Tetrahedron 66 (2010) 9061–9066

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis of (±)-phthalascidin 650 analogue: new synthetic route to (±)-phthalascidin 622

Christian R. Razafindrabe [a,b], Sylvain Aubry [b], Benjamin Bourdon [b], Marta Andriantsiferana [a], Stéphane Pellet-Rostaing [b,c,*], Marc Lemaire [b,*]

[a] Laboratoire de Chimie des Produits Naturels et Biotechnologie (LPNB), Université d'Antananarivo, 17 Cité Mahatazana, Ampandrianomby, 101 Antananarivo, Madagascar
[b] ICBMS, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, CNRS, UMR5246, Laboratoire de Catalyse et Synthèse Organique, 43 boulevard du 11 novembre 1918, Villeurbanne F-69622, France
[c] ICSM, institut de Chimie Séparative de Marcoule, CNRS/CEA/UM2/ENSCM, UMR 5257, Laboratoire de Tri Ionique par des Systèmes Moléculaires auto-assemblés, Bat 426, route de Marcoule, 30207 Bagnols sur Cèze, France

ARTICLE INFO

Article history:
Received 9 July 2010
Received in revised form 17 August 2010
Accepted 20 August 2010
Available online 25 August 2010

ABSTRACT

A synthesis of functionalized phenolic α-amino-alcohol (±)-**13** as synthetic precursor of the catechol tetrahydroisoquinoline structure of phthalascidin 650 is disclosed. Starting from 3-methylcatechol **5**, eight steps of synthesis give rise to the synthesis of phenolic α-amino-alcohol (±)-**13** in 27% overall yield. This synthetic strategy involves the elaboration of fully functionalized aromatic aldehyde **8** and its transformation into a phenolic α-amino-alcohol (±)-**13**, through a Knoevenagel condensation, simultaneous reduction of nitroketene and ester functions and hydrogenolysis of the benzyl protecting group. The pentacycle (±)-**18** was obtained after four additional steps. The Pictet–Spengler cyclisation between the phenolic α-amino-alcohol (±)-**13** and *N*-protected α-amino-aldehyde **4** allowed to obtain (1,3′)-bis-tetrahydroisoquinoline **14** with *N*-methylated and *N*-Fmoc removed. The last step was a Swern oxidation for allowing an intramolecular condensation.

1. Introduction

The interest for the tetrahydroisoquinoline alkaloids is essentially aroused from their natural architectural complexity and their noteworthy biological properties as antitumour antibiotics.[1] The most active member of this family, Ecteinascidin 743 (**1**, Et 743) was isolated from the Caribbean tunicate *Ecteinascidia turbinate*[2] (Fig. 1) and displayed highly potent cytotoxic activity against a variety of tumour cancer cells in vitro[3] and is approved for the treatment of soft tissue sarcoma under the brand name of Yondelis. The natural scarcity and potent medical use of Et 743 have attracted several groups to embark on its total synthesis.[4] With regard to the structural complexity of Et 743 and its relative unstability in solution, synthetic phthalascidins analogues were envisaged. Thus, the synthesis and biological evaluation of Pt 650 **2** were first reported by Corey[4b,5] and exhibited similar biological activity to the natural

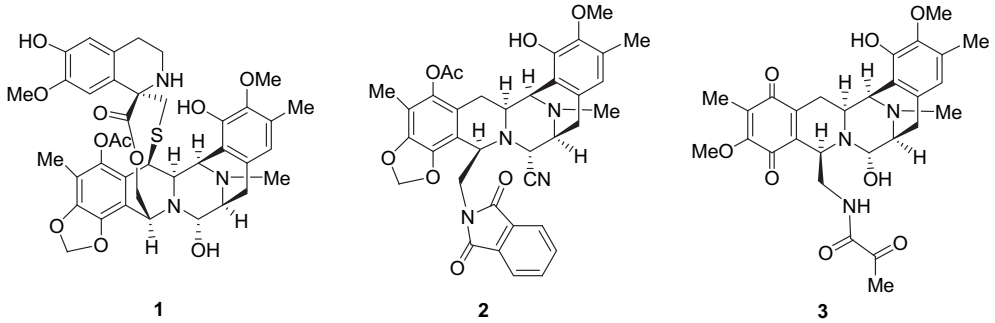


Fig. 1. Ecteinascidin 743 (**1**), Phthalascidin 650 (**2**) and Cyanosafracin B (**3**).

* Corresponding authors. E-mail address: stephane.pellet-rostaing@cea.fr (S. Pellet-Rostaing).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.08.053

product. A semi-synthetic route was achieved by Cuevas[6] through fermentation of the bacteria *Pseudomonas fluorescens* to produce cyanosafracin B (**3**),[7] an antibiotic of bacterial origin.

In our previous communications, we reported the synthesis of a functionalized *N*-protected α-amino-aldehyde bearing a phthalimidomethyl function constituting the sesamol tetrahydroisoquinoline scaffold of phthalascidin 650 by a new synthetic approach involving a Bischler–Napieralski reaction.[8] Our ongoing project concerning the synthesis and biological evaluation of Pt 650 synthetic analogues,[9] encouraged us towards the synthesis of the iminobenzazocine pentacyclic system contained in the Pt 650 starting from 3-methylcatechol **5**.

Herein, we report an efficient synthesis of a functionalized phenol α-amino-alcohol as precursor for the building block of the tetrahydroisoquinoline alkaloid (±)-phthalascidin 650 by Pictet–Spengler condensation with *N*-protected α-amino-aldehyde **4**. Then, we could considered after suitable functionalization (nitrogen methylation and Fmoc deprotection), an intramolecular Strecker cyclisation to give rise to the formation of a (±)-Pt 650 analogue containing a methoxy group in place of the classical acetoxy group (Fig. 2). This 16-[(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)methyl]-6,6a,7,13,14,16-hexahydro-8-hydroxy-5,9-dimethoxy-4,10,17-trimethyl-7,13-Imino-12*H*-1,3-dioxolo [7,8]isoquino[3,2-b]3-benzazocine (phthalascidin 622 **18**) was already obtained and evaluated by Corey.[5a]

compatible for the stereoselectivity and regioselectivity of the Pictet–Spengler cyclization.[4d,10]

We started our synthesis with the commercially available 3-methylcatechol **5** by a regioselective isopropylation of the less hindered hydroxyl group in presence of *i*-PrBr and K_2CO_3 in a 2:1 mixture of DMF/acetone to give **6a** in 69% yield as previously described (Scheme 1).[11] The resulting compound **6a** was then formylated in the Duff conditions with HMTA in AcOH at 100 °C to give **7a** in 85% yield[12] and subsequent methylation of the free hydroxyl group in acetone by Me_2SO_4 in the presence of K_2CO_3 took place, giving the aldehyde **8** in 88% yield. The isopropyl group of **8** was then cleaved with $AlCl_3$ allowing to **9** in 83% yield and the resultant hydroxyl group protected by BnBr in DMF to produce **10** in 94% yield. An alternative route for the preparation of **10** was also performed based on the direct regioselective benzylation of **5** with BnBr, followed by Duff formylation. Then, O-methylation of the residual hydroxyl group gave **10** in a global yield of 85% in three steps.

