Tetrahedron 65 (2009) 9944–9951

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

C(3)-alkylation and cyclization of pyrazino[1,2-*b*]isoquinolin-4-ones

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ARTICLE INFO

Article history:
Received 29 July 2009
Received in revised form
23 September 2009
Accepted 6 October 2009
Available online 12 October 2009

Keywords:
Diastereoselective alkylation
Tetrahydroisoquinolines
Pictet–Spengler
Superacid catalysis

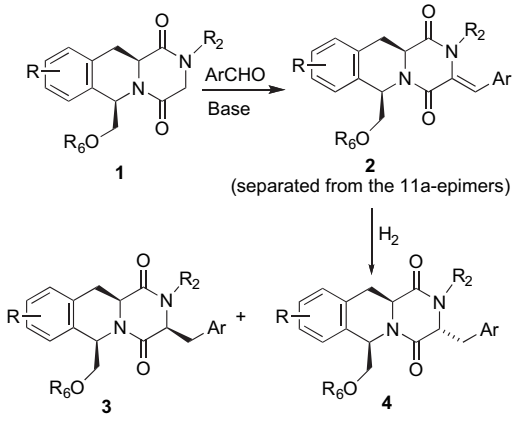
ABSTRACT

To avoid the epimerization of the C(11a)-stereocenter previously observed in 6,11a-*cis*-pyrazino[1,2-*b*]isoquinolin-1,4-diones, we present in this paper the C(3)-alkylation of 1-methoxy-pyrazino[1,2-*b*]isoquinolin-4-ones to obtain all-*cis* derivatives through a very reliable protocol. The success of the acid-promoted cyclization to get pentacyclic (R_3=arylmethyl) or tetracyclic (R_3=2-bromo-2-propenyl) compounds is dependent on the nature of the C(3)-unsaturated chain and of the *N*-substituent, but these limitations have been overcome by using trifluoromethanesulfonic as a superacid catalyst. The C-(3)-alkylation of pyrazino[1,2-*b*]isoquinolin-4-one is also studied.

1. Introduction

We are working on the synthesis and biological evaluation of analogues of antitumour alkaloids belonging to the tetrahydroisoquinoline family[1] from readily accessible 1-acetyl-3-arylmethylpiperazine-2,4-diones. The common structural features of these compounds are two tetrahydroisoquinoline moieties, either as quinones and/or hydroquinones, and a pirazine core. As previously described,[2] 14,14a-dehydro-6,15-imino-7-oxo-isoquino[3,2-*b*]-3-benzazocin compounds, that contain rings *A*–*E* of the natural products, and more complex octacyclic derivatives were obtained in good yields and a total diastereoselective control. To avoid the observed epimerization of the C(11a) stereocenter, the starting materials were 11,11a-dehydro-pyrazino[1,2-*b*]isoquinoline-1,4-diones,[3] which were condensed with aromatic aldehydes, the exocyclic double bond thus formed was regio- and diastereoselectively hydrogenated, and the new isoquinoline moiety was finally obtained by a reductive cyclization involving the carbonyl group at C-1. The extension of this protocol to 6-substituted (6,11a-*cis*)-pyrazino[1,2-*b*]isoquinoline-1,4-diones **1**, to get compounds **2**, was conflictive because the epimerization of the C(11a)-stereocenter could not be avoided, and the subsequent hydrogenation showed a poor diastereoselectivity giving mixtures of all-*cis*-compounds **3** and their C(3)-epimers **4**[4] (Scheme 1).

Here, we report the insertion of alkyl chains at the C(3)-position in enolates derived from compounds pyrazino[1,2-*b*]isoquinoline-4-ones and their 1-methoxy derivatives **5a** and **5b** in which the deprotonation at the C(11a)-position is eluded, the equilibration of diastereoisomers resulting from an α-attack, and the cyclization of *cis*-arylmethyl and allyl derivatives. We also report the C(3)-alkylation of analogues of the cytotoxic compounds **5c**[5] and **5d** in order to establish further structure–activity correlations (Scheme 2).



Scheme 1.

2. Results and discussion

Compounds **5a** and **5b** were obtained from the corresponding carbamates **1a**[5] and **1b**[5] by treatment with $LiAlH(^tBuO)_3$ and

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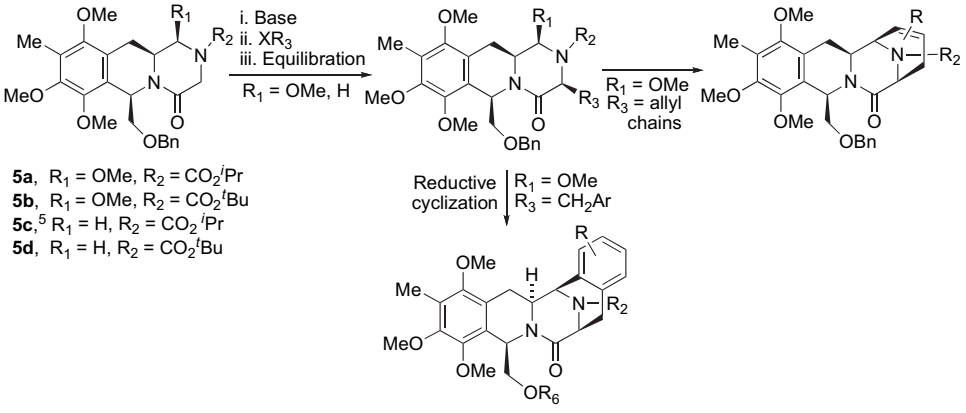
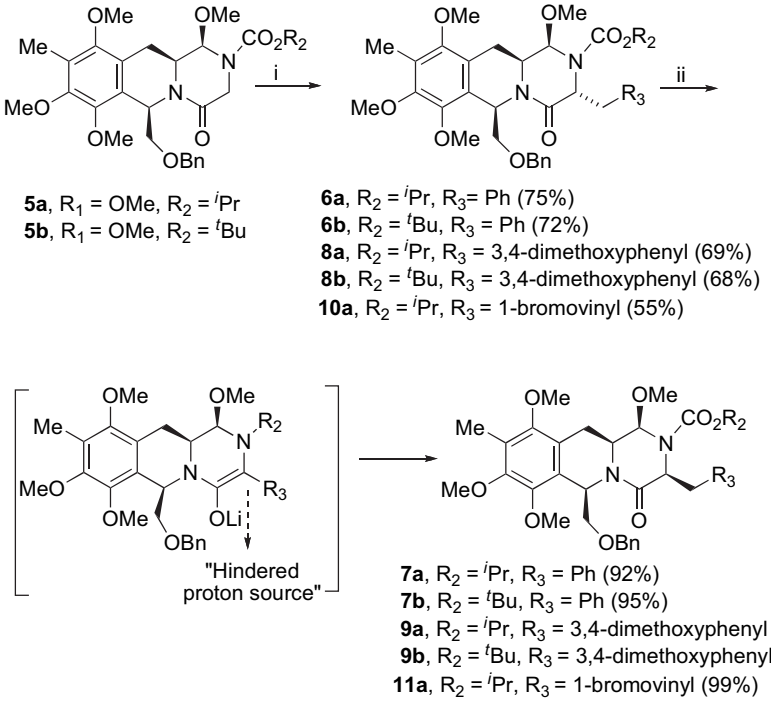
doi:10.1016/j.tet.2009.10.016



Scheme 2.

subsequent quenching with methanol in the presence of pyridinium *p*-toluene sulfonate.[6] The relative configuration of the new stereocenter at C(1) was assigned by conclusive ^{1}H NMR/NOE experiments. Alkylation of the corresponding enolates with benzyl chloride, 3,4-dimethoxybenzyl chloride and 2-bromo-2-propenyl bromide occurred from the α face of the piperazine ring, giving compounds **6**, **8** and **10** whose relative stereochemistry could be established by conclusive ^{1}H NMR/NOE studies in **6a**. When H-6 (δ 5.69) was irradiated, nuclear Overhauser enhancement (NOE)[7] (0.31%) of the H-11a proton (δ 3.96) and (1.17%) of H-2′,6′ protons of the R_3-substituent (δ 6.82) was observed. Furthermore, irradiation of H-11a proton produced NOE (0.26%) of the H-6 and (2.48%) of the H-1 (δ 5.22) protons. Their C(3)-epimers **7**, **9** and **11**, which are the all-*cis* kinetically controlled products, were obtained in nearly quantitative yields by equilibration through deprotonation with *tert*-butyllithium in THF at −78 °C and subsequent stereoselective reprotonation with a solution of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a hindered proton source[8] (Scheme 3). ^{1}H NMR spectra of compounds **6**, **8** and **10** are simple in contrast to those of their C(3)-epimers **7**, **9** and **11**, which appear as mixtures of rotamers. The chemical shifts of H-1, H-3, H-6 and H-11a proton signals are always higher in the all-*cis*-isomers.

