55.8, 52.7, 51.7, 28.7, 9.5, 9.3. Anal. Calcd for $C_{28}H_{34}N_2O_9$: C, 61.98; H, 6.32; N, 5.16. Found: C, 61.66; H, 6.25; N, 5.06.

4.3. General procedure for the hydrogenation of the exocyclic double bond

A solution of **5** or **13b** (2.04 mmol) in methanol (150 mL) containing 50% palladium on carbon (120 mg) was vigorously stirred under 4.0 atm of hydrogen, at room temperature for 16 h. The reaction mixture was filtered through Celite and the solvent evaporated under reduced pressure to give a residue.

4.3.1. (3S,6S*,11aR*)-6-Methyl-7,10-dimethoxy-3-(2,5-dimethoxybenzyl)-2,3,11,11a-tetrahydro-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**8**)*

According to the general procedure, compound **5** (0.11 mmol) was hydrogenated and the crude product was purified by flash chromatography on silica gel column using as eluants hexane/ethyl acetate (1:1) for **8** (76% yield) and (2:8) for **9** (22% yield). Data for **8**. Yellow solid. Mp: 193 °C; IR (NaCl) ν_{max} 2936, 2835, 1683, 1652, 1604, 1502 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.73 (m, 3H, ArH), 6.60 (s, 2H), 6.03 (s, 1H, NH), 5.87 (q, 1H, *J*=6.7 Hz), 4.27 (dd, 1H, *J*=7.6 and 4.1 Hz), 4.08 (dd, 1H, *J*=12.3 and 4.5 Hz), 3.75 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 3.67 (s, 3H), 3.49 (dd, 1H, *J*=13.6 and 4.1 Hz), 3.32 (dd, 1H, *J*=17.4 and 4.5 Hz), 2.91 (dd, 1H, *J*=13.6 and 7.6 Hz), 2.54 (dd, 1H, *J*=17.4 and 12.3 Hz), 1.31 (d, 3H, *J*=6.7 Hz). ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.3, 163.3, 153.6, 151.8, 150.8, 149.8, 127.0, 124.9, 121.7, 117.6, 113.1, 111.6, 108.1, 107.9, 55.9, 55.6, 55.5, 55.4, 54.8, 50.7, 44.9, 34.3, 28.3, 18.7. Anal. Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.01; H, 6.33; N, 6.05.

4.3.2. (3R,6S*,11aR*)-6-Methyl-7,10-dimethoxy-3-(2,5-dimethoxybenzyl)-2,3,11,11a-tetrahydro-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**9**)*

Yellow solid. Mp: 173 °C; IR (NaCl) ν_{max} 3245, 2935, 2837, 1682, 1652, 1504 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.73 (d, 1H, *J*=8.9 Hz), 6.62 (dd, 1H, *J*=8.9 and 3.0 Hz), 6.59 (s, 2H), 6.41 (d, 1H, *J*=3.0 Hz), 5.98 (s, 1H, NH), 5.88 (q, 1H, *J*=6.7 Hz), 4.33 (dd, 1H, *J*=5.6 and 4.8 Hz), 4.16 (dd, 1H, *J*=12.5 and 4.8 Hz), 3.73 (s, 3H), 3.71 (s, 3H), 3.68 (s, 3H), 3.20 (s, 3H), 3.31 (dd, 1H, *J*=13.5 and 4.8 Hz), 3.20 (s, 3H), 3.01 (dd, 1H, *J*=17.6 and 4.8 Hz), 2.92 (dd, 1H, *J*=13.5 and 5.6 Hz), 1.39 (dd, 1H, *J*=17.6 and 12.5 Hz), 1.34 (d, 3H, *J*=6.7 Hz). ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.7, 163.4, 153.8, 152.3, 151.3, 150.0, 127.0, 124.6, 122.4, 116.3, 114.6, 112.2, 108.3, 108.2, 56.6, 56.2, 55.9, 55.8, 55.5, 50.5, 44.9, 35.6, 28.6, 18.8. Anal. Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.15; H, 6.06; N, 6.12.

4.3.3. (3S,6R*,11aS*)-6-Hydroxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxy-benzyl)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**16a**)*

According to the general procedure, compound **13b** (0.11 mmol) was hydrogenated and the crude product was purified by flash chromatography on silica gel column with ethyl acetate as eluant, giving **16a** (50% yield) and with hexane/ethyl acetate (2:8) to give **16b** (23% yield). Data for **16a**. White solid. Mp: 111–112 °C; IR (NaCl) ν_{max} 3396, 2940, 1668, 1634 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.75 (s, 1H), 6.46 (s, 1H), 5.99 (dd, 1H, *J*=8.9 and 3.9 Hz), 4.49 (ws, 1H), 4.38 (dd, 1H, *J*=11.9 and 4.6 Hz), 4.03 (dd, 1H, *J*=11.8 and 4.0 Hz), 3.92 (s, 3H), 3.83 (m, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.66 (s, 3H), 3.60 (s, 3H), 3.46 (s, 3H), 3.30 (dd, 1H, *J*=13.7 and 4.6 Hz), 3.19 (dd, 1H, *J*=17.0 and 4.6 Hz), 3.06 (dd, 1H, *J*=13.7 and 6.0 Hz), 2.18 (s, 3H), 2.16 (s, 3H), 1.83 (dd, 1H, *J*=17.0 and 11.9 Hz). ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.1, 165.3, 152.3, 151.3, 150.1, 149.2, 147.2, 145.8, 125.8, 125.0, 122.9, 122.0, 121.8, 111.1, 63.1, 60.6, 60.4, 60.1, 60.0, 59.9, 55.3, 56.2, 51.2, 51.1, 34.9, 27.7, 9.7, 9.3. Anal. Calcd for $C_{28}H_{36}N_2O_9$: C, 61.75; H, 6.66; N, 5.14. Found: C, 61.66; H, 6.42; N, 4.95.