By a Knoevenagel condensation a 1:1 mixture of *E*/*Z* nitroketene **11** was obtained in 74% yield.[13] The lower yield in comparison to those obtained for the Knoevenagel condensation with sesamol derivative[8] could be explained by a partial cleavage of the benzyl protecting group by $TiCl_4$ and confirmed by lowering the $TiCl_4$ stoichiometry. Compound **11** was then reduced with $LiAlH_4$ to afford the corresponding racemic α-amino-alcohol **12** in 93% yield.

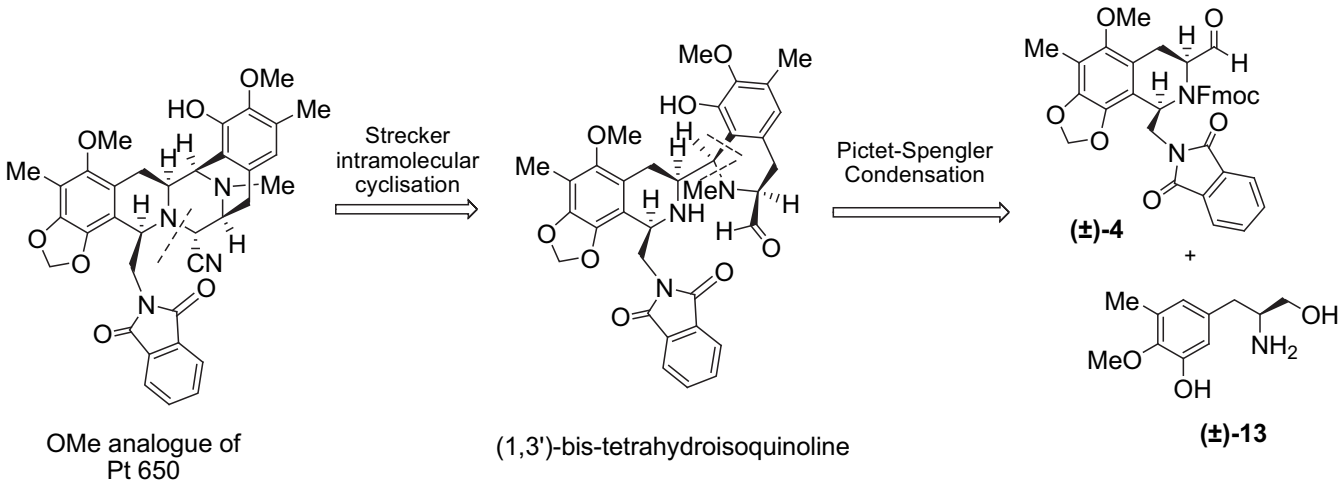
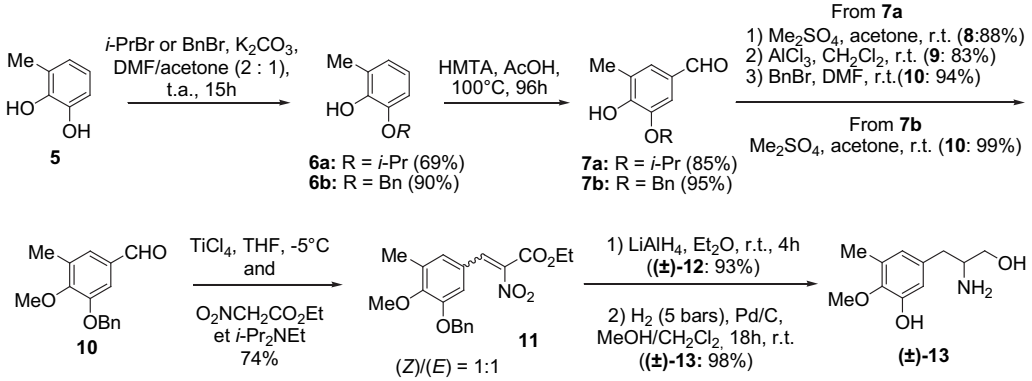


Fig. 2. Retrosynthetic analysis of Phthalascidin 650.



Scheme 1. Synthesis of phenolic α-amino-alcohol **13**.

2. Results and discussion

At first, we focused on the synthesis of a phenolic α-amino-alcohol synthetic precursor, which could be readily accessible and

Finally, hydrogenolysis of the benzyl group of **12** was realized in presence of Pd/C under 5 bar of H_2 in a 1:1 mixture of MeOH/CH_2Cl_2, to obtain the corresponding phenol **13** in 98% yield.[13] The synthesis of phenolic α-amino-alcohol **13** has been conducted in six

steps of classical chemical transformation with an overall yield of 57% through a Knoevenagel condensation.

The iminobenzazocine pentacyclic system **18** was finally obtained in four steps from the preliminary Pictet–Spengler condensation of the diastereoisomer **4** with the racemic amino-alcohol **13** (Scheme 2). Cyclisation was performed at 80 °C in a 85:15 mixture of toluene/TFA[14,15] to give a mixture of (1, 3′)-bistétrahydroisoquinolines as two regioisomers **14** and **15**, respectively, in 33% and 18% yields. Isomers **14** arised from cyclization *ortho*- to the 3-phenolic group of **13**, and **15** from cyclization *para*- to the same 3-phenolic group. The complete stereochemical assignments of (1,3′)-bistetrahydroisoquinolines was achieved by NMR. Structural elucidation of **14** and **15** was determined by 2D NMR (HSQC, COSY, HMBC and NOESY techniques). Moreover, **14** and **15** were obtained as mixtures of two diastereoisomers. The *syn* configuration of diastereoisomers **14** and **15** was determined on the basis of the 500 MHz NOESY spectrum analysis from a correlation analysis of the cross-peak protons between H-1 and H-3′. After methylation of the secondary amine of **14** in the Eschweiler Clarke conditions (HCO_2H/HCOH, 2:1.7),[16] the cleavage of the *N*-Fmoc group of **16** occurred by treatment with DBU affording the amine **17** in 67% yield. Finally, **18** was obtained in 72% yield by an intramolecular Stecker reaction based on the Swern oxidation of the primary alcohol of **17** followed the treatment of the corresponding hemiaminal formed in situ with TMSCN.