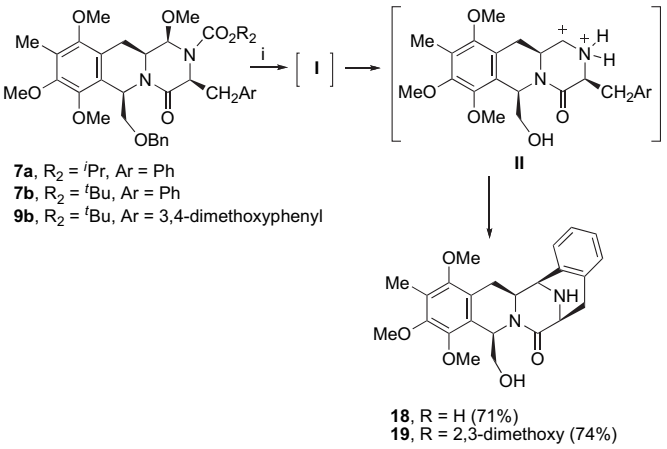
Following intramolecular Pictet–Spengler conditions,[9] the reductive cyclization involving the partial reduction of the C(1)-carbonyl group followed by an acid-promoted generation of an electrophilic iminium intermediate[10] was next studied in compounds **7**, **9** and **11** with the same relative stereochemistry at C-3, C-6 and C-11a as the natural products. Similar procedures were previously applied to 3-arylmethyl-2,5-piperazinedione derivatives in the initial steps of the synthesis of (±)-saframycin A[11] and B,[12,13] and to 3-arylalkyl-pyrazino[1,2-*b*]isoquinoline-1,4-diones in the last steps of the synthesis of (−)-renieramycin G,[14] (±)-renieramycin G,[15] and analogues,[2–4] but due to steric interactions between the C(3)- and C(6)-side chains (that have to adopt nearly axial positions), formation of the fused tetrahydroisoquinoline ring competes in some instances with elimination of the 11a proton to give enamines.[4,15] On the other hand, acid-promoted cyclizations



Scheme 3. (i) (1) 1.2 equiv LHMDS, THF, −78 °C. (2) 3 equiv arylmethyl chloride or allyl bromide. (ii) (1) 2.5 equiv *t*-BuLi, THF, −78 °C. (2) 5.8 equiv BHT, THF, −78 °C.

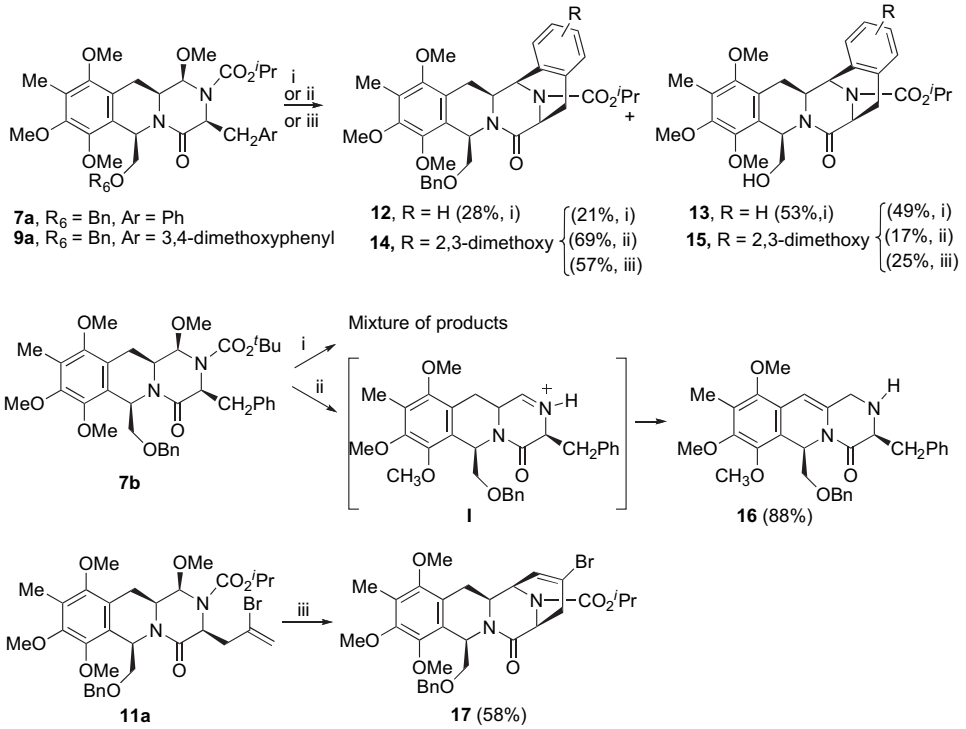
involving 3-allyl-2,5-piperazinedione derivatives have been also applied to construct a fused pyrrolidine ring in the synthesis of (±)-quinocarcin (R_3=3-phenylthio-2-propenyl)[16] and precursors of (−)-lemonomycin (R_3=3-trimethylsilylmethyl-2-propenyl),[17] but an approach to 1,5-iminoisoquino[2,3-*a*]azocin derivatives from compounds similar to **10** or **11** has no precedents in the literature.

N-Isopropoxycarbonyl derivatives **7a** and **9a** gave, after 2 h of treatment with trifluoroacetic acid under reflux (i conditions), a mixture of the pentacyclic products **12** and **14** and their debenzylated analogues **13** and **15**, which were isolated and purified by flash chromatography. Treatment of **9a** under ii and iii conditions increased the amount of compound **14** regarding to **15**. Formation of 1,2-dimethoxy regioisomers was not observed in all experiments. The *N*-Boc derivative **7b** gave a complex mixture of products under i conditions and enamine **16** under ii conditions. Compound **16** is formed by loss of the H-11a proton in the iminium intermediate **I** and subsequent double bond isomerization. The different behaviour of *N*-Boc derivative **7b** as compared to the *N*-isopropoxycarbonyl derivatives is due to the previous deprotection of *N*-Boc to give the iminium intermediate **I**, which is less reactive than acyliminium intermediates derived from the *N*-isopropoxycarbonyl compounds. TFA-promoted cyclization under iii conditions of compound **11a** gave the 1,5-iminoisoquino[2,3-*a*]azocin derivative **17** (Scheme 4).



Scheme 5. (i) Triflic acid, rt, 2 h.

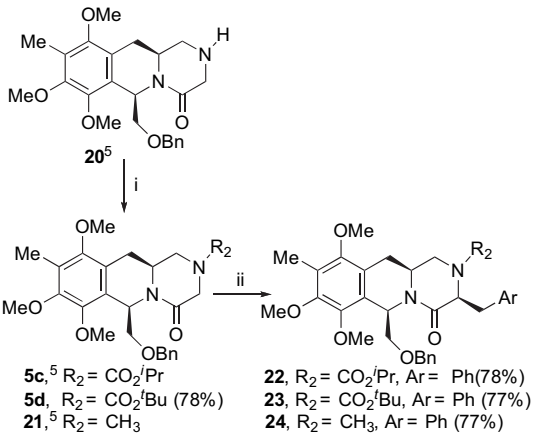
Treatment of **1a** and **1b** with LiAlH(^{t}BuO)$_3$ and subsequent ionic reduction[19] with trifluoroacetic acid and triethyl silane afforded **5c** and **20**, respectively,[5] and the last compound was later derived to



Scheme 4. (i) TFA, reflux, 2 h. (ii) TFA, DCM, molecular sieves, reflux, 2 h. (iii) TFA, DCM, molecular sieves, rt, 24 h.

In an extension of the superacid-catalyzed Pictet–Spengler reaction of imines of 2-phenethylamine,[18] we treated compounds **7b** and **9b** with trifluoromethanesulfonic acid obtaining in good yields the cyclization products **18** and **19** probably through the *C*,*N*-biscationic intermediates **II**, more reactive than iminium cation **I**. Under these conditions the *N*-isopropyloxycarbonyl group was also hydrolyzed, and **7a** gave **18** exclusively (Scheme 5). The C-15 ^{13}C NMR signal is characteristic of the pentacyclic compounds, while the position of the double bond in enamine **16** was established by HMBC experiments.

the *N*-Boc derivative **5d**. When the C(3)-alkylation of compounds **5c**,[5] **5d** and **21**[5] was studied, a total diastereoselectivity was observed but, in contrast to the enolates derived from **5a** and **5b**, the attack takes place here from the β-face of the piperazine ring giving the all-*cis* derivatives **22**–**24**, which showed similar chemical shifts in H-3, H-6 and H-11a protons to those of compounds **7**, **9** and **11**. This stereochemical selectivity may be attributed either to the absence of the 1-methoxy group (kinetic control) or to an easier equilibration of the C(3)-epimers (thermodynamic control) (Scheme 6).