4.3.4. (3R,6R*,11aS*)-6-Hydroxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxy-benzyl)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**16b**)*

White solid. Mp: 104–105 °C; IR (NaCl) ν_{max} 3367, 2940, 1682, 1663 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.42 (s, 1H), 6.30 (s, 1H), 5.77 (dd, 1H, *J*=8.4 and 3.6 Hz), 4.17 (m, 2H), 3.83 (dd, 1H, *J*=11.7 and 3.6 Hz), 3.70 (s, 3H), 3.62 (s, 3H), 3.57 (s, 6H), 3.56 (m, 1H), 3.50 (s, 3H), 3.45 (s, 3H), 3.27 (dd, 1H, *J*=13.9 and 3.9 Hz), 3.19 (dd, 1H, *J*=16.9 and 4.4 Hz), 2.87 (dd, 1H, *J*=13.9 and 8.3 Hz), 2.50 (dd, 1H, *J*=11.1 and 4.4 Hz), 2.01 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.1, 165.4, 152.3, 150.8, 150.3, 149.5, 147.3, 146.0, 126.1, 125.1, 123.5, 123.3, 121.7, 111.6, 63.4, 60.7, 60.4, 60.2, 60.0, 59.9, 55.4, 52.0, 51.4, 34.5, 27.7, 9.7, 9.3. Anal. Calcd for $C_{28}H_{36}N_2O_9$: C, 61.75; H, 6.66; N, 5.14. Found: C, 61.58; H, 6.38; N, 5.06.

4.4. General procedure to obtain-*O*-acyl derivatives 18, 19a, 19b, 20a, and 20b

A 0.1 M solution of **13b** (0.2 mmol) in dry DCM, EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) (0.4 m mol), DIMAP (0.22 mmol), and the corresponding acid compound (0.2 mmol) was stirred under argon atmosphere at room temperature for 21 h. Then, the solvent was evaporated and the residue was dissolved in EtOAc. The organic solution was washed with 0.1 N HCl solution, with 1 N aqueous solution of $NaHCO_3$, water, and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo.

4.4.1. (6R,11aS*)-6-Naphthylcarbonyloxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzylidene)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**18**)*

The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (7:3) as eluant yielding **18** (99% yield) as a yellow solid. Mp: 121–122 °C; IR (NaCl) ν_{max} 2933, 1694, 1682, 1630 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.94 (dd,

1H, *J*=7.3 and 1.2 Hz), 7.26 (m, 3H), 6.64 (s, 1H), 6.28 (s, 1H), 6.26 (dd, 1H, *J*=9.1 and 3.3 Hz), 4.78 (dd, 1H, *J*=11.6 and 9.1 Hz), 4.62 (dd, 1H, *J*=12.5 and 4.4 Hz), 4.51 (dd, 1H, *J*=11.6 and 3.3 Hz), 3.80 (s, 3H), 3.62 (s, 3H), 3.59 (s, 3H), 3.56 (s, 3H), 3.44 (s, 3H), 3.36 (dd, 1H, *J*=16.8 and 4.4 Hz), 3.11 (s, 3H), 2.62 (dd, 1H, *J*=16.8 and 12.5 Hz), 2.01 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.0, 164.6, 157.6, 152.3, 150.4, 149.5, 148.8, 148.6, 146.2, 133.6, 133.4, 131.3, 130.6, 128.3, 127.7, 126.4, 126.3, 126.1, 125.6, 125.4, 124.7, 124.5, 122.5, 121.9, 121.5, 113.9, 111.6, 63.8, 60.6, 60.5, 60.3, 60.1, 60.0, 55.8, 52.7, 49.0, 28.7, 9.5, 9.3. Anal. Calcd for $C_{39}H_{40}N_2O_{10}$: C, 67.23; H, 5.79; N, 4.02. Found: C, 66.85; H, 5.88; N, 4.06.

4.4.2. (3S,6R*,11aS*)-6-Cinnamoyloxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**19a**)*

The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (1:1) as eluant to give **19a** (95% yield) as a white solid. Mp: 106–107 °C; IR (NaCl) ν_{max} 2938, 1710, 1688, 1661 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.61 (d, 1H, *J*=16.0 Hz), 7.46 (m, 2H), 7.33 (m, 3H), 6.35 (s, 1H), 6.34 (d, 1H, *J*=16.0 Hz), 6.16 (s, 1H), 6.13 (dd, 1H, *J*=8.8 and 3.8 Hz), 4.50 (m, 2H), 4.33 (m, 2H), 3.88 (s, 3H), 3.73 (s, 3H), 3.63 (s, 3H), 3.55 (s, 3H), 3.54 (s, 3H), 3.40 (s, 3H), 3.20 (m, 2H), 2.93 (dd, 1H, *J*=13.7 and 6.7 Hz), 2.11 (s, 6H), 1.91 (dd, 1H, *J*=16.9 and 11.8 Hz). ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.7, 166.6, 164.3, 152.3, 151.3, 150.2, 149.3, 147.3, 146.0, 145.5, 134.2, 130.4, 128.8, 128.2, 126.0, 125.5, 122.9, 122.1, 121.9, 117.4, 111.0, 63.4, 60.6, 60.5, 60.2, 60.1, 60.0, 56.1, 55.4, 51.5, 48.3, 35.0, 27.8, 9.7, 9.4. Anal. Calcd for $C_{37}H_{42}N_2O_{10}$: C, 65.86; H, 6.27; N, 4.15. Found: C, 65.72; H, 6.38; N, 3.98.