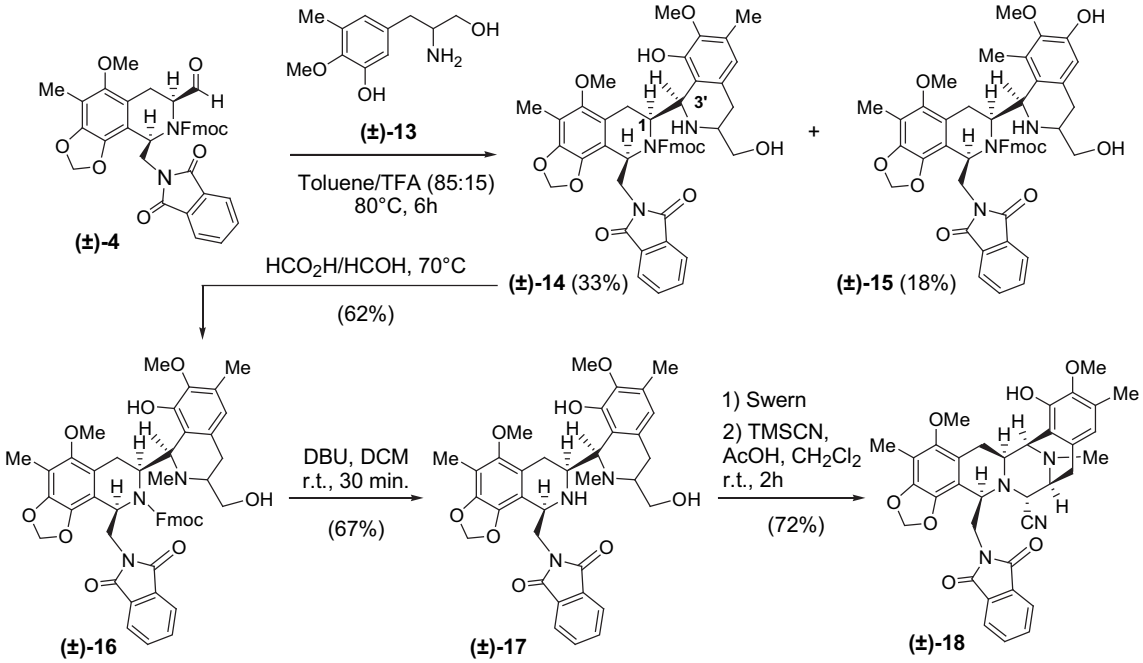
cross peaking correlation with the OH group at 5.75 ppm. COSY experiment allowed us to assign all of the resonance signals to the corresponding protons and the proposed stereochemistry of **18** was confirmed by NOESY experiment, especially for the *cis* position of H_4, H_3 and H_{11} as well as the *anti* position of H_{21} towards H_1 and H_{13}, which is also in trans with $H_{14'}$. HSQC experiment allowed us to attribute all of the primary, secondary and tertiary carbons. Finally, resonance signals of the quaternary carbons were deduced from the HMBC experiment.

To conclude, a practical synthesis of fully functionalized phenolic α-amino-alcohol (±)-**13**, which constitutes the catechol aromatic fragment of the tetrahydroisoquinoline of (±)-Pt 622, has been synthesized in six steps from 3-methylcatechol **5** with an overall yield of 57%. Four additional steps involving a Pictet–Spengler condensation from the synthetic precursors (±)-**4** and (±)-**13**, Pt 622 **18** was finally obtained in an overall yield of 5.6%.

3. Experimental section

3.1. General

Starting materials were obtained from commercial suppliers and used without further purification. Solvents were distilled prior to use. Flash chromatographic purification was carried out on 230–400 mesh silica gel 60. NMR spectra were recorded on DRX 300 and 500 Brücker



Scheme 2. Synthesis of (±)-Pt 622 **18**.

High-resolution EI-MS of (±)-phtalascidin 622 **18** demonstrated a molecular composition of $C_{35}H_{35}O_7N_4$ $(M+H)^+$ by observation of the peak at a *m*/*z* 623.2510 (Δ −0.4 mmu). The lack of published data for **18** frustrated our attempts to identify our sample by simple comparison of NMR data. Therefore, extensive analyses of spectral data were necessary to confirm the structure. All protons and carbons were assigned by NMR experiments including COSY, HSQC, HMBC and NOESY techniques (Figs. 3 and 4).

More especially, the resonance signal of the residual aromatic proton H_{15} was located at 6.41 ppm based on the cross peaking correlation with H_{14}, $H_{14'}$ and Me_{16} resonance signals identified from the COSY and NOESY spectra and located at 2.24 ppm, 2.62 ppm and 3.07 ppm, respectively. From these hypotheses, OMe_{17} was characterized by a singlet at 3.74 ppm, which was confirmed by a NOESY FT spectrometers. Abbreviation was used as: s (singlet), d (doublet), dd (divided doublet), t (triplet), q (quadruplet), m (multiplet).

3.1.1. 4-Hydroxy-3-isopropoxy-5-methylbenzaldehyde ***7a***. A solution of **6a** (5 g, 30.12 mmol) in AcOH (150 mL) and HMTA (10.54 g, 75.3 mmol) was stirred at 100 °C for 96 h. After this period, the solution was cooled and a saturated solution of $NaHCO_3$ was added. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The organic layer was dried over $MgSO_4$, evaporated and purified by flash column chromatography (silica gel, cyclohexane) to give **7a** in 85% yield (4.97 g), R_f=0.3 (cyclohexane/AcOEt=9:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ=9.77 (s, 1H, CHO), 7.26 (s, 1H, Ar*H*), 7.25 (s, 1H, Ar*H*), 6.32 (s, 1H, OH), 4.68 (sept, 1H, *J*=6.0 Hz, *CH*(CH_3)$_2$), 2.31 (s, 3H, CH_3), 1.38 (d, 6H, *J*=6.0 Hz, CH(*CH*$_3$)$_2$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ=191.6 (CHO), 151.0

