Tetrahedron 66 (2010) 9270–9276

Contents lists available at ScienceDirect

Tetrahedron

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

A fast and straightforward route towards the synthesis of the lissoclimide class of anti-tumour agents

Tuan Minh Nguyen [a], Nguyen Quang Vu [a], Jean-Jacques Youte [a], Jacelyn Lau [a], Angie Cheong [a], Ying San Ho [a], Benjamin S.W. Tan [a], Kanagasundaram Yoganathan [b], Mark S. Butler [b], Christina L.L. Chai [a,c,*]

[a] Institute of Chemical and Engineering Sciences (ICES), Agency for Science Technology and Research, 8 Biomedical Grove, #07-01/2/3, Neuros, Singapore 138665
[b] MerLion Pharmaceuticals Pte Ltd, 1 Science Park Road, #05-01 The Capricorn, Singapore Science Park II, Singapore 117528
[c] Department of Pharmacy, Faculty of Science, National University of Singapore, Singapore 117543

ARTICLE INFO

Article history:
Received 22 May 2010
Received in revised form 23 August 2010
Accepted 13 September 2010
Available online 17 September 2010

Dedicated to the memory of the late Professor Athel Beckwith, FRS

Keywords:
Aldol reaction
anti-Tumour agents
Lissoclimides
Natural products
Terpenoids

ABSTRACT

The synthesis of the chiral core structure of the lissoclimide class of anti-tumour agents containing three rings, including a chiral succinimide subunit and an exocyclic double bond, has been investigated. The compound **7** was obtained, without the use of any protecting groups for the alcohol at C-12, via an asymmetric boron-mediated aldol addition as the key step to install the chiral centres of the rare succinimido methanol moiety. This was followed by a sequence of lactonisation, microwave-assisted amidation and imidation reactions.

1. Introduction

The first member of the lissoclimide class of compounds, dichlorolissoclimide **1** (Fig. 1), was isolated in 1991 from a specimen of New Caledonian ascidian