4.4.3. (3R,6R*,11aS*)-6-Cinnamoyloxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**19b**)*

The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (6:4) as eluant to give **19b** (99% yield) as a white solid. Mp: 98–99 °C; IR (NaCl) ν_{max} 2938, 1714, 1682, 1664 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.65 (d, 1H, *J*=16.0 Hz), 7.46 (m, 2H), 7.31 (m, 3H), 6.44 (s, 1H), 6.37 (d, 1H, *J*=16.0 Hz), 6.16 (m, 1H), 6.13 (s, 1H), 4.61 (dd, 1H, *J*=11.7 and 9.2 Hz), 4.46 (m, 2H), 4.26 (dd, 1H, *J*=10.1 and 3.0 Hz), 3.89 (s, 3H), 3.74 (s, 3H), 3.70 (s, 3H), 3.69 (s, 3H), 3.59 (s, 3H), 3.56 (s, 3H), 3.46 (dd, 1H, *J*=13.9 and 3.0 Hz), 3.40 (dd, 1H, *J*=17.0 and 4.4 Hz), 2.73 (m, 1H), 2.66 (m, 1H), 2.12 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.9, 166.7, 164.9, 152.5, 150.8, 150.3, 149.7, 147.5, 146.4, 145.7, 134.1, 130.5, 129.0, 128.2, 126.3, 125.5, 123.7, 122.5, 122.0, 117.4, 111.3, 63.5, 60.6, 60.4, 60.2, 60.0, 60.1, 56.0, 55.2, 52.3, 48.7, 35.3, 27.8, 9.8, 9.5. Anal. Calcd for $C_{37}H_{42}N_2O_{10}$: C, 65.86; H, 6.27; N, 4.15. Found: C, 65.94; H, 6.37; N, 3.96.

4.4.4. (3S,6R*,11aS*)-6-Naphthylcarbonyloxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**20a**)*

The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (3:7) as eluant to give **20a** (92% yield) as a yellow solid. Mp: 120–121 °C; IR (NaCl) ν_{max} 2939, 1716, 1687, 1656 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.58 (d, 1H, *J*=7.7 Hz), 7.96 (d, 1H, *J*=6.4 Hz), 7.84 (d, 1H, *J*=8.1 Hz), 7.69 (d, 1H, *J*=7.2 Hz), 7.35 (m, 3H), 6.22 (s, 1H), 6.16 (dd, 1H, *J*=9.2 and 3.4 Hz), 6.0 (s, 1H), 4.65 (dd, 1H, *J*=11.6 and 9.2 Hz), 4.44 (dd, 1H, *J*=11.6 and 3.4 Hz), 4.33 (dd, 1H, *J*=11.8 and 4.7 Hz), 4.09 (t, 1H, *J*=4.5 Hz), 3.80 (s, 3H), 3.63 (s, 3H), 3.51 (s, 3H), 3.42 (s, 3H), 3.41 (s, 3H), 3.28 (s, 3H), 3.10 (dd, 1H, *J*=13.5 and 4.7 Hz), 3.04 (m, 1H), 2.81 (dd, 1H, *J*=13.7 and 6.6 Hz), 1.98 (s, 3H), 1.78 (s, 3H), 1.77 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.0, 166.6, 164.4, 152.4, 151.3, 150.2, 149.3, 147.3, 146.0, 133.7, 133.5, 131.3, 130.5, 128.5, 127.7, 126.5, 126.2, 126.0, 125.6, 125.5, 124.6, 122.8, 122.2, 122.1, 110.9, 63.8, 60.5, 60.4, 60.1, 60.0, 59.9, 56.2, 55.4, 51.5, 48.4, 34.9, 27.7, 9.7, 9.4. Anal. Calcd for $C_{39}H_{42}N_2O_{10}$: C, 67.04; H, 6.06; N, 4.01. Found: C, 66.92; H, 6.18; N, 3.89.

4.4.5. (3R,6R*,11aS*)-6-Naphthylcarbonyloxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**20b**)*