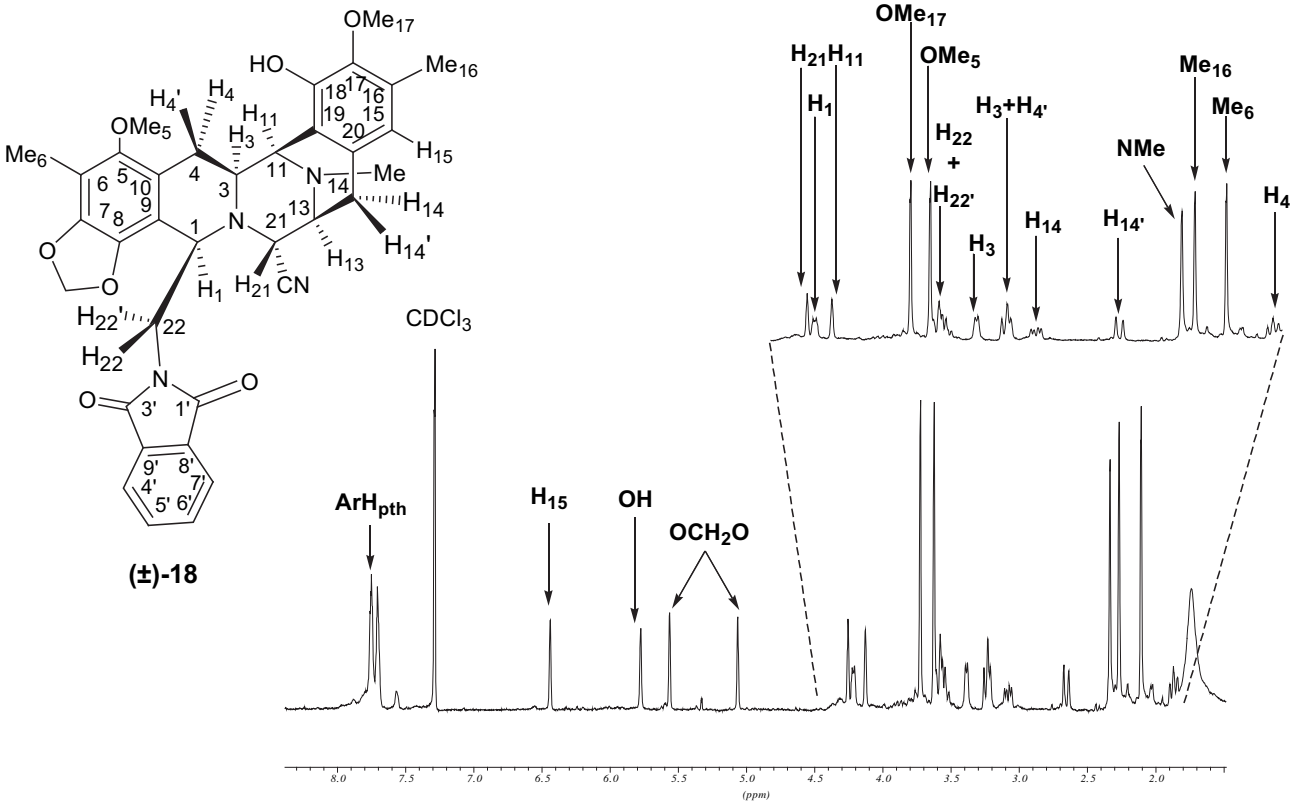


Fig. 3. ^{1}H NMR spectrum of **18** ($CDCl_3$).

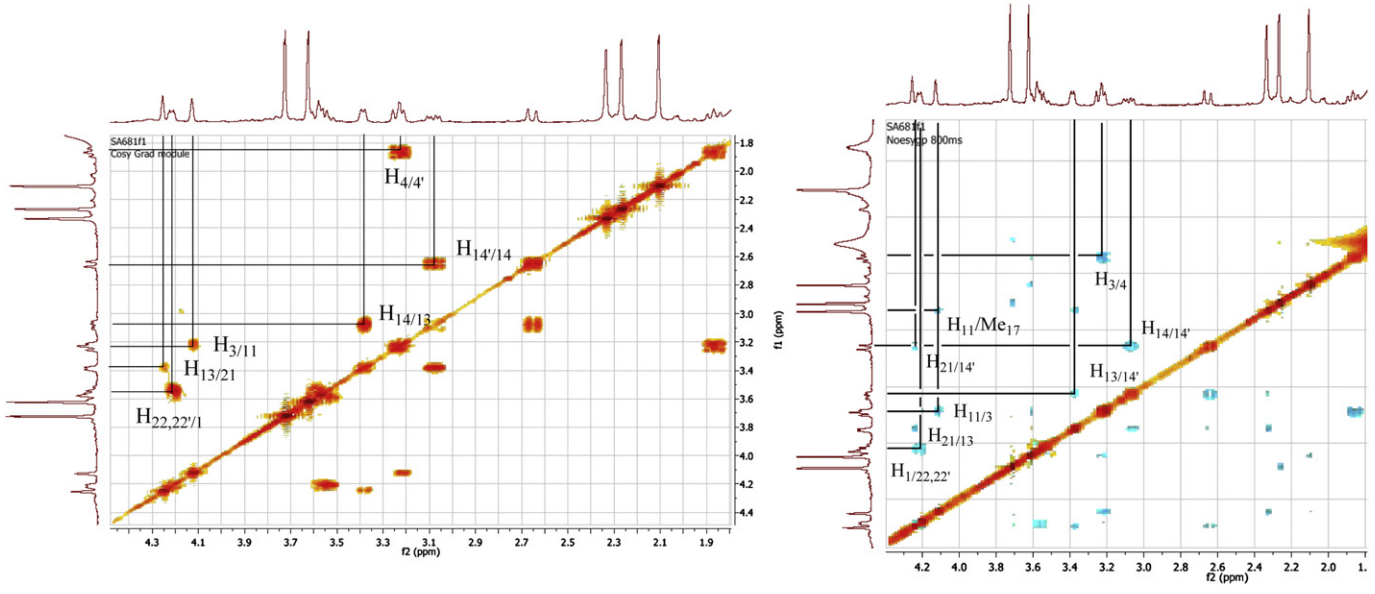


Fig. 4. 2D COSY and NOESY spectra of **18** ($CDCl_3$).

(Ar*C*), 145.1 (Ar*C*), 129.1 (Ar*C*H), 128.8 (Ar*C*H), 124.5 (Ar*C*), 109.3 (Ar*C*), 72.3 (*C*H(CH_3)$_2$), 22.4 (CH(CH_3)$_2$), 15.8 (CH_3). ESI-MS: *m*/*z* (%)=194 $[M]^+$ (27), 152 $[M-C_3H_6]^+$ (82), 151 $[M-C_3H_7]^+$ (100). Anal. Calcd for $C_{11}H_{14}O_3$ C 68.02; H 7.27%, found C 68.07; H 7.37%.

3.1.2. 3-Isopropoxy-4-methoxy-5-methylbenzaldehyde ***8***. To a solution of **7a** (38.1 g, 0.196 mmol) was added K_2CO_3 (81.4 g, 0.589 mmol) in acetone (212 mL) and Me_2SO_4 (49.5 g, 0.393 mmol) dropwise. After stirring at room temperature for 4 h, the reaction mixture was filtered and the solid washed with Et_2O. The organic layer was washed with a 1.5 N HCl solution (180 mL) and 1 N NaOH solution (200 mL). Then, the residue was extracted with Et_2O, dried over $MgSO_4$, evaporated and purified by flash column chromatography (silica gel, cyclohexane/AcOEt=100:2→95:5) to yield **8** as a pale yellow oil (35.8 g, 88%), R_f=0.6 (cyclohexane/ACOEt=9:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ=9.75 (s, 1H, C*H*O), 7.20 (s, 1H, ArH), 7.19 (s, 1H, ArH), 4.56 (sept, 1H, *J*=6.0 Hz, C*H*(CH_3)$_2$), 3.82 (s, 3H, OCH_3), 2.22 (s, 3H, CH_3), 1.31 (d, 6H, *J*=6.0 Hz, CH (*CH*$_3$)$_2$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ=191.8 (*C*HO), 154.2 (Ar*C*), 151.5 (Ar*C*), 133.0 (Ar*C*H), 132.3 (Ar*C*H), 127.1 (Ar*C*), 112.1 (Ar*C*), 71.2 (*C*H(CH_3)$_2$), 60.5 (OCH_3), 22.4

($CH(CH_3)_2$), 16.4 (CH_3). EI-MS: *m*/*z* (%)=208 $[M]^+$ (36), 166 $[M-C_3H_6]^+$ (100), 165 $[M-C_3H_7]^+$ (56), 151 $[M-CH_3-C_3H_6]^+$ (30), 123 $[M-C_3H_6-CH3-CO]^+$ (22). Anal. Calcd for $C_{12}H_{16}O_3$ C 69.21; H 7.74%, found C 69.03; H 7.93%.