Scheme 6. (i) Boc_2O (1.6 equiv), DMAP (cat.), CH_3CN, rt, 12 h. (ii) (1) 1.2 equiv LHMDS, THF, −78 °C. (2) 3 equiv $PhCH_2Cl$.

3. Conclusions

In conclusion, the C(3)-alkylation of 1-unsubstituted or 1-methoxy-pyrazino[1,2-*b*]isoquinoline-4-ones is a very reliable procedure to get all-*cis* derivatives. The success of the Pictet–Spengler cyclization in all-*cis*-1-methoxy-3-allyl or 3-arylmethyl derivatives is dependent on the nature of the unsaturated chain and on the steric bulk of the *N*-alkoxycarbonyl group, but these problems may be overcome in superacid-catalyzed reactions.

4. Experimental section

4.1. General experimental information

All reagents were of commercial quality and were used as received. Solvents were dried and purified using standard techniques. 'Petroleum ether' refers to the fraction boiling at 40–60 °C. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator. Separations by flash chromatography were performed on silica gel with 40–63 μm particle size. Melting points were measured in a hot stage microscope, and are uncorrected. Infrared spectra were recorded on an FT-IR spectrophotometer examined as films on NaCl disks. NMR spectra were obtained at 250 MHz for ^1H and 63 MHz for ^{13}C, and 300 MHz for ^1H and 75 MHz for ^{13}C with $CDCl_3$ or MeOD as solvents (Servicio de Resonancia Magnética Nuclear, Universidad Complutense). Elemental analyses were determined by the Servicio de Microanálisis Elemental, Universidad Complutense.

4.2. General procedure to obtain compounds 5a and 5b

To a stirred solution of lithium tri-*tert*-butoxyaluminium hydride (18.47 mmol) in dry THF (50 mL) cooled in ice water was added the corresponding compound **1** (6.15 mmol), and the mixture was stirred under argon atmosphere at room temperature for 16 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 intermediates. The crude product, thus obtained, pyridinium *p*-toluene sulfonate (0.15 equiv, 0.92 mmol) in dry MeOH (130 mL), under argon atmosphere, was stirred at room temperature for 48 h. 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 with a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo.

4.2.1. (1R,6R*,11aS*)-6-Benzyloxymethyl-2-isopropyloxycarbonyl-1,7,8,10-tetramethoxy-9-methyl-1,2,3,6,11,11a-hexahydro-pyrazino[1,2-b]isoquinolin-4-one (**5a**).* The reaction was performed with 5.05 g (8.6 mmol) of compound **1a**.[5] The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (7:3) as eluant to give **5a** as an orange oil (4.69 g, 91% yield). IR (film) ν_{max} 2939, 1707, 1659 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.18 (m, 5H), 5.95 (t, J=5.7 Hz, 1H), 4.92 (sp, J=6.2 Hz, 1H), 4.61 (d, J=12.5 Hz, 1H), 4.43 (m, 1H), 4.41 (d, J=12.5, 1H), 4.17 (dd, J=12.6 and 4.0 Hz, 1H), 3.77 (m, 1H), 3.76 (m, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.61 (m, 1H), 3.57 (s, 3H), 3.30 (s, 3H), 2.89 (dd, J=16.1 and 4.0 Hz, 1H), 2.46 (dd, J=16.1 and 12.6 Hz, 1H) 2.10 (s, 3H), 1.20 (m, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 163.5, 155.2, 152.2, 150.0, 146.1, 138.4, 128.1, 127.5, 127.3, 124.6, 124.4, 122.7, 81.9, 72.7, 70.4, 70.0, 60.2, 60.0, 59.8, 54.9, 52.9, 48.9, 43.4, 27.2, 21.9, 9.3. Anal. Calcd for $C_{29}H_{38}N_2O_8$: C, 64.19; H, 7.06; N, 5.16. Found: C, 64.57; H, 6.95; N, 5.09.

4.2.2. (1R,6R*,11aS*)-6-Benzyloxymethyl-2-tert-butyloxycarbonyl-1,7,8,10-tetramethoxy-9-methyl-1,2,3,6,11,11a-hexahydro-pyrazino[1,2-b]isoquinolin-4-one (**5b**).* The reaction was performed with 3.7 g (6.15 mmol) of compound **1b**.[5] The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (7:3) as eluant to give **5b** (3.3 g, 5.35 mmol, 87% yield) as an orange solid. Mp 58–59 °C. IR (NaCl) ν_{max} 2938, 1705, 1659 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.17 (m, 5H), 6.02 (t, J=5.5 Hz, 1H), 5.48 (s, 0.7H), 5.30 (s, 0.3H), 4.66 (d, J=12.4 Hz, 1H), 4.46 (d, J=12.4 Hz, 1H), 4.45 (m, 1H), 4.23 (dd, J=12.5 and 3.8 Hz, 1H), 3.83 (m, 1H), 3.79 (s, 3H), 3.76 (m, 2H), 3.73 (s, 3H), 3.62 (s, 3H), 3.35 (s, 3H), 2.95 (dd, J=16.7 and 3.8 Hz, 1H), 2.53 (dd, J=16.7 and 12.5 Hz, 1H), 2.15 (s, 3H), 1.47 (s, 9H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 163.5, 154.4, 152.0, 149.7, 145.9, 138.1, 127.9, 127.3, 126.9, 124.4, 124.1, 123.1, 82.8, 80.9, 72.4, 70.2, 59.9, 59.6, 59.5, 54.6, 52.7, 48.7, 43.6, 27.8, 27.0, 9.0. Anal. Calcd for $C_{30}H_{40}N_2O_8$: C, 64.73; H, 7.24; N, 5.03. Found: C, 64.57; H, 7.15; N, 4.89.

4.2.3. (1R,6R*,11aS*)-6-Benzyloxymethyl-2-tert-butyloxycarbonyl-7,8,10-trimethoxy-9-methyl-1,2,3,6,11,11a-hexahydro-pyrazino[1,2-b]isoquinolin-4-one (**5d**).* A solution of **20**[5] (490 mg, 1.15 mmol), Boc anhydride (400 mg, 1.84 mmol) and a catalytic amount of DMAP (70 mg, 0.58 mmol) in anhydrous DCM (25 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 1 N aqueous solution of HCl, 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 chromatography on a silica gel column with hexane/ethyl acetate (1:1) as eluant to afford **5d** (470 mg, 78% yield) as a yellow solid. Mp 68–69 °C. IR (NaCl) ν_{max} 2938, 1698, 1659 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.08 (m, 5H), 5.94 (dd, J=7.6 and 3.6 Hz, 1H), 4.58 (d, J=11.9 Hz, 1H), 4.28 (d, J=11.9 Hz, 1H), 3.77 (m, 2H), 3.73 (m, 1H), 3.68 (s, 3H), 3.62 (s, 3H), 3.60 (m, 2H), 3.49 (s, 3H), 3.38 (m, 2H), 2.74 (dd, J=16.8 and 4.2 Hz, 1H), 2.55 (m, 1H), 2.03 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.9, 154.3, 152.2, 149.9, 146.0, 138.2, 128.3, 127.8, 127.6, 124.5, 124.3, 123.1, 80.7, 72.6, 70.1, 60.3, 59.9, 59.7, 48.4, 47.8, 44.5, 43.7, 28.2, 27.5, 9.3. Anal. Calcd for $C_{29}H_{38}N_2O_7$: C, 66.14; H, 7.27; N, 5.32. Found: C, 66.27; H, 7.15; N, 5.14.

4.3. General procedure to obtain compounds 6, 8, 10a, 22, 23 and 24

To a stirred solution of compound **5a**, **5b**, **5c**,[5] **5d** or **21**[5] (0.31 mmol) in dry THF (5 mL) at −78 °C was added LiHMDS (1.0 M in hexane, 0.37 mL, 0.37 mmol) dropwise within 5 min.

The yellow solution was stirred for 45 min at −78 °C, and arylmethyl chloride or allyl bromide (3 equiv 0.93 mmol) was added. After 20 min the reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (3×10 mL). The combined extracts were washed with water, with saturated aqueous solution of NaCl (5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo.