The residue was purified by flash column chromatography on silica gel with ethyl acetate as eluant to give **20b** (98% yield) as a yellow solid. Mp: 96–97 °C; IR (NaCl) ν_{max} 2936, 1715, 1686, 1660 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.81 (d, 1H, *J*=8.0 Hz), 8.15 (dd, 1H, *J*=7.3 and 1.3 Hz), 7.93 (d, 1H, *J*=8.2 Hz), 7.79 (d, 1H, *J*=8.0), 7.48 (m, 3H), 6.29 (dd, 1H, *J*=9.4 and 3.5 Hz), 6.19 (s, 1H), 5.96 (s, 1H), 4.85 (dd, 1H, *J*=11.6 and 9.4 Hz), 4.60 (dd, 1H, *J*=11.6 and 3.5 Hz), 4.53 (m, 1H), 4.21 (dd, 1H, *J*=10.6 and 3.1 Hz), 3.92 (s, 3H), 3.75 (s, 3H), 3.65 (s, 3H), 3.62 (s, 3H), 3.57 (s, 3H), 3.39 (m, 1H), 3.37 (s, 3H), 3.27 (dd, 1H, *J*=13.8 and 3.1 Hz), 2.67 (dd, 1H, *J*=16.9 and 12.6 Hz), 2.27 (dd, 1H, *J*=13.8 and 10.6 Hz), 2.14 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.9, 166.6, 164.7, 152.4, 150.7, 150.4, 149.3, 147.3, 146.3, 133.7, 133.6, 131.4, 131.0, 128.5, 127.8, 126.3, 126.2, 126.1, 125.8, 125.5, 124.5, 123.6, 122.5, 122.0, 111.3, 70.5, 60.5, 60.4, 60.2, 60.1, 60.0, 55.9, 55.0, 52.1, 48.7, 35.4, 27.8, 9.6, 9.4. Anal. Calcd for $C_{39}H_{42}N_2O_{10}$: C, 67.04; H, 6.06; N, 4.01. Found: C, 66.86; H, 6.22; N, 3.92.

4.5. General procedure to obtain compounds 11, 21a, 21b, and 22a

A solution of **19a**, **19b** or **20a** (6.6 mmol), triethylamine (39.8 mmol), and 4-dimethylaminopyridine (19.2 mmol) in dry DCM (125 mL) was cooled in ice water, and isopropyl chloroformate (39.8 mmol) was added dropwise. The solution was stirred under argon atmosphere at room temperature for 24 h and then an aqueous solution of $NaHCO_3$ was added to quench the reaction. After extraction with DCM, the extracts were washed with H_2O, an aqueous solution of HCl, and a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo.

4.5.1. (6R,11aS*)-6-Benzyloxymethyl-9-methyl-2-pivaloyl-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**11**)*

The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (7:3) as eluant to give **11** (89% yield) as a yellow oil. IR (NaCl) ν_{max} 2940, 1695, 1672 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.15 (m, 5H), 5.93 (dd, 1H, *J*=6.6 and 3.8 Hz), 4.64 (dd, 1H, *J*=11.7 and 4.9 Hz), 4.56 (d, 1H, *J*=12.1 Hz), 4.36 (d, 1H, *J*=12.1 Hz), 4.22 (d, 1H, *J*=17.4 Hz), 4.11 (d, 1H, *J*=17.4 Hz), 3.76 (s, 3H), 3.70 (s, 3H), 3.69 (m, 2H), 3.60 (s, 3H), 3.34 (dd, 1H, *J*=16.8 and 4.9 Hz), 2.78 (dd, 1H, *J*=16.8 and 11.7 Hz), 2.12 (s, 3H), 1.26 (s, 9H), ^{13}C NMR (63 MHz, $CDCl_3$) δ 185.8, 168.8, 162.9, 152.2, 150.3, 145.9, 137.8, 128.4, 127.7, 127.6, 125.0, 123.8, 121.6, 72.8, 70.3, 60.3, 60.0, 59.9, 53.7, 48.6, 48.0, 43.8, 27.3, 27.0, 9.4. Anal. Calcd for $C_{29}H_{36}N_2O_7$: C, 66.39; H, 6.92; N, 5.34. Found: C, 66.19; H, 6.80; N, 5.25.

4.5.2. (3S,6R*,11aS*)-6-(Cinnamoyloxymethyl)-2-isopropyloxycarbonyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6H-pyrazino-[1,2-b]isoquinoline-1,4-dione (**21a**)*

The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (1:1) as eluant to give **21a** (78% yield) as a white solid. Mp: 76–77 °C; IR (NaCl) ν_{max} 2940, 1779, 1725, 1666, 1633 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.56 (d, 1H, *J*=16.0 Hz), 7.44 (m, 2H), 7.31 (m, 3H), 6.31 (d, 1H, *J*=16.0 Hz), 6.27 (s, 1H), 6.07 (dd, 1H, *J*=87.4 and 4.5 Hz), 5.04 (sp, 1H, *J*=6.3 Hz), 5.02 (m, 1H), 4.42 (m, 3H), 3.86 (s, 3H), 3.71 (s, 3H), 3.58 (s, 3H), 3.46 (s,

3H), 3.45 (s, 3H), 3.44 (m, 1H), 3.27 (s, 3H), 3.08 (dd, 1H, *J*=3.8 and 2.2 Hz), 3.01 (t, 1H, *J*=4.8 Hz), 2.10 (s, 3H), 2.00 (s, 3H), 1.30 (d, 1H, *J*=6.3 Hz), 1.29 (d, 1H, *J*=6.3 Hz), 1.05 (dd, 1H, *J*=13.1 and 6.3 Hz). ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.5, 165.5, 163.9, 152.2, 151.7, 151.6, 150.1, 149.0, 147.4, 145.7, 145.5, 134.1, 130.4, 128.8, 128.2, 125.9, 125.3,122.5, 122.0, 121.5, 117.3, 111.7, 72.0, 63.6, 60.4, 60.3, 60.2, 60.0, 59.9, 59.4, 55.2, 53.0, 48.1, 33.4, 27.0, 14.1, 9.6, 9.3. Anal. Calcd for $C_{41}H_{48}N_2O_{12}$: C, 64.72; H, 6.36; N, 3.68. Found: C, 64.69; H, 6.29; N, 3.64.