3.1.3. 3-Hydroxy-4-methoxy-5-methylbenzaldehyde ***9***. To a stirring solution of **8** (1 g, 4.81 mmol) in CH_2Cl_2 (18.4 mL) was added $AlCl_3$ (1.85 g, 13.94 mmol) at room temperature. After stirring for 90 min, the reaction mixture was hydrolyzed with NH_4Cl (50 ml) and the aqueous layer extracted with CH_2Cl_2 (3×50 mL). Then, the organic layers weres dried with $MgSO_4$, evaporated and purified by flash column chromatography (silica gel, cyclohexane/AcOEt=90:10→80:20) to yield **9** as pale yellow oil (0.666 g, 83%), R_f=0.4 (cyclohexane/AcOEt=8:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ=9.76 (s, 1H, CHO), 7.25 (d, 1H, *J*=2.0 Hz, ArH), 7.20 (m, 1H, *J*=2.0 Hz ArH), 6.10 (s, 1H, OH), 3.80 (s, 3H, OCH_3), 2.29 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ=192.13 (*C*HO), 151.29 (Ar*C*), 149.99 (Ar*C*), 133.23 (Ar*C*), 132.11 (Ar*C*), 125.68 (Ar*C*H), 114.31 (Ar*C*H), 61.09 (OCH_3), 16.48 (CH_3). EI-MS: *m*/*z* (%)=166 $[M]^+$ (100), 151 $[M-CH_3]^+$ (21), 123 $[M-CH_3CO]^+$ (60). Anal. Calcd for $C_9H_{10}O_3$ C, 65.05; H, 6.07%, found C, 65.00; H, 6.15%.

3.1.4. 3-(Benzyloxy)-4-methoxy-5-methylbenzaldehyde ***10***. To a solution of **9** (600 mg, 3.61 mmol) was added K_2CO_3 (1.5 g, 10.84 mmol) in DMF (12 mL) and BnBr (680 mg, 3.97 mmol). After stirring at room temperature for 2 h, the reaction mixture was filtered and the solid washed with Et_2O (100 mL). The organic layer was washed with a 1.5 N HCl solution (20 mL). Then, the residue was extracted with Et_2O (3×50 mL), dried over $MgSO_4$, evaporated and purified by flash column chromatography (silica gel, cyclohexane/ethyl acetate=8:2) to yield **10** as an orange oil (870 mg, 94%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ=9.75 (s, 1H, C*H*O), 7.45 (m, 5H, Ar*H*), 7.33 (m, 2H, Ar*H*), 5.16 (s, 2H, CH_2), 3.93 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ=191.8 (*C*HO), 153.7 (Ar*C*O), 152.7 (Ar*C*O), 136.8 (2C, Ar*C*), 133.0 (Ar*C*), 132.4 (Ar*C*H), 129.0 (Ar*C*H), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 111.0 (Ar*C*H), 71.1 (CH_2), 60.8 (OCH_3), 16.5 (CH_3). EI-MS: *m*/*z* (%)=256 $[M]^+$ (5), 228 $[M-CO]^+$ (4), 165 $[M-CH_2C_6H_5]^+$ (3), $[C_6H_5CH_2]^+$ (100). Anal. Calcd for $C_{16}H_{16}O_3$: C 74.98, H 6.29%, found C 75.45, H 6.36%.

3.1.5. 2-Amino-3-(3-(benzyloxy)-4-methoxy-5-methylphenyl) propan-1-ol ***12***. To a stirred solution of $TiCl_4$ (2.66 g, 14.04 mmol) in THF (9 mL) was added dropwise at −5 °C **10** (0.6 g, 2.34 mmol) contained in THF (4.1 mL). After stirring at room temperature for 30 min, ethyl nitroacetate (0.685 g, 5.15 mmol) was added at −5 °C. Then, the mixture was stirred for an additional time of 30 min and *i*-Pr_2NEt (2.76 g, 21.09 mmol) was added. The mixture was then stirred at room temperature stirring for 24 h and H_2O (20 mL) was added. The residue was extracted with CH_2Cl_2 (3×50 mL). The organic layer was washed with brine, dried over $MgSO_4$, evaporated and purified by flash column chromatography (SiO_2, cyclohexane/AcOEt=100:0→90:10) to yield a 40:60 mixture of **11** as a yellow oil (0.64 g, 74%). Nitroesters **11** (0.2 g, 0.539 mmol) was then reduced with $LiAlH_4$ (0.205 g, 5.39 mmol) in a stirred solution of Et_2O (12 mL), under an atmosphere of argon. After stirring at room temperature for 4 h, CH_2Cl_2 (25 mL), H_2O (0.2 mL), 2 N NaOH (0.2 mL) and H_2O (0.6 mL) were added at 0 °C until a white solid appears. The mixture was then filtered and the solid washed with CH_2Cl_2 (3×30 mL), dried over Na_2SO_4, evaporated to yield **12** as a pale yellow oil (151 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.48 (d, 2H, *J*=7.23 Hz, ArH), 7.42 (m, 2H, ArH), 7.35 (m, 1H, *J*=7.3 Hz, ArH), 6.66 (s, 1H, ArH), 6.65 (s, 1H, ArH), 5.14 (s, 2H, CH_2), 3.87 (s, 3H, CH_3), 3.61 (dd, 1H, *J*=10.8, 3.8 Hz, CH_AH_B), 3.38 (dd, 1H, 10.8, 7.0 Hz, CH_AH_B), 3.08 (m, 1H, CH), 2.94 (m, 1H, OH), 2.7 (dd, 1H, *J*=13.6, 5.1 Hz, CH_CH_D), 2.43 (m, 1H, CH_AH_B), 2.29 (s, 3H, CH_3), 2.26 (br s, 21H, NH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ=152.0 (Ar*C*O), 147.0 (Ar*C*O), 137.6 (Ar*C*), 134.3 (Ar*C*), 132.5 (Ar*C*), 128.9 (2C, Ar*C*H), 128.3 (Ar*C*H), 127.7 (2C, Ar*C*H), 124.3 (Ar*C*H), 113.5 (Ar*C*H), 71.1 (CH_2), 66.7 (CH_2), 60.6 (OCH_3), 54.5 (CH), 40.9 (CH_2), 16.3 (CH_3). ESI-MS: *m*/*z* (%)=302 $[M+H]^+$ (100), 272 $[M+H-CH_3OH]^+$ (21), 241 $[M+H-H_3NCHCH_2OH]^+$ (13). HRMS (ESI) calcd for $C_{18}H_{23}NO_3Na$ $[M+Na]^+$ 324.1576, found 324.1577. Anal. Calcd for $C_{18}H_{23}NO_3$: C 71.73, H 7.69, N 4.65%, found C 71.54, H 7.80, N 4.52%.