4.3.1. (1R,3R*,6R*,11aS*)-3-Benzyl-6-benzyloxymethyl-2-isopropyloxycarbonyl-1,7,8,10-tetramethoxy-9-methyl-1,2,3,6,11,11a-hexahydro-pyrazino[1,2-b]isoquinolin-4-one (**6a**).* The reaction was performed with 166 mg (0.31 mmol) of compound **5a**. The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (8:2) as eluant to give **6a** (145 mg, 75% yield) as a yellow solid. Mp 60–61 °C. IR (NaCl) ν_{max} 2938, 1710, 1651 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.17 (m, 5H), 6.82 (d, *J*=7.8 Hz, 2H), 6.65 (m, 3H), 5.69 (t, *J*=4.8 Hz, 1H), 5.22 (ws, 1H), 5.10 (sp, *J*=6.2 Hz, 1H), 4.59 (d, *J*=12.4 Hz, 1H), 4.39 (d, *J*=12.4 Hz, 1H), 4.39 (dd, *J*=5.1 and 2.8 Hz, 1H), 3.96 (dd, *J*=13.0 and 3.9 Hz, 1H), 3.89 (dd, *J*=13.7 and 5.1 Hz, 1H), 3.78 (s, 3H), 3.75 (m, 2H), 3.71 (s, 3H), 3.38 (s, 3H), 3.34 (dd, *J*=13.7 and 2.8 Hz, 1H), 3.24 (s, 3H), 2.26 (dd, *J*=16.2 and 3.9 Hz, 1H), 2.07 (s, 3H), 1.33 (d, *J*=6.2 Hz, 6H), 0.92 (dd, *J*=16.2 and 13.0 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.5, 156.9, 151.9, 149.7, 145.8, 138.5, 136.4, 129.9, 128.1, 127.4, 127.3, 127.2, 126.5, 124.4, 123.7, 123.5, 83.1, 72.7, 70.8, 70.1, 60.2, 60.0, 59.9, 57.9, 55.3, 51.4, 49.9, 37.6, 25.5, 22.2, 21.9, 9.3. Anal. Calcd for $C_{36}H_{44}N_2O_8$: C, 68.34; H, 7.01; N, 4.43. Found: C, 68.22; H, 6.83; N, 4.19.

4.3.2. (1R,3R*,6R*,11aS*)-3-Benzyl-6-benzyloxymethyl-2-tert-butyloxycarbonyl-1,7,8,10-tetramethoxy-9-methyl-1,2,3,6,11,11a-hexahydro-pyrazino[1,2-b]isoquinolin-4-one (**6b**).* The reaction was performed with 467 mg (0.84 mmol) of compound **5b**. The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (8:2) as eluant to give **6b** (390 mg, 72% yield) as a yellow solid. Mp 68–69 °C. IR (NaCl) ν_{max} 2938, 1709, 1652 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (m, 5H), 6.71 (m, 3H), 6.60 (m, 2H), 5.64 (t, *J*=3.9 Hz, 1H), 5.14 (ws, 1H), 4.46 (d, *J*=10.1 Hz, 1H), 4.31 (d, *J*=10.1 Hz, 1H), 4.22 (dd, *J*=3.9 and 2.1 Hz, 1H), 3.93 (dd, *J*=10.8 and 3.3 Hz, 1H), 3.75 (dd, *J*=11.2 and 3.9 Hz, 1H), 3.73 (s, 3H), 3.69 (m, 2H), 3.63 (s, 3H), 3.34 (s, 3H), 3.21 (s, 3H), 3.1 (dd, *J*=11.2 and 2.1 Hz, 1H), 2.24 (dd, *J*=13.5 and 3.3 Hz, 1H), 2.03 (s, 3H), 1.50 (s, 9H), 0.86 (dd, *J*=13.5 and 10.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 158.3, 154.3, 151.9, 147.8, 140.5, 138.2, 131.7, 130.0, 129.5, 129.4, 129.3, 128.8, 126.1, 125.9, 125.6, 85.4, 83.8, 74.6, 72.4, 61.7, 61.4, 61.3, 59.8, 56.9, 53.3, 52.3, 38.9, 29.4, 27.4, 10.5. Anal. Calcd for $C_{37}H_{46}N_2O_8$: C, 68.71; H, 7.17; N, 4.33. Found: C, 68.53; H, 7.02; N, 4.06.

4.3.3. (1R,3R*,6R*,11aS*)-6-Benzyloxymethyl-2-isopropyloxycarbonyl-1,7,8,10-tetramethoxy-3-(3,4-dimethoxybenzyl)-9-methyl-1,2,3,6,11,11a-hexahydro-pyrazino[1,2-b]isoquinolin-4-one (**8a**).* The reaction was performed with 560 mg (1.032 mmol) of compound **5a**. The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (1:1) as eluant to give **8a** as an orange solid (490 mg, 69% yield). Mp 82–83 °C. IR (film) ν_{max} 2938, 1708, 1651 cm^{-1}. ^1H NMR (250 MHz, MeOD) δ 7.26 (m, 5H), 6.45 (d, *J*=8.1 Hz, 1H), 6.41 (s, 1H), 6.36 (d, *J*=8.1 Hz, 1H), 5.89 (t, *J*=4.8 Hz, 1H), 5.66 (s, 1H), 5.11 (sp, *J*=6.2 Hz, 1H), 4.66 (d, *J*=11.9 Hz, 1H), 4.51 (d, *J*=11.9 Hz, 1H), 4.43 (m, 1H), 3.96 (dd, *J*=13.1 and 3.8 Hz, 1H), 3.86 (m, 1H), 3.85 (s, 3H), 3.84 (m, 2H), 3.77 (s, 6H), 3.54 (s, 3H), 3.43 (s, 6H), 3.27 (dd, *J*=13.5 and 2.6 Hz, 1H), 2.45 (dd, *J*=16.2 and 3.8 Hz, 1H), 2.14 (s, 3H), 1.42 (d, *J*=6.2 Hz, 6H), 1.11 (dd, *J*=16.2 and 13.1 Hz, 1H). ^{13}C NMR (63 MHz, MeOD) δ 169.0, 158.5, 153.7, 151.3, 149.8, 149.3, 147.3, 139.9, 139.8, 129.6, 129.2, 128.9, 125.8, 125.2, 125.1, 123.7, 114.7, 112.1, 77.1, 74.1, 71.9, 71.7, 61.0, 60.6, 60.3, 59.1, 56.6, 56.2, 55.9, 55.0, 51.9, 38.0, 27.6, 22.9, 22.5, 9.9. Anal. Calcd for $C_{38}H_{48}N_2O_{10}$: C, 65.88; H, 6.98; N, 4.04. Found: C, 65.51; H, 6.96; N, 3.87.

4.3.4. (1R,3R*,6R*,11aS*)-6-Benzyloxymethyl-2-tert-butyloxycarbonyl-1,7,8,10-tetramethoxy-3-(3,4-dimethoxybenzyl)-9-methyl-1,2,3,6,11,11a-hexahydro-pyrazino[1,2-b]isoquinolin-4-one (**8b**).* The reaction was performed with 755 mg (1.36 mmol) of compound **5b**. The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (1:1) as eluant to give **8b** as a yellow solid (650 mg, 68% yield). Mp 71–72 °C. IR (film) ν_{max} 2938, 1704, 1651 cm^{-1}. ^1H NMR (250 MHz, MeOD) δ 7.28 (m, 5H), 6.47 (d, *J*=7.9 Hz, 1H), 6.44 (s, 1H), 6.38 (d, *J*=7.9 Hz, 1H), 5.76 (m, 1H), 5.34 (s, 1H), 4.62 (d, *J*=12.1 Hz, 1H), 4.49 (d, *J*=12.1 Hz, 1H), 4.32 (dd, *J*=4.4 and 2.3 Hz, 1H), 4.11 (dd, *J*=12.5 and 3.7 Hz, 1H), 3.87 (s, 3H), 3.85 (m, 1H), 3.83 (m, 2H), 3.80 (s, 3H), 3.57 (s, 3H), 3.49 (s, 3H), 3.48 (s, 3H), 3.34 (s, 3H), 3.22 (dd, *J*=13.8 and 4.4 Hz, 1H), 2.46 (dd, *J*=16.1 and 3.7 Hz, 1H), 2.16 (s, 3H), 1.66 (s, 9H), 1.18 (dd, *J*=16.1 and 12.5 Hz, 1H). ^{13}C NMR (63 MHz, MeOD) δ 168.8, 158.3, 153.7, 151.5, 149.8, 149.3, 147.4, 139.9, 139.6, 129.5, 128.9, 128.7, 125.6, 125.3, 125.2, 123.6, 114.7, 112.0, 84.7, 83.3, 74.0, 71.9, 61.0, 60.6, 60.2, 59.3, 56.6, 56.2, 55.9, 52.9, 51.9, 37.9, 28.9, 27.2, 10.0. Anal. Calcd for $C_{39}H_{50}N_2O_{10}$: C, 66.27; H, 7.13; N, 3.96. Found: C, 66.02; H, 6.93; N, 3.79.