4.5.3. (3R,6R*,11aS*)-6-Cinnamoyloxymethyl-2-isopropyloxycarbonyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6H-pyrazino-[1,2-b]isoquinoline-1,4-dione (**21b**)*

The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (4:6) as eluant to give **21b** (85% yield) as a white solid. Mp: 84–85 °C; IR (NaCl) ν_{max} 2941, 1778, 1716, 1674, 1636 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.56 (d, 1H, *J*=16.0 Hz), 7.42 (m, 2H), 7.28 (m, 3H), 6.45 (s, 1H), 6.30 (d, 1H, *J*=16.0 Hz), 6.03 (dd, 1H, *J*=7.6 and 3.8 Hz), 5.07 (dd, 1H, *J*=7.9 and 5.7 Hz), 4.78 (dd, 1H, *J*=11.5 and 7.6 Hz), 4.70 (sp, 1H, *J*=6.2 Hz), 4.45 (dd, 1H, *J*=7.6 and 4.9 Hz), 4.15 (dd, 1H, *J*=11.5 and 3.8 Hz), 3.83 (s, 3H), 3.71 (s, 6H), 3.68 (s, 3H), 3.64 (m, 1H), 3.62 (s, 3H), 3.51 (s, 3H), 3.15 (m, 1H), 3.09 (m, 2H), 2.11 (s, 3H), 2.10 (s, 3H), 1.06 (d, 1H, *J*=6.2 Hz), 0.96 (d, 1H, *J*=6.2 Hz). ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.1, 166.7, 166.4, 151.9, 151.3, 151.0, 150.1, 149.1, 147.4, 145.7, 145.6, 134.0, 130.5, 128.9, 128.2, 125.7, 125.6, 123.3, 122.9, 121.3, 117.3, 111.8, 71.6, 64.4, 60.7, 60.6, 60.5, 60.1, 60.0, 59.9, 55.9, 53.7, 48.1, 32.2, 23.3, 21.5, 21.3, 9.7, 9.5. Anal. Calcd for $C_{41}H_{48}N_2O_{12}$: C, 64.72; H, 6.36; N, 3.68. Found: C, 64.35; H, 6.11; N, 3.60.

4.5.4. (3S,6R*,11aS*)-2-Isopropyloxycarbonyl-6-naphthylcarbonyloxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6H-pyrazino-[1,2-b]isoquinoline-1,4-dione (**22a**)*

The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (1:1) as eluant to give **22a** (83% yield) as a white solid. Mp: 81–82 °C; IR (NaCl) ν_{max} 2941, 1779, 1725, 1665 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.63 (d, 1H, *J*=5.6 Hz), 8.03 (d, 1H, *J*=6.1 Hz), 7.93 (d, 1H, *J*=6.8 Hz), 7.77 (d, 1H, *J*=8.1 Hz), 7.47 (m, 3H), 6.27 (s, 1H), 6.21 (dd, 1H, *J*=7.2 and 2.6 Hz), 4.92 (t, 1H, *J*=3.9 Hz), 4.72 (dd, 1H, *J*=9.7 and 7.2 Hz), 4.53 (m, 1H), 4.50 (m, 1H), 4.00 (sp, 1H, *J*=7.7 Hz), 3.90 (s, 3H), 3.73 (s, 3H), 3.58 (s, 3H), 3.45 (s, 3H), 3.42 (s, 3H), 3.38 (m, 1H), 3.28 (s, 3H), 3.06 (m, 1H), 3.01 (m, 1H), 2.10 (s, 3H), 2.00 (s, 3H), 1.25 (m, 6H), 1.14 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.0, 165.6, 164.0, 152.3, 151.8, 151.7, 150.2, 149.1, 147.5, 146.0, 133.8, 133.6, 131.3, 130.5, 128.5, 127.7, 126.4, 126.1, 126.0, 125.5, 125.4, 124.6, 122.5, 122.1, 121.6, 111.9, 71.9, 64.1, 60.5, 60.3, 60.0, 59.9, 59.4, 55.2, 53.0, 48.3, 33.4, 26.9, 21.7, 9.7, 9.3. Anal. Calcd for $C_{43}H_{48}N_2O_{12}$: C, 65.80; H, 6.16; N, 3.57. Found: C, 65.53; H, 6.40; N, 3.43.

4.6. General procedure to obtain compounds 23a, 23b, 24a, and 25a

A solution of **20a**, **20b** or **16a** (0.6 mmol), Boc anhydride (0.96 mmol, 2 equiv for **16a**), and a catalytic amount of DMAP in anhydrous acetonitrile (10 mL) was stirred overnight under argon atmosphere at room temperature, and then the reaction mixture was quenched by addition of ice and extracted with DCM. The extracts were washed with H_2O, a 1.0 M aqueous solution of HCl, and a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo.