3.1.6. (±)-5-(2-Amino-3-hydroxypropyl)-2-methoxy-3-methylphenol ***13***[17]. A mixture of **12** (0.16 g, 0.532 mmol) and 10% Pd/C (64 mg), in 1:1 mixture of MeOH/CH_2Cl_2 (9 mL), was stirred overnight at room temperature under 5 bar of H_2 atmosphere. After the catalyst was filtered, washed with MeOH and dried over Na_2SO_4 and evaporated to give **13** as a colourless oil (110 mg, 98%). ^{1}H NMR (MeOD, 500 MHz) δ=6.65 (d, 1H, *J*=1.9 Hz, Ar*H*), 6.6 (d, 1H, *J*=1.0 Hz, Ar*H*), 4.93 (s, 4H, NH_2, ArCOH, OH), 3.77 (s, 3H, OCH_3), 3.71 (m, 1H, OCH_AH_B), 3.53 (dd, 1H, *J*=11.7, 1.3 Hz, OCH_AH_B), 3.39 (br, 1H, CH), 2.79 (d, 2H, *J*=7.5 Hz, CH_2CHN), 2.25 (s, 3H, CH_3). ^{13}C NMR (MeOH, 125 MHz) δ=150.4 (Ar*C*O), 145.5 (Ar*C*O), 132.1 (Ar*C*), 132.0 (Ar*C*), 122.5 (Ar*H*), 115.0 (Ar*H*), 60.9 (OCH_2), 59.4 (OCH_3), 54.8 (CH), 35.3 (CH_2CHN), 15.0 (CH_3). ESI-MS: *m*/*z* (%)=212 $[M+H]^+$ (100), 151 $[M+H-H_3NCHCH_2OH]^+$ (40). HRMS (EI) calcd for $C_{11}H_{17}O_3N$ $[M]^+$ 211.1208, found 212.1207.

3.1.7. (7S,9R)-(9H-Fluoren-9-yl)methyl 9-((1,3-dioxoisoindolin-2-yl) methyl)-7-((1R,3S)-8-hydroxy-3-(hydroxymethyl)-7-methoxy-2,6-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-5-methoxy-6,7-dihydro-[1,3] dioxolo[4,5-h]isoquinoline-8(9H)-carboxylate ***14***. A mixture of aldehyde **4** (550 mg, 0.873 mmol) and (±)-5-(2-amino-3-hydroxypropyl)-2-methoxy-3-methylphenol **13** (368 mg, 1.74 mmol) in 7:3 mixture of toluene/TFA (4.7 mL) was stirred overnight at 80 °C. Then, the reaction mixture was neutralized with a saturated Na_2CO_3 aqueous solution (15 mL) at 0 °C and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The organic layer was dried over Na_2SO_4, evaporated and purified by flash column chromatography (silica gel, cyclohexane/AcOEt=90:10→40:60) to yield the regioisomers **14** and **15**, bis-1,3′-tetrahydroisoquinolines as a brown oil **14** (210 mg, 33%), R_f=0.3, **15** (130 g, 18%), R_f=0.2 (cyclohexane/AcOEt=50/50). ^{1}H NMR ($CDCl_3$, 300 MHz) δ=7.80 (m, 2H, 2ArH), 7.7 (m, 4H, 4ArH), 7.53 (m, 1H, 1ArH), 7.35 (m, 3H, 3ArH), 7.26 (s, 2H, 2ArH), 6.50 (s, 1H, ArH), 6.35 (m, 1H, C*H*CH_2N), 6.22 (s, 1H, OCH_AH_BO), 5.96 (m, 1H, C*H*CHCN), 5.84(s, 1H, OCH_AH_BO), 5.65 (br s, 2H, OH and NH), 5.56 (s, 1H, ArOH), 5.11 (m, 1H, C*H*CH_2O), 4.57 (d, 1H, *J*=6.4 Hz, CHC*H*CN), 4.22 (m, 2H, OCH_AH_BCH and OCH_AH_BCH), 4.04 (m, 2H, CHCH_2N), 3.76 (s, 6H, $2OCH_3$), 3.73 (m, 2H, OCH_AH_B and OCH_AH_B), 3.57 (m, 1H, CH), 3.46 (m, 2H, CH_2CHN), 2.54 (m, 1H, CH_AH_BCHN), 2.26 (s, 3H, CH_3), 2.21 (m, 1H, CH_AH_BCHN), 2.08 (s, 3H, CH_3).

3.1.8. (7S,9R)-(9H-Fluoren-9-yl)methyl 9-((1,3-dioxoisoindolin-2-yl) methyl)-7-((1R,3S)-8-hydroxy-3-(hydroxymethyl)-7-methoxy-2,6-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-5-methoxy-4-methyl-6,7-dihydro-[1,3]dioxolo[4,5-h]isoquinoline-8(9H)-carboxylate ***16***. Compound **14** (110 mg, 0.13 mmol) was dissolved in 8:9 mixture of CH_2O/HCO_2H (1.7 mL) and stirred under atmosphere of argon at 70 °C. After 23 h the reaction mixture was made alkaline with $NaHCO_3$ (100 mL) aqueous solution at 0 °C, extracted with DCM. The combinated organic layers was dried over Na_2SO_4, filtered, evaporated and purified by flash column chromatography (SiO_2, cyclohexane/80:20→50:50) to give rise the protected amine **16**. R_f=0.6 (cyclohexane/ACOEt=5:5). ^{1}H NMR ($CDCl_3$, 300 MHz) δ=7.80 (m, 4H, 4Ar*H*), 7.70 (m, 2H, 2ArH), 7.58 (m, 1H, ArH), 7.49 (m, 2H, ArH), 7.41 (m, 2H, ArH), 7.26 (s, 1H, ArH), 6.55 (s, 1H, ArH), 6.06 (m, 1H, C*H*CH_2N), 5.66 (s, 1H, OCH_AH_BO), 5.46 (s, 3H, NCH_3), 4.90 (s, 1H, OCH_AH_BO), 4.70 (br s, 1H, ArOH), 4.65 (br s, 1H, OH), 4.45 (m, 1H, C*H*CHCN), 4.42 (m, 1H, C*H*CH_2O), 4.19 (m, 1H, OCH_AH_BCH), 4.13 (m,