4.3.5. (1R,3R*,6R*,11aS*)-6-Benzyloxymethyl-3-(2-bromo-2-propenyl)-2-isopropyloxycarbonyl-1,7,8,10-tetramethoxy-9-methyl-1,2,3,6,11,11a-hexahydro-pyrazino[1,2-b]isoquinolin-4-one (**10a**).* The reaction was performed with 110 mg (0.21 mmol) of compound **5b**. The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (8:2) as eluant to give **10a** (74 mg, 55% yield) as brown oil. IR (NaCl) ν_{max} 2938, 1710, 1658 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.28–723 (m, 5H), 5.84 (t, *J*=4.2 Hz, 1H), 5.49 (s, 1H), 5.43 (s, 1H), 5.16–5.06 (sp, *J*=6.2 Hz, 1H), 4.70 (d, *J*=12.3 Hz, 1H), 4.52 (d, *J*=12.3 Hz, 1H), 4.40 (dd, *J*=5.7 and 2.6 Hz, 1H), 4.30 (dd, *J*=10.3 and 6.3 Hz, 1H), 3.91 (m, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.68 (m, 1H), 3.34 (s, 6H), 3.33 (m, 1H), 2.93 (m, 2H), 2.24 (s, 3H), 1.28 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 156.6, 152.3, 150.7, 145.9, 138.8, 128.2, 128.1, 127.7, 127.3, 127.2, 125.1, 124.1, 123.2, 121.3, 120.8, 83.2, 72.6, 70.2, 69.4, 60.1, 59.9, 59.8, 56.4, 55.2, 50.2, 50.0, 42.2, 26.7, 22.0, 21.8, 9.2. Anal. Calcd for $C_{32}H_{41}BrN_2O_8$: C, 58.09; H, 6.25; N, 4.23. Found: C, 57.84; H, 6.06; N, 3.96.

4.3.6. (3S,6R*,11aS*)-3-Benzyl-6-benzyloxymethyl-2-isopropyloxycarbonyl-7,8,10-trimethoxy-9-methyl-1,2,3,6,11,11a-hexahydro-pyrazino[1,2-b]isoquinolin-4-one (**22**).* The reaction was performed with 185 mg (0.36 mmol) of compound **5c**.[5] The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (7:3) as eluant to give **22** as a white solid (170 mg, 78% yield). Mp 64–65 °C. IR (film) ν_{max} 2938, 1698, 1651 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.29 (m, 10H), 6.17 (dd, *J*=8.5 and 5.0 Hz, 1H), 4.99 (m, 0.5H), 4.90 (m, 0.5H), 4.80 (d, *J*=11.9 Hz, 1H), 4.73 (d, *J*=6.2 Hz, 1H), 4.38 (d, *J*=11.9 Hz, 1H), 4.20 (m, 1H), 3.90 (s, 1.5H), 3.88 (s, 1.5H), 3.83 (m, 1H), 3.81 (s, 1.5H), 3.80 (s, 1.5H), 3.78 (m, 2H), 3.67 (s, 1.5H), 3.64 (s, 1.5H), 3.27 (m, 2H), 3.20 (m, 1H), 2.85 (dd, *J*=16.7 and 4.0 Hz, 1H), 2.65 (dd, *J*=16.7 and 12.1 Hz, 1H), 2.22 (s, 1.5H), 2.19 (s, 1.5H), 1.11 (d, *J*=6.2 Hz, 3H), 0.88 (d, *J*=6.2 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.0, 166.7, 154.9, 152.4, 149.9, 146.0, 145.7, 138.2, 137.3, 129.6, 129.5, 128.3, 128.2, 127.8, 127.6, 127.4, 127.3, 126.6, 126.5, 124.5, 124.4, 123.2, 121.1, 72.6, 72.5, 69.6, 69.1, 60.3, 60.2, 59.9, 59.8, 59.7, 58.4, 48.6, 47.9, 39.9, 37.1, 27.7, 21.9, 9.2. Anal. Calcd for $C_{35}H_{42}N_2O_7$: C, 69.75; H, 7.02; N, 4.65. Found: C, 69.46; H, 6.81; N, 4.34.

4.3.7. (3S,6R*,11aS*)-3-Benzyl-6-benzyloxymethyl-2-tert-butyloxycarbonyl-7,8,10-trimethoxy-9-methyl-1,2,3,6,11,11a-hexahydro-pyrazino[1,2-b]isoquinolin-4-one (**23**).* The reaction was performed with 140 mg (0.27 mmol) of compound **5d**. The crude product was purified by flash chromatography on silica gel with hexane/ethyl

acetate (9:1) as eluant to give **23** as a white solid (125 mg, 77% yield). Mp 65–66 °C. IR (film) ν_{max} 2937, 1694, 1651 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.31 (m, 10H), 6.19 (dd, *J*=8.4 and 3.7 Hz, 1H), 4.81 (m, 1H), 4.80 (d, *J*=11.8 Hz, 1H), 4.39 (d, *J*=11.8 Hz, 1H), 4.20 (m, 1H), 3.90 (s, 1.5H), 3.88 (s, 1.5H), 3.87 (m, 1H), 3.81 (s, 1.5H), 3.80 (s, 1.5H), 3.79 (m, 2H), 3.68 (s, 1.5H), 3.63 (s, 1.5H), 3.30 (m, 1H), 3.25 (m, 2H), 2.98 (dd, *J*=17.0 and 3.8 Hz, 1H), 2.65 (dd, *J*=17.0 and 11.7 Hz, 1H), 2.22 (s, 1.5H), 2.19 (s, 1.5H), 1.18 (s, 9H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.2, 166.9, 154.2, 152.4, 149.9, 146.1, 145.8, 138.3, 137.7, 129.7, 129.6, 128.4, 128.3, 127.8, 127.6, 127.5, 127.2, 126.6, 124.5, 124.4, 123.5, 121.1, 80.3, 80.2, 72.6, 72.5, 69.8, 60.4, 60.3, 59.9, 59.8, 59.6, 58.9, 48.6, 47.9, 39.3, 37.1, 28.1, 27.8, 9.3. Anal. Calcd for $C_{36}H_{44}N_2O_7$: C, 70.11; H, 7.19; N, 4.54. Found: C, 69.86; H, 7.84; N, 4.11.

4.3.8. (3S,6R*,11aS*)-3-Benzyl-6-benzyloxymethyl-7,8,10-trimethoxy-2,9-dimethyl-1,2,3,6,11,11a-hexahydro-pyrazino[1,2-b]isoquinolin-4-one (**24**).* The reaction was performed with 170 mg (0.39 mmol) of compound **21**.[5] The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (7:3) as eluant to give **24** as an orange oil (160 mg, 77% yield). IR (film) ν_{max} 2939, 1644 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5H), 7.17 (s, 1H), 7.16 (d, *J*=7.3 Hz, 2H), 6.99 (d, *J*=7.3 Hz, 2H), 6.03 (dd, *J*=7.6 and 3.9 Hz, 0.1H), 4.81 (d, *J*=11.9 Hz, 1H), 4.50 (d, *J*=11.9 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.80 (m, 1H), 3.79 (m, 2H), 3.53 (s, 3H), 3.44 (dd, *J*=13.8 and 3.4 Hz, 1H), 3.24 (t, *J*=4.1 Hz, 1H), 3.11 (dd, *J*=13.8 and 4.5 Hz, 1H), 2.83 (d, *J*=3.0 Hz, 2H), 2.56 (dd, *J*=16.5 and 4.0 Hz, 1H), 2.48 (s, 3H), 2.29 (dd, *J*=16.5 and 11.9 Hz, 1H), 2.19 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.2, 152.0, 149.4, 145.8, 138.4, 138.3, 129.8, 128.2, 127.7, 127.4, 127.3, 125.7, 124.4, 124.1, 123.7, 72.3, 70.0, 68.4, 60.3, 60.0, 59.7, 54.2, 48.7, 48.5, 43.5, 35.7, 27.9, 9.2. Anal. Calcd for $C_{32}H_{38}N_2O_5$: C, 72.43; H, 7.22; N, 5.28. Found: C, 72.16; H, 7.03; N, 5.04.

4.4. General procedure to obtain compounds 7, 9 and 11a

To a stirred solution of compound (**6a**, **6b**, **8a**, **8b** or **10a**) (0.13 mmol) in dry THF (5 mL), under argon, at −78 °C was added *t*-BuLi (1.7 M in pentane, 0.2 mL, 0.325 mmol). Upon complete addition the solution became deep orange/brown in colour. After 10 s a solution of 2,6-di-*tert*-butyl-4-methylphenol (BHT) (0.166 mg, 0.75 mmol) in dry THF (3 mL) was added in one portion. The brown colour faded pale yellow. After 30 s, to the reaction mixture was added aqueous HCl (0.1 N, 5 mL). The solution was warmed to room temperature and extracted with EtOAc (3×10 mL). The combined extracts were washed with water, with saturated aqueous solution of NaCl (5 mL), dried over Na_2SO_4, filtered and concentrated under vacuum.