4.6.1. (3S,6R*,11aS*)-9-Methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-6-naphthylcarbonyoxylmethyl-2,3,11,11a-tetrahydro-2-tert-butyloxycarbonyl-7,8,10-trimethoxy-6H-pyrazino[1,2-b]isoquinoline-1,4-dione (**23a**)*

The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (3:7) as eluant to give **23a** (83% yield) as a white solid. Mp: 85–86 °C; IR (NaCl) ν_{max} 2936, 1778, 1727, 1662 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.59 (dd, 1H, *J*=9.2 and 2.4 Hz), 7.95 (dd, 1H, *J*=7.3 and 1.3 Hz), 7.90 (d, 1H, *J*=8.2 Hz), 7.76 (dd, 1H, *J*=6.9 and 2.5 Hz), 7.40 (m, 3H), 6.25 (s, 1H), 6.18 (dd, 1H, *J*=8.6 and 3.2 Hz), 4.86 (t, 1H, *J*=4.5 Hz), 4.67 (dd, 1H, *J*=11.7 and 8.6 Hz), 4.52 (m, 1H), 4.45 (m, 1H), 3.87 (s, 3H), 3.70 (s, 3H), 3.56 (s, 3H), 3.43 (s, 3H), 3.40 (s, 3H), 3.36 (dd, 1H, *J*=4.9 and 2.9 Hz), 3.30 (s, 3H), 3.04 (m, 1H), 2.97 (m, 1H), 2.07 (s, 3H), 1.96 (s, 3H), 1.39 (m, 9H), 1.16 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.0, 166.8, 164.2, 152.3, 151.8, 150.5, 150.1, 149.0, 147.4, 145.9, 133.7, 133.5, 131.3, 130.5, 128.5, 127.7, 126.4, 126.1, 125.9, 125.5, 125.4, 124.6, 122.6, 122.2, 121.7, 111.9, 84.0, 64.2, 60.5, 60.3, 60.1, 60.0, 59.9, 59.3, 55.2, 53.0, 48.2, 33.6, 27.8, 26.9, 9.6, 9.3. Anal. Calcd for $C_{44}H_{50}N_2O_{12}$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.22; H, 6.16; N, 3.33.

4.6.2. (3R,6R*,11aS*)-9-Methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-6-naphthylcarbonyoxylmethyl-2,3,11,11a-tetrahydro-2-tert-butyloxycarbonyl-7,8,10-trimethoxy-6H-pyrazino-[1,2-b]isoquinoline-1,4-dione (**23b**)*

The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (7:3) as eluant to give **23b** (76% yield) as a yellow solid. Mp: 89–90 °C; IR (NaCl) ν_{max} 2933, 1778, 1726, 1672 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.72 (dd, 1H, *J*=7.4 and 2.1 Hz), 8.13 (dd, 1H, *J*=7.3 and 1.3 Hz), 8.00 (d, 1H, *J*=8.2 Hz), 7.86 (dd, 1H, *J*=7.1 and 1.2 Hz), 7.53 (m, 3H), 6.45 (s, 1H), 6.27 (dd, 1H, *J*=7.7 and 3.7 Hz), 5.11 (m, 1H), 5.08 (m, 1H), 4.53 (dd, 1H, *J*=7.5 and 5.4 Hz), 4.41 (dd, 1H, *J*=11.6 and 3.7 Hz), 3.97 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 3.73 (m, 1H), 3.68 (s, 3H), 3.64 (s, 3H), 3.47 (s, 3H), 3.23 (dd, 1H, *J*=17.0 and 7.5 Hz), 2.98 (m, 2H), 2.21 (s, 3H), 2.11 (s, 3H), 1.29 (m, 9H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.2, 167.1, 166.8, 152.0, 151.2, 150.2, 149.7, 149.0, 147.3, 145.7, 133.7, 133.5, 131.2, 130.5, 128.5, 127.7, 126.5, 126.2, 125.8, 125.5, 125.4, 124.5, 123.3, 122.9, 121.4, 111.9, 83.7, 64.8, 60.7, 60.5, 60.4, 60.0, 60.0, 59.7, 55.9, 53.7, 48.0, 32.2, 27.5, 23.6, 9.6, 9.4. Anal. Calcd for $C_{44}H_{50}N_2O_{12}$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.03; H, 6.36; N, 3.41.

4.6.3. (3S,6R*,11aS*)-9-Methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-2-tert-butyloxycarbonyl-6-(tert-butyloxycarbonyloxymethyl)-2,3,11,11a-tetrahydro-7,8,10-trimethoxy-6H-pyrazino[1,2-b] isoquinoline-1,4-dione (**24a**)*

The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (6:4) as eluant to give **24a** (35% yield) and with hexane/ethyl acetate (7:3) to give **25a** (35% yield). Data for **24a**. Yellow solid. Mp: 149–150 °C; IR (NaCl) ν_{max} 2980, 2938, 1778, 1731, 1665 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.36 (s, 1H), 6.11 (t, 1H, *J*=6.1 Hz), 5.07 (t, 1H, *J*=4.5 Hz), 4.51 (dd, 1H, *J*=12.5 and 4.8 Hz), 4.34 (d, 2H, *J*=6.1 Hz), 3.92 (s, 3H), 3.79 (s, 3H), 3.71 (s, 3H), 3.56 (s, 3H), 3.54 (s, 3H), 3.49 (dd, 1H, *J*=4.5 and 1.2 Hz), 3.36 (s, 3H), 3.14 (dd, 1H, *J*=4.5 and 1.2 Hz), 3.08 (dd, 1H, *J*=4.8 and 4.6 Hz), 2.16 (s, 3H), 2.10 (s, 3H), 1.58 (s, 9H), 1.45 (s, 9H), 1.25 (dd, 1H, *J*=12.5 and 4.6 Hz). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.8, 164.2, 153.3, 152.2, 151.8, 150.5, 150.0, 148.9, 147.3, 145.9, 125.9, 125.3, 122.7, 122.2, 121.4, 111.8, 83.8, 82.3, 65.2, 60.4, 60.2, 60.0, 59.9, 59.8, 59.3, 55.2, 52.8, 48.2, 33.6, 27.9, 27.6, 26.8, 9.7, 9.3. Anal. Calcd for $C_{38}H_{52}N_2O_{13}$: C, 61.28; H, 7.04; N, 3.76. Found: C, 61.16; H, 6.87; N, 3.34.