1H, OCH_AH_BCH), 4.08 (d, 1H, J=6.4 Hz, $CHCHCN$), 3.98 (m, 2H, $CHCH_2N$), 3.82 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.45 (m, 2H, OCH_AH_B and OCH_AH_B), 3.23 (m, 1H, CH), 2.90 (m, 1H, CH_AH_BN), 2.60 (m, 1H, CH_AH_BCHN), 2.35 (m, 1H, CH_CH_DCHN), 2.27 (s, 3H, CH_3), 2.17 (m, 1H, CH_CH_DCHN), 2.01 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6 (NCO), 157.2 (NCO), 150.4 (ArC), 150.0 (ArC), 146.8 (ArC), 144.7 (ArC), 143.6 (ArC), 141.4 (ArC), 141.2 (ArC), 139.3 (ArC), 137.6 (ArC), 133.9 (ArCH), 132.4 (ArCH), 131.8 (ArCH), 131.3 (ArC), 130.5 (ArC), 130.0 (ArCH), 128.2 (2ArCH), 128.1 (2ArCH), 127.8 (ArC), 127.7 (ArCH), 127.2 (ArC), 125.5 (ArC), 123.2 (ArCH), 120.3 (ArC), 120.0 (ArCH), 119.9 (ArCH), 114.2 (ArCH), 113.1 (ArC), 112.8 (ArC), 100.9 (OCH_2O), 69.0 (CH), 63.8 (OCH_2), 63.7 (CH_2), 61.1 (OCH_3), 59.9 (NCH_3, OCH_3), 47.8 (2CH), 47.1 (CH), 39.8 (CH_2), 31.8 (CH_2), 26.8 (CH_2), 15.8 (CH_3), 9.0 (CH_3). ESI-MS: m/z (%)=838 $[M+H]^+$ (100), 837 $[M+2H]^+$ (51).

3.1.9. 2-(((7S,9R)-7-((1R,3S)-8-Hydroxy-3-(hydroxymethyl)-7-methoxy-2,6-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-5-methoxy-4-methyl-6,7,8,9-tetrahydro-[1,3]dioxolo[4,5-h]isoquinolin-9-yl) methyl)isoindoline-1,3-dione ***17***. To a solution of **16** (210 mg, 0.25 mmol) in DCM (0.84 mL) was added DBU (49 μL) under atmosphere of argon. After stirring at room temperature for 30 min, the reaction mixture was dissolved in DCM (20 mL) and washed, respectively, with water and brine. The organic layer was then dried over Na_2SO_4, filtered, evaporated and purified by flash column chromatography (SiO_2, DCM/MeOH 100:00→90:10) to give **17** as a brown solid (150 mg, 97%), R_f=0.5 (DCM/MeOH=90:10). ^{1}H NMR ($CDCl_3$, 500 MHz) δ=7.84 (dd, 1H, J=5.4, 3.0 Hz, ArH), 7.74 (dd, 1H, J=5.5, 3.0 Hz, ArH), 7.70 (dd, 1H, J=5.4, 3.0 Hz, ArH), 7.68 (dd, 1H, J=5.4, 3.1 Hz, ArH), 7.26 (s, 1H, ArH), 6.65 (d, 1H, J=9.3 Hz, OCH_AH_BO), 5.83 (d, 1H, J=16.6 Hz, OCH_AH_BO), 5.82 (s, 1H, ArOH), 4.59 (m, 1H, $CHCH_2N$), 4.51 (br s, 1H, OH), 4.4 (m, 1H, $CHCH_AH_BN$), 4.0 (br s, 1H, NH), 3.95 (m, 1H, $CHCH_AH_BN$), 3.79 (m, 1H, CH_AH_BOH), 3.71 (m, 1H, CH), 3.57 (s, 1H, CH), 3.55 (s, 3H, OCH_3), 3.44 (dd, 1H, J=10.9, 2.5 Hz, CH_AH_BOH), 3.41 (s, 3H, OCH_3), 3.15 (m, 1H, CH), 3.07 (dd, J=16.4, 3.4 Hz, CH_AH_BCHN), 2.52 (dd, J=15.3, 4.1 Hz, CH_AH_BCHN), 2.46 (s, 3H, NCH_3), 2.43 (m, 1H, CH_AH_BCHN), 2.2 (m, 1H, CH_AH_BCHN), 2.14 (s, 3H, CH_3), 2.08 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8 (NCO), 168.0 (NCO), 151.0 (ArC), 150.8 (ArC), 145.9 (ArC), 143.6 (ArC), 139.4 (2ArC), 139.3 (ArC), 133.9 (ArCH), 133.5 (ArCH), 131.9 (2ArC), 123.3 (ArCH), 123.1 (ArCH), 120.9 (ArCH), 120.8 (ArC), 120.7 (ArC), 112.2 (ArC), 112.1 (ArC), 101.0 (OCH_2O), 64.2 (CH), 63.6 (OCH_2), 60.1 (OCH_3), 59.9 (NCH_3, OCH_3), 52.5 (CH), 49.0 (CH), 45.7 (CH), 39.6 (CH_2), 31.7 (CH_2), 26.6 (CH_2), 15.6 (CH_3), 8.9 (CH_3). ESI-MS: m/z (%)=616 $[M+H]^+$ (100), 617 $[M+2H]^+$ (35). HRMS (EI) calcd for $C_{34}H_{38}O_8N_3$ $[M]^+$ 616.2659, found 616.2659.

3.1.10. Phthalascidin 622 ***18***. DMSO (571 mg, 7.32 mmol) was added to the stirred solution of $(COCl)_2$ (929 mg, 7.32 mmol) in DCM (20 mL), at −60 °C. After stirring for 30 min, the amine **17** (150 mg, 0.244 mL) dissolved in DCM (6 mL) was added at −60 °C. Then the reaction mixture was stirred for an additional time of 30 min at −60 °C and *i*-Pr_2NEt (1.6 g, 12.19 mmol) was added. The mixture was stirred for 1 h at room temperature and the TMSCN (474 mg, 4.78 mmol) was added dropwise, kept overnight at room temperature, washed with water (3×50 mL) and brine, dried over Na_2SO_4, filtered, evaporated and purified by flash column chromatography (SiO_2, cyclohexane/AcOEt 100:00→00:100 then MeOH) to yield the phenol **18** as a brown solid (40 mg, 27%). R_f=0.3 (DCM/MeOH=86:14). ^{1}H NMR ($CDCl_3$, 500 MHz) δ=7.73 (m, 2H, 2ArH), 7.68 (m, 2H, 2ArH), 6.41 (s, 1H, ArH_{15}), 5.75 (s, 1H, ArOH), 5.54 (s, 1H, OCH_AH_BO), 5.04 (s, 1H, OCH_AH_BO), 4.23 (s, 1H, H_{12}), 4.19(d, 1H, J=8.2 Hz, H_1), 4.11 (s, 1H, H_{11}), 3.74 (s, 3H, OMe_{17}), 3.71 (s, 3H, OMe_5), 3.60 (m, 2H, H_{22} and $H_{22'}$), 3.36 (d, 1H, J=7.5 Hz, H_{13}), 3.21 (m, 2H, H_3 and $H_{4'}$), 3.07 (dd, 1H, J=7.6, 18.1 Hz, $H_{14'}$), 2.62 (d, 1H, J=19.9 Hz, H_{14}), 2.31 (s, 3H, NMe), 2.24 (s, 3H, Me_{16}) 2.08 (s, 3H, Me_6), 1.84 (m, 1H, H_4). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4 (2 NCO), 150.4($ArCOMe_1$), 146.9 (ArCOH), 144.5 (ArCO), 142.9 ($ArCOMe_2$), 139.8 (ArCO), 134.1 (2ArCH), 132.3 (2ArC), 131.3 (ArC), 128.9 (ArC), 123.5 (2ArCH), 121.3 (ArC), 121.2 (ArCH), 118.7 (CN), 116.9 (ArC), 113.9 (ArC) 112.6 (ArC), 101.2 (OCH_2O), 61.4 (OMe), 61.1 (OMe), 61.0 (CH), 58.1 (CH), 57.0 (CH_2), 55.9 (CH_3), 55.6 (CH), 42.9 (CH_2), 42.2 (NMe), 26.5 (CH_2), 25.9 (CH_2), 16.4 (Me), 9.7 (Me). ESI-MS: m/z (%)= 623 $[M+H]^+$ (100), 624 $[M+2H]^+$ (33). HRMS (EI) calcd for $C_{35}H_{35}O_7N_4$ $[M]^+$ 623.2506, found. 623.2510.