4.4.1. (1R,3S*,6R*,11aS*)-3-Benzyl-6-benzyloxymethyl-2-isopropyloxycarbonyl-1,7,8,10-tetramethoxy-9-methyl-1,2,3,6,11,11a-hexahydro-pyrazino[1,2-b]isoquinolin-4-one (**7a**).* The reaction was performed with 80 mg (0.13 mmol) of compound **6a**. The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (8:2) as eluant to give **7a** as a yellow solid (75 mg, 92% yield). Mp 74–75 °C. IR (NaCl) ν_{max} 2938, 1698, 1651 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.15 (m, 5H), 7.21 (m, 5H), 5.98 (dd, *J*=7.5 and 3.5 Hz, 1H), 5.43 (s, 0.7H), 5.23 (s, 0.3H), 4.74 (dd, *J*=7.6 and 6.1 Hz, 1H), 4.62 (sp, *J*=6.3 Hz, 1H), 4.58 (d, *J*=12.3 Hz, 1H), 4.37 (d, *J*=12.3 Hz, 1H), 4.18 (dd, *J*=12.1 and 3.6 Hz, 1H), 3.74 (m, 2H), 3.65 (s, 3H), 3.61 (s, 3H), 3.47 (s, 3H), 3.38 (s, 3H), 3.29 (dd, *J*=13.8 and 6.1 Hz, 1H), 3.02 (dd, *J*=13.8 and 7.6 Hz, 1H), 2.81 (dd, *J*=16.5 and 3.6 Hz, 1H), 2.30 (dd, *J*=16.5 and 12.1 Hz, 1H), 2.01 (s, 3H), 0.98 (d, *J*=6.3 Hz, 3H), 0.78 (d, *J*=6.3 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.7, 155.4, 152.3, 150.1, 146.1, 139.1, 138.5, 129.5, 128.2, 128.1, 127.6, 127.4, 126.2, 124.8, 124.4, 122.7, 83.2, 72.7, 70.4, 69.9, 60.2, 60.0, 59.8, 57.7, 56.3, 53.1, 48.7, 41.5, 27.7, 21.8, 21.3, 9.3. Anal. Calcd for $C_{36}H_{44}N_2O_8$: C, 68.34; H, 7.01; N, 4.43. Found: C, 68.06; H, 6.76; N, 4.08.

4.4.2. (1R,3S*,6R*,11aS*)-3-Benzyl-6-benzyloxymethyl-2-tert-butyloxycarbonyl-1,7,8,10-tetramethoxy-9-methyl-1,2,3,6,11,11a-hexahydro-pyrazino[1,2-b]isoquinolin-4-one (**7b**).* The reaction was performed with 582 mg (0.90 mmol) of compound **6b**. The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (8:2) as eluant to give **7b** as an orange solid (560 mg, 95% yield). Mp 93–94 °C. IR (NaCl) ν_{max} 2940, 1698, 1652 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.31 (m, 10H), 6.17 (m, 1H), 5.59 (s, 0.9H), 5.36 (s, 0.1H), 5.03 (dd, *J*=8.7 and 5.4 Hz, 0.1H), 4.90 (dd, *J*=8.7 and 5.4 Hz, 0.9H), 4.77 (d, *J*=12.5 Hz, 1H), 4.56 (d, *J*=12.5 Hz, 1H), 4.36 (dd, *J*=13.5 and 4.9 Hz, 1H), 3.86 (m, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 3.65 (s, 3H), 3.60 (s, 3H), 3.49 (dd, *J*=13.2 and 5.4 Hz, 1H), 3.21 (dd, *J*=13.2 and 8.7 Hz, 1H), 2.99 (dd, *J*=15.7 and 4.9 Hz, 1H), 2.46 (dd, *J*=15.7 and 13.5 Hz, 1H), 2.20 (s, 3H), 1.25 (s, 9H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.0, 154.7, 152.3, 150.1, 146.2, 139.1, 138.5, 129.8, 128.3, 128.2, 127.6, 127.4, 126.2, 124.9, 124.4, 122.7, 82.9, 81.3, 72.7, 70.5, 60.2, 60.0, 59.7, 58.1, 56.5, 52.9, 48.8, 41.4, 28.2, 27.5, 9.3. Anal. Calcd for $C_{37}H_{46}N_2O_8$: C, 68.71; H, 7.17; N, 4.33. Found: C, 68.59; H, 6.86; N, 4.06.

4.4.3. (1R,3S*,6R*,11aS*)-6-Benzyloxymethyl-2-isopropyloxycarbonyl-1,7,8,10-tetramethoxy-3-(3,4-dimethoxybenzyl)-9-methyl-1,2,3,6,11,11a-hexahydro-pyrazino[1,2-b]isoquinolin-4-one (**9a**).* The reaction was performed with 200 mg (0.29 mmol) of compound **8a**. The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (1:1) as eluant to give **9a** as a yellow oil (180 mg, 90% yield). IR (NaCl) ν_{max} 2938, 1699, 1651 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) 7.20 (m, 5H), 6.75 (m, 3H), 6.70 (m, 2H), 6.06 (dd, *J*=7.3 and 3.6 Hz, 1H), 5.51 (s, 0.8H), 5.31 (s, 0.2H), 4.92 (m, 0.4H), 4.77 (dd, *J*=7.7 and 5.7 Hz, 0.6H), 4.70 (m, 1H), 4.66 (d, *J*=12.2 Hz, 1H), 4.45 (d, *J*=12.2 Hz, 1H), 4.26 (dd, *J*=12.8 and 4.2 Hz, 1H), 3.80 (m, 2H), 3.77 (s, 6H), 3.73 (s, 3H), 3.69 (s, 3H), 3.55 (s, 3H), 3.49 (s, 3H), 3.29 (dd, *J*=13.8 and 5.7 Hz, 1H), 3.05 (dd, *J*=13.8 and 7.7 Hz, 1H), 2.89 (dd, *J*=16.5 and 4.2 Hz, 1H), 2.38 (dd, *J*=16.5 and 12.8 Hz, 1H), 2.09 (s, 3H), 1.04 (d, *J*=6.2 Hz, 3H), 0.86 (d, *J*=6.2 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ. 165.8, 155.5, 152.3, 150.1, 148.7, 147.6, 146.1, 138.5, 131.6, 128.2, 127.5, 127.4, 124.8, 124.5, 122.6, 112.5, 110.9, 110.4, 83.3, 72.7, 70.4, 69.8, 60.2, 60.0, 59.8, 57.9, 56.4, 55.8, 55.7, 53.0, 48.7, 41.1, 27.7, 21.9, 21.4, 9.3. Anal. Calcd for $C_{38}H_{48}N_2O_{10}$: C, 65.88; H, 6.98; N, 4.04. Found: C, 65.53; H, 6.74; N, 3.82.

4.4.4. (1R,3S*,6R*,11aS*)-6-Benzyloxymethyl-2-tert-butyloxycarbonyl-1,7,8,10-tetramethoxy-3-(3,4-dimethoxybenzyl)-9-methyl-1,2,3,6,11,11a-hexahydro-pyrazino[1,2-b]isoquinolin-4-one (**9b**).* The reaction was performed with 293 mg (0.42 mmol) of compound **8b**. The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (6:4) as eluant to give **9b** as an orange solid (268 mg, 93% yield). Mp 72–73 °C. IR (film) ν_{max} 2938, 1798, 1651 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5H), 6.85 (m, 3H), 6.16 (dd, *J*=7.1 and 3.3 Hz, 1H), 5.59 (s, 0.7H), 5.33 (s, 0.3H), 4.82 (dd, *J*=9.0 and 4.9 Hz, 1H), 4.75 (d, *J*=12.2 Hz, 1H), 4.55 (d, *J*=12.2 Hz, 1H), 4.35 (dd, *J*=12.7 and 3.5 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (m, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.64 (s, 3H), 3.40 (dd, *J*=13.6 and 4.9 Hz, 1H), 3.16 (dd, *J*=13.6 and 9.0 Hz, 1H), 2.98 (dd, *J*=16.5 and 3.5 Hz, 1H), 2.46 (dd, *J*=16.5 and 12.7 Hz, 1H), 2.19 (s, 3H), 1.24 (s, 9H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.9, 154.6, 152.2, 150.0, 148.6, 147.5, 146.0, 138.4, 131.7, 128.1, 127.5, 127.3, 124.8, 124.4, 122.6, 121.6, 112.7, 110.9, 82.9, 81.0, 72.6, 70.4, 60.1, 59.9, 59.6, 58.2, 55.8, 55.7, 55.6, 52.8, 48.7, 40.9, 28.2, 27.7, 9.2. Anal. Calcd for $C_{39}H_{50}N_2O_{10}$: C, 66.27; H, 7.13; N, 3.96. Found: C, 66.43; H, 7.06; N, 3.64.