4.6.4. (3S,6R*)-9-Methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-1-tert-butyloxycarbonyloxy-6-(tert-butyloxycarbonyoxylmethyl)-2,3,6,11-tetrahydro-7,8,10-trimethoxy-pyrazino[1,2-b]isoquinoline-4-one (**25a**)*

Yellow solid. Mp: 70–71 °C; IR (NaCl) ν_{max}, 2980, 2936, 1773, 1747, 1647 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.57 (s, 1H), 6.14 (t, 1H,

J=5.7 Hz), 5.02 (m, 1H), 4.12 (d, 1H, J=5.7 Hz), 3.83 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H), 3.59 (s, 3H), 3.46 (m, 5H), 2.91 (dd, 1H, J=13.2 and 4.8 Hz), 2.40 (dd, 1H, J=13.2 and 10.8 Hz), 2.10 (s, 3H), 2.00 (s, 3H), 1.46 (s, 9H), 1.29 (s, 9H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.5, 152.9, 151.1, 150.8, 150.0, 149.5, 148.7, 146.5, 146.1, 125.4, 124.9, 124.7, 124.1, 120.4, 112.3, 83.4, 81.9, 66.9, 60.6, 60.5, 60.2, 60.0, 59.9, 57.8, 55.7, 46.4, 29.3, 27.9, 27.6, 20.4, 9.5, 9.3. Anal. Calcd for $C_{38}H_{52}N_2O_{13}$: C, 61.28; H, 7.04; N, 3.76. Found: C, 61.11; H, 6.88; N, 3.45.

4.7. General procedure for partial reduction of compounds 21a, 21b, 23a, 23b, and 24a

A solution of the corresponding compound (0.26 mmol) in dry THF (6 mL) was added over a solution of lithium tri-*tert*-butoxyaluminum hydride (397 mg, 1.56 mmol) in dry THF (4 mL) cooled in ice water. After stirring at room temperature for 5 h, the reaction mixture was quenched by addition of ice and extracted with ethyl acetate. The extracts were washed with H_2O and a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give the amino alcohol intermediate as a diastereomeric mixture.

4.7.1. (3S,6R*)-6-Hydroxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-2,3,6,11-tetrahydro-7,8,10-trimethoxy-pyrazino[1,2-b]isoquinoline-4-one (**26**)*

A solution of amino alcohol mixture in formic acid (4 mL) was heated for 30 min at 80 °C and then the reaction was quenched by addition over a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. The extracts were washed with H_2O and 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 methanol/ethyl acetate (1:9) as eluant to give **26** (62% yield) as a yellow oil. IR (NaCl) ν_{max} 2934, 1681, 1634, 1464 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.65 (s, 1H), 6.13 (t, 1H, J=6.6 Hz), 5.85 (s, 1H), 4.13 (m, 1H), 3.94 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.70 (s, 3H), 3.68 (s, 3H), 3.61 (m, 2H), 3.46 (dd, 1H, J=13.9 and 3.7 Hz), 2.96 (dd, 1H, J=13.9 and 9.2 Hz), 2.20 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.6, 150.9, 150.5, 149.4, 149.3, 146.7, 145.7, 132.4, 125.5, 125.4, 124.8, 120.0, 119.7, 110.8, 99.6, 64.8, 61.3, 61.1, 60.8, 60.6, 60.1, 60.0, 55.7, 46.4, 32.3, 9.7, 9.2. Anal. Calcd for $C_{28}H_{36}N_2O_8$: C, 63.62; H, 6.86; N, 5.30. Found: C, 63.41; H, 6.58; N, 5.15.

4.7.2. (3R,6R*)-6-Cinnamoyloxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-2,3,6,11-tetrahydro-7,8,10-trimethoxy-pyrazino[1,2-b]isoquinoline-4-one (**28**)*