Acknowledgements

The authors wish to thank the 'AUF Antananarivo, Région Rhône-Alpes and EGIDE Lyon' for the grant to C.R.R.'s Ph.D.

References and notes

1. (a) Scott, J.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669; (b) Siengalewicz, P.; Rinner, U.; Mulzer, J. *Chem. Soc. Rev.* **2008**, *37*, 2676.
2. (a) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Perun, T. J., Jr.; Seigler, D. S.; Wilson, G. R.; Shield, L. S. *Pure Appl. Chem.* **1990**, *62*, 1277; (b) Wright, A. E.; Forleo, D. A.; Gunawardana, G. P.; Gunasekera, S. P.; Koehn, F. E.; McConnel, O. J. *J. Org. Chem.* **1990**, *55*, 4508; (c) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Keifer, P. A.; Sun, F.; Li, H.; Martin, D. G. *J. Org. Chem.* **1990**, *55*, 4512; (d) Sakai, R.; Rinehart, K. L.; Guan, Y.; Wang, A. H.-J. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 11456; (e) Sakai, R.; Jares-Erijaman, E.; Manzanares, I.; Elipe, M. V.; Rinehart, K. L. *J. Am. Chem. Soc.* **1996**, *118*, 9017.
3. Aune, G. J.; Furuta, T.; Pommier, Y. *Anti-Cancer Drugs* **2002**, *13*, 545.
4. (a) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202; (b) Martinez, E. J.; Corey, E. J. *Org. Lett.* **2000**, *2*, 993; (c) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552; (d) Chen, J.; Chen, X.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2006**, *128*, 87; (e) Zheng, S.; Chan, C.; Furuuchi, T.; Wright, B. J. D.; Zhou, B.; Guo, J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1754.
5. (a) Martinez, E. J.; Owa, T.; Schreiber, S. L.; Corey, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 3496; (b) Martinez, E. J.; Corey, E. J.; Owa, T. *Chem. Biol.* **2001**, *8*, 1151; (c) Gonzáles, J. F.; Salazar, L.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2005**, *61*, 7447; (d) Ortìn, I.; Gonzáles, J. F.; de la Cuesta, E.; Manguan-Garcia, C.; Perona, R.; Avendaño, C. *Bioorg. Med. Chem.* **2008**, *16*, 9065; (e) Ortìn, I.; Gonzáles, J. F.; de la Cuesta, E.; Perona, R.; Avendaño, C. *Tetrahedron* **2009**, *65*, 2201.
6. (a) Cuevas, C.; Pérez, M.; Martín, M. J.; Chicharro, J. L.; Fernández-Rivas, C.; Flores, M.; Francesch, A.; Gallego, P.; Zarzuelo, M.; de la Calle, F.; García, J.; Polanco, C.; Rodríguez, I.; Manzanares, I. *Org. Lett.* **2000**, *2*, 2545; (b) Menchaca, R.; Martínez, V.; Rodríguez, A.; Rodríguez, N.; Flores, M.; Gallego, P.; Manzanares, I.; Cuevas, C. *J. Org. Chem.* **2003**, *68*, 8859.
7. Ikeda, Y.; Idemeto, H.; Hirayama, F.; Yamamoto, K.; Iwao, K.; Asao, T.; Munakata, T. *J. Antibiot.* **1983**, *36*, 1279.
8. Aubry, S.; Bourdon, B.; Razafindrabe, R. C.; Pellet-Rostaing, S.; Lemaire, M. *Tetrahedron Lett.* **2007**, *48*, 9163.
9. (a) Aubry, S.; Pellet-Rostaing, S.; Fenet, R.; Lemaire, M. *Tetrahedron Lett.* **2006**, *47*, 1319; (b) Aubry, S.; Pellet-Rostaing, S.; Fenet, R.; Lemaire, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2598.
10. (a) Lane, J. W.; Chen, Y.; Williams, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 12684; (b) Vincent, G.; Lanea, J. W.; Williams, R. M. *Tetrahedron Lett.* **2007**, *48*, 3719.
11. Naoki, S.; Masashi, T.; Seki, R.; Sugawara, Y.; Takeuchi, E.; Kubo, A. *Synth. Commun.* **2000**, 2407.
12. (a) Duff, J. C. *J. Chem. Soc.* **1932**, 1987; (b) Ferguson, L. N. *Chem. Rev.* **1946**, *38*, 227.
13. (a) Knoevenagel, E. *Chem. Ber.* **1896**, *29*, 172; (b) Lehnert, W. *Tetrahedron* **1972**, *28*, 666; (c) versleijen, J. P. G.; Van Leusen, A. M.; Feringa, B. L. *Tetrahedron Lett.* **1999**, *40*, 5803.
14. Ong, C. W,; Chang, Y. A.; Wu, J. Y.; Chien-Chung Cheng, C. C. *Tetrahedron* **2003**, *59*, 8245.
15. Chang, Y. A.; Sun, T. H.; Chiang, M. Y.; Lu, P. J.; Yi-Ting Huang, Y. T.; Liang, L. C.; Ong, C. W. *Tetrahedron* **2007**, *63*, 8781.
16. Cundasawmy, N. E.; Maclean, D. B. *Can. J. Chem.* **1972**, *50*, 3026.
17. (a) Chen, X.; Chen, J.; Paolis, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4397; (b) Chen, R.; Zhu, D.; Hu, Z.; Chen, X. *Tetrahedron: Asymmetry* **2010**, *21*, 39.