4.4.5. (1R,3S*,6R*,11aS*)-6-Benzyloxymethyl-3-(2-bromo-2-propenyl)-2-isopropyloxycarbonyl-1,7,8,10-tetramethoxy-9-methyl-1,2,3,6,11,11a-hexahydro-pyrazino[1,2-b]isoquinolin-4-one (**11a**).* The reaction was

performed with 70 mg (0.108 mmol) of compound **10a**. The crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (8:2) as eluant to give **11a** (69 mg, 99% yield) as brown oil. IR (NaCl) ν_{max} 2838, 1700, 1658 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H), 6.15 (dd, J=7.4 and 3.4 Hz), 5.59 (d, J=1.3 Hz, 1H), 5.58 (s, 1H), 5.47 (d, J=1.3 Hz, 1H), 5.11 (m, 1H), 5.05 (sp, J=6.2 Hz, 1H), 4.72 (d, J=12.1 Hz, 1H), 4.51 (d, J=12.1 Hz, 1H), 4.30 (dd, J=12.6 and 3.7 Hz, 1H), 3.95 (m, 1H), 3.88 (m, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 3.66 (s, 3H), 3.49 (s, 3H), 3.20 (dd, J=14.2 and 6.6 Hz, 1H), 3.01 (m, 1H), 2.49 (dd, J=16.5 and 12.6 Hz, 1H), 2.10 (s, 3H), 1.31 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 155.4, 152.3, 150.1, 146.0, 138.4, 131.3, 128.1, 127.5, 127.3, 124.9, 124.7, 124.4, 122.5, 119.2, 82.8, 72.4, 70.2, 69.7, 60.2, 60.0, 59.8, 55.9, 53.8, 53.0, 48.5, 47.0, 27.6, 21.9, 21.5, 9.3. Anal. Calcd for $C_{32}H_{41}BrN_2O_8$: C, 58.09; H, 6.25; N, 12.08. Found: C, 57.81; H, 5.96; N, 11.87.

4.5. General procedure to obtain compounds 12–15

A solution of **7a** or **9a** (0.15 mmol) 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.

4.5.1. (6S,9R*,14aS*,15R*)-9-Benzyloxymethyl-N-isopropyloxycarbonyl-10,11,13-trimethoxy-12-methyl-5,6,9,14,14a,15-hexahydro-6,15-iminoisoquino[3,2-b]3-benzazocine-7-one (**12**).* According to the general procedure, compound **7a** (100 mg, 0.15 mmol) was cyclised and the crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (6:4) as eluant to give **12** (25 mg, 28% yield) and **13** (40 mg, 53% yield). Data for **12**. Yellow solid, Mp 90–91 °C. IR (NaCl) ν_{max} 2939, 1698, 1652 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.10 (m, 5H), 7.00 (m, 2H), 6.79 (m, 2H), 5.88 (dd, J=7.6 and 2.8 Hz, 1H), 5.32 (s, 0.6H), 5.20 (s, 0.4H), 5.07 (m, 0.3H), 4.94 (m, 0.7H), 4.88 (sp, J=6.3 Hz, 1H), 4.07 (m, 1H), 3.89 (d, J=14.2 Hz, 1H), 3.79 (d, J=14.2 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.62 (s, 3H), 3.46 (m, 2H), 3.12 (m, 2H), 3.07 (m, 1H), 2.80 (m, 1H), 2.11 (s, 3H), 1.10 (m, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.1, 154.1, 153.5, 150.0, 146.2, 138.2, 134.9, 132.6, 127.9, 127.1, 127.0, 124.5, 123.6, 122.6, 72.7, 70.9, 69.6, 60.2, 60.0, 59.9, 57.1, 53.4, 52.6, 49.3, 31.6, 28.8, 22.1, 9.3. Anal. Calcd for $C_{35}H_{40}N_2O_7$: C, 69.98; H, 6.71; N, 4.66. Found: C, 69.71; H, 6.48; N, 4.31.

4.5.2. (6S,9R*,14aS*,15R*)-9-Hydroxymethyl-N-isopropyloxycarbonyl-10,11,13-trimethoxy-12-methyl-5,6,9,14,14a,15-hexahydro-6,15-iminoisoquino[3,2-b]3-benzazocine-7-one (**13**).* Data for **13**: orange solid (40 mg, 53% yield). Mp 87–88 °C. IR (NaCl) ν_{max} 3412, 2940, 1787, 1704 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.11 (m, 4H), 6.04 (dd, J=9.4 and 3.7 Hz, 1H), 5.36 (s, 0.6H), 5.24 (s, 0.4H), 5.07 (d, J=6.5 Hz, 0.4H), 4.94 (d, J=6.5 Hz, 0.6H), 4.89 (sp, J=6.3 Hz, 1H), 4.51 (t, J=3.7 Hz, 0.4H), 4.47 (t, J=3.7 Hz, 0.6H), 4.09 (t, J=9.4 Hz, 1H), 3.82 (s, 3H), 3.71 (m, 1H), 3.69 (s, 3H), 3.62 (s, 3H), 3.19 (m, 1H), 3.15 (m, 1H), 3.10 (m, 1H), 2.82 (dd, J=13.8 and 9.9 Hz, 1H), 2.12 (s, 1.8H), 2.10 (s, 1.2H), 1.18 (m, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.9, 167.8, 154.0, 152.5, 152.4, 150.2, 150.1, 146.4, 146.3, 134.1, 133.9, 132.7, 132.1, 129.5, 129.3, 128.1, 127.9, 126.9, 126.8, 126.2, 125.9, 125.7, 125.6, 123.6, 123.3, 121.7, 121.6, 69.7, 69.6, 65.8, 65.6, 60.4, 60.0, 59.9, 57.1, 56.9, 53.4, 53.2, 52.4, 52.3, 47.6, 31.7, 31.6, 28.5, 28.4, 22.1, 22.0, 9.4. Anal. Calcd for $C_{28}H_{34}N_2O_7$: C, 65.87; H, 6.71; N, 5.49. Found: C, 65.62; H, 6.44; N, 5.18.

4.5.3. (6S,9R*,14aS*,15R*)-9-Benzyloxymethyl-N-isopropyloxycarbonyl-2,3,10,11,13-pentamethoxy-12-methyl-5,6,9,14,14a,15-hexahydro-6,15-iminoisoquino[3,2-b]3-benzazocine-7-one (**14**).* According to the general procedure, compound **9a** (50 mg, 0.29 mmol) was cyclised and the crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate (1:1) as eluant to give **14** (10 mg, 21% yield) and **15** (20 mg, 49% yield). Data for **14**. Yellow solid, Mp 98–99 °C. IR (NaCl) ν_{max} 2938, 1698, 1652 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.11 (m, 3H), 6.86 (m, 2H), 6.57 (s, 1H), 6.37 (s, 1H), 5.89 (dd, J=7.2 and 2.6 Hz, 1H), 5.23 (s, 0.7H), 5.12 (s, 0.3H), 5.05 (m, 0.3H), 4.94 (m, 0.7H), 4.89 (sp, J=6.3 Hz, 1H), 4.10 (m, 1H), 3.99 (d, J=11.9 Hz, 1H), 3.82 (d, J=11.9 Hz, 1H), 3.77 (s, 3H), 3.65 (s, 6H), 3.59 (s, 6H), 3.52 (m, 2H), 3.14 (m, 2H), 3.07 (m, 1H), 2.82 (m, 1H), 2.10 (s, 3H), 1.16 (m, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.0, 154.2, 152.3, 149.9, 148.5, 147.8, 146.1, 138.3, 128.0, 127.1, 126.8, 126.5, 124.7, 124.4, 123.6, 111.4, 108.9, 72.8, 71.3, 69.5, 60.2, 59.9, 56.9, 55.9, 55.7, 53.4, 53.1, 52.4, 52.3, 49.6, 31.3, 28.8, 22.1, 9.3. Anal. Calcd for $C_{37}H_{44}N_2O_9$: C, 67.26; H, 6.71; N, 4.24. Found: C, 66.85; H, 6.62; N, 3.95.

4.5.4. (6S,9R*,14aS*,15R*)-9-Hydroxymethyl-N-isopropyloxycarbonyl-2,3,10,11,13-pentamethoxy-12-methyl-5,6,9,14,14a,15-hexahydro-6,15-iminoisoquino[3,2-b]3-benzazocine-7-one (**15**).* Data for **15**: Orange solid, Mp 85–86 °C. IR (NaCl) ν_{max} 2939, 1790, 1700 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 6.57 (s, 1H), 6.50 (s, 1H), 6.04 (dd, J=9.6 and 3.7 Hz, 1H), 5.26 (s, 0.7H), 5.23 (s, 0.3H), 5.05 (m, 0.3H), 4.98 (m, 0.7H), 4.92 (sp, J=6.3 Hz, 1H), 4.52 (m, 1H), 4.20 (m, 1H), 3.82 (s, 3H), 3.78 (s, 6H), 3.71 (m, 1H), 3.69 (s, 3H), 3.62 (s, 3H), 3.16 (m, 2H), 3.10 (m, 1H), 2.87 (m, 1H), 2.12 (s, 3H), 1.16 (m, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.9, 154.1, 152.5, 150.2, 148.8, 148.1, 146.3, 125.6, 124.3, 123.6, 123.4, 111.5, 111.3, 108.9, 108.6, 69.7, 69.5, 65.9, 65.6, 60.5, 60.0, 59.9, 56.9, 56.6, 56.0, 55.7, 53.4, 52.1, 47.7, 31.3, 28.5, 22.2, 22.1, 9.4. Anal. Calcd for $C_{30}H_{38}N_2O_9$: C, 63.14; H, 6.71; N, 4.91. Found: C, 62.92; H, 6.48; N, 4.72.