A solution of amino alcohol mixture in formic acid (4 mL) was heated for 30 min at 80 °C and then the reaction was quenched by addition over a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. The extracts were washed with H_2O and 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 (3:7) as eluant to give **28** (22% yield) as an orange solid. Mp: 88–89 °C; IR (NaCl) ν_{max} 2934, 1713, 1690, 1633 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.60 (d, 1H, J=16.1 Hz), 7.45 (m, 2H), 7.31 (m, 3H), 7.17 (s, 1H), 6.47 (s, 1H), 6.39 (dd, 1H, J=7.0 and 3.8 Hz), 6.30 (d, 1H, J=16.1 Hz), 4.30 (m, 2H), 4.14 (dd, 1H, J=11.4 and 3.8 Hz), 3.89 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H), 3.70 (s, 3H), 3.62 (s, 3H), 3.57 (s, 3H), 3.52 (dd, 1H, J=14.0 and 2.8 Hz), 2.81 (dd, 1H, J=14.0 and 10.2 Hz), 2.10 (s, 6H), 1.14 (m, 1H), 0.87 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.3, 165.3, 160.8, 153.1, 151.7, 150.8, 149.6, 147.4, 145.9, 145.5, 134.3, 130.4, 128.9, 128.1, 126.3, 126.2, 123.7, 121.2, 119.0, 117.4, 111.3, 110.7, 64.2, 62.0, 60.7, 60.6, 60.2, 60.1, 55.9, 55.3, 47.9, 33.4, 29.7, 9.7, 9.3. Anal. Calcd for $C_{37}H_{42}N_2O_9$: C, 67.46; H, 6.43; N, 4.25. Found: C, 67.21; H, 6.37; N, 4.16.

4.7.3. (3S,6R*)-6-Naphthylcarbonyloxymethyl-9-methyl-3-(3-methyl-2,4,5-trimethoxybenzyl)-1,2,3,6-tetrahydro-7,8,10-trimethoxy-pyrazino[1,2-b]isoquinoline-4-one (**27**)*

A solution of amino alcohol in trifluoroacetic acid (4 mL) was stirred for 20 h at room temperature and then the reaction was quenched by addition over a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. The extracts were washed with H_2O and 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 (8:2) as eluant to give **27** (70% yield) as an orange solid. Mp: 83–84 °C; IR (NaCl) ν_{max} 2938, 1715, 1678, 1691, 1593 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.90 (d, 1H, J=4.3 Hz), 8.17 (d, 1H, J=3.6 Hz), 8.02 (d, 1H, J=4.1 Hz), 7.88 (d, 1H, J=4.0 Hz), 7.59 (m, 1H), 7.53 (m, 1H), 7.50 (m, 1H), 6.60 (s, 1H), 6.43 (dd, 1H, J=3.3 and 1.8 Hz), 5.84 (s, 1H), 4.65 (dd, 1H, J=5.7 and 3.3 Hz), 4.53 (dd, 1H, J=5.7 and 1.8 Hz), 4.00 (s, 3H), 3.94 (dd, 1H, J=4.6 and 1.8 Hz), 3.82 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 3.64 (s, 3H), 3.62 (s, 3H), 3.63 (m, 2H), 3.46 (dd, 1H, J=7.0 and 1.8 Hz), 2.92 (dd, 1H, J=7.0 and 4.6 Hz), 2.20 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.3, 167.0, 150.9, 150.5, 149.3, 149.2, 146.6, 145.8, 133.7, 133.6, 133.5, 131.4, 130.7, 128.4, 127.7, 126.4, 126.1, 125.8, 125.5, 125.4, 125.3, 124.4, 120.4, 119.7, 110.8, 99.1, 64.7, 61.3, 61.2, 60.7, 60.6, 60.1, 60.0, 55.7, 47.5, 46.8, 32.2, 9.6, 9.2. Anal. Calcd for $C_{39}H_{42}N_2O_9$: C, 68.61; H, 6.20; N, 4.10. Found: C, 68.80; H, 6.19; N, 4.16.

4.7.4. (6R,9R*,14aS*,15R*)-1,2,4,10,11,13-Hexamethoxy-5,6,9,14,-14a,15-hexahydro-3,12-dimethyl-9-naphthylcarbonyloxymethyl-6,15-imino-isoquino[3,2-b]-3-benzazocine-7-one (**29**)*

A solution of amino alcohol (from **23b**) in trifluoroacetic acid (2 mL) was stirred for 2 h under reflux and then the reaction was quenched by addition over a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. The extracts were washed with H_2O and 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 ethyl acetate as eluant to give **29** (82% yield) as a less brown solid. Mp: 147–148 °C; IR (NaCl) ν_{max} 2939, 1716, 1640 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.75 (d, 1H, J=4.2 Hz), 7.96 (d, 1H, J=4.1 Hz), 7.85 (d, 1H, J=4.7 Hz), 7.83 (d, 1H, J=3.8 Hz), 7.52 (m, 3H), 6.34 (dd, 1H, J=5.1 and 1.5 Hz), 4.60 (t, 1H, J=5.1 Hz), 4.32 (m, 2H), 4.02 (d, 1H, J=3.2 Hz), 3.97 (m, 1H), 3.95 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.58 (s, 3H), 3.23 (dd, 1H, J=8.3 and 6.1 Hz), 3.14 (s, 3H), 3.16 (m, 1H), 3.07 (d, 1H, J=8.6 Hz), 2.88 (dd, 1H, J=8.6 and 3.2 Hz), 2.25 (s, 3H), 1.41 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.9, 166.0, 152.5, 152.1, 150.0, 149.6, 146.3, 145.2, 133.7, 133.0, 131.3, 131.0, 128.2, 127.4, 127.3, 125.8, 125.7, 125.5, 125.2, 124.8, 124.2, 123.9, 123.6, 121.7, 62.6, 60.5, 60.0, 59.9, 59.8, 58.9, 53.9, 53.2, 49.2, 47.8, 28.6, 27.9, 9.3, 8.4. Anal. Calcd for $C_{39}H_{42}N_2O_9$: C, 68.61; H, 6.20; N, 4.10. Found: C, 68.49; H, 6.05; N, 4.07.

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