4.5.5. (3S,6R*)-3-Benzyl-6-benzyloxymethyl-7,8,10-trimethoxy-9-methyl-1,2,3,6-tetrahydro-pyrazino[1,2-b]isoquinolin-4-one (**16**).* To a solution of **7b** (100 mg, 0.16 mmol) in dry DCM (5 mL) under argon, and molecular sieves as dry agent, trifluoroacetic acid (0.3 mL) was added and reaction was refluxed for 2 h. Then, cooled reaction was quenched by addition over a saturated aqueous solution of $NaHCO_3$ filtered 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 chromatography on a silica gel column with hexane/ethyl acetate (8:2) as eluant to afford **16** (85 mg, 88% yield) as an orange solid. Mp 68–69 °C. IR (film) ν_{max} 2930, 1684 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.19 (m, 10H), 6.36 (dd, J=8.7 and 4.2 Hz, 1H), 5.73 (s, 1H), 4.59 (d, J=11.9 Hz, 1H), 4.35 (d, J=11.9 Hz, 1H), 3.79 (s, 3H), 3.75 (m, 2H), 3.71 (s, 3H), 3.62 (m, 1H), 3.60 (s, 3H), 3.50 (m, 1H), 3.33 (m, 1H), 3.29 (m, 1H), 2.94 (dd, J=14.0 and 9.0 Hz, 1H), 2.09 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ. 169.0, 150.3, 149.0, 145.7, 138.2, 138.1, 133.6, 129.6, 129.5, 128.2, 127.8, 127.5, 126.7, 125.1, 120.5, 120.3, 98.7, 72.6, 69.8, 61.2, 60.7, 60.3, 60.2, 46.7, 44.7, 37.1, 9.3. Anal. Calcd for $C_{31}H_{34}N_2O_5$: C, 72.35; H, 6.66; N, 5.44. Found: C, 72.16; H, 6.34; N, 5.29.

4.5.6. (4S,7R*,12aS*,13R*)-6-Benzyloxymethyl-2-bromo-N-isopropyloxycarbonyl-8,9,11-trimethoxy-10-methyl-3,4,7,12,12a,13-hexahydro-4,13-iminoisoquino[2,3-a]azocin-5-one (**17**).* To a solution of **11a** (23 mg, 0.036 mmol) in dry DCM (5 mL) under argon, at −78 °C and molecular sieves as dry agent, trifluoroacetic acid (0.5 mL) was added and reaction was stirred at room temperature for 24 h. Then the reaction was quenched by addition over a saturated aqueous solution of $NaHCO_3$, filtered 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 chromatography on a silica gel column with hexane/ethyl acetate (1:1) as eluant to afford **17** (13 mg 58% yield) as a yellow oil. IR (NaCl) ν_{max} 1699, 1497, 1367 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 7.30–720 (m, 5H), 6.22 (d, J=4.5 Hz, 0.8H), 6.18 (d, J=4.5 Hz, 0.2H), 6.03 (m, 1H),

5.02 (m, 1H), 4.95 (dd, *J*=18.2 and 6.0 Hz, 1H), 4.80 (t, *J*=7.2 Hz, 1H), 4.64 (d, *J*=11.9 Hz, 1H), 4.43 (d, *J*=11.9 Hz, 1H), 3.94 (dd, *J*=8.5 and 3.5 Hz, 1H), 3.89 (s, 3H), 3.85–3.75 (m, 2H), 3.79 (s, 3H), 3.67 (s, 3H), 2.96 (m, 2H), 2.78 (m, 2H), 2.20 (s, 3H), 1.32 (m, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.3, 153.8, 152.3, 150.0, 146.1, 138.2, 128.4, 127.7, 127.5, 127.2, 124.5, 123.2, 123.1, 121.7, 73.1, 70.7, 69.7, 60.3, 59.9, 59.8, 54.0, 52.6, 50.9, 48.9, 37.5, 28.2, 22.1, 9.3. Anal. Calcd for $C_{31}H_{37}BrN_2O_7$: C, 59.14; H, 5.92; N, 4.45. Found: C, 58.86; H, 5.73; N, 4.07.

4.6. General procedure to obtain compounds 18 and 19

To trifluoromethanesulfonic acid (2 mL, 23 mmol) was added compound **7a**, **7b** or **9b** (0.23 mmol) in one portion, and the mixture was stirred for 1 h at room temperature under argon atmosphere. Then, the reaction mixture was poured into 3 mL ice water, basified with saturated aq $NaHCO_3$ and extracted with ethyl acetate. The organic extracts were washed with saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo.

4.6.1. (6S,9R*,14aS*,15R*)-9-Hydroxymethyl-10,11,13-trimethoxy-12-methyl-5,6,9,14,14a,15-hexahydro-6,15-iminoisoquino[3,2-b]3-benzazocine-7-one (**18**).* The reaction was performed with 190 mg (0.30 mmol) of compound **7b**. The crude product was purified by flash chromatography on silica gel with ethyl acetate/methanol (9:1) as eluant to give **18** (90 mg, 71% yield) as an orange solid. Mp 113–114 °C. IR (film) ν_{max} 3330, 2936, 1634 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24 (m, 2H), 7.18 (m, 2H), 5.80 (dd, *J*=8.7 and 4.0 Hz, 1H), 4.11 (s, 1H), 3.95 (dd, *J*=5.5 and 1.9 Hz, 1H), 3.79 (s, 3H), 3.71 (m, 1H), 3.70 (s, 3H), 3.65 (s, 3H), 3.64 (dd, *J*=11.2 and 4.0 Hz, 1H), 3.27 (dd, *J*=11.2 and 8.7 Hz, 1H), 3.08 (m, 2H), 3.02 (m, 2H), 2.12 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.2, 152.3, 150.0, 146.3, 136.7, 132.8, 129.4, 127.7, 126.8, 126.2, 124.5, 124.2, 123.1, 64.0, 60.3, 60.0, 59.9, 56.7, 54.0, 53.8, 51.2, 33.1, 29.0, 9.3. Anal. Calcd for $C_{24}H_{28}N_2O_5$: C, 67.91; H, 6.65; N, 6.60. Found: C, 67.64; H, 6.28; N, 6.39.

4.6.2. (6S,9R*,14aS*,15R*)-9-Hydroxymethyl-2,3,10,11,13-pentamethoxy-12-methyl-5,6,9,14,14a,15-hexahydro-6,15-iminoisoquino[3,2-b]-3-benzazocine-7-one (**19**).* The reaction was performed with 60 mg (0.084 mmol) of compound **9b**. The crude product was purified by flash chromatography on silica gel with ethyl acetate/methanol (9:1) as eluant to give an orange solid **19** (30 mg, 74% yield). Mp 109–110 °C. IR (film) ν_{max} 3350, 2938, 1632 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.63 (s, 1H), 6.61 (s, 1H), 5.90 (dd, *J*=8.6 and 3.9 Hz, 1H), 4.18 (s, 1H), 4.08 (m, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.82 (m, 1H), 3.80 (dd, *J*=11.0 and 3.9 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.45 (dd, *J*=11.0 and 8.6 Hz, 1H), 3.17 (m, 2H), 3.16 (m, 2H), 2.22 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.9, 152.3, 150.1, 148.7, 147.9, 146.4, 127.9, 124.7, 124.6, 124.1, 123.4, 111.5, 108.7, 64.4, 60.3, 60.0, 59.9, 56.6, 55.9, 55.8, 53.8, 53.6, 51.5, 32.5, 29.1, 9.3. Anal. Calcd for $C_{26}H_{32}N_2O_7$: C, 64.45; H, 6.66; N, 5.78. Found: C, 64.03; H, 6.22; N, 5.52.

Acknowledgements

This work was supported by CICYT CTQ2006-10930/BQU and Comunidad Autónoma de Madrid (Group 920234 grant). A FPI fellowship to I. Ortín and the collaboration of J. Lamariano in the synthesis of compounds **11a** and **19** are also acknowledged.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.10.016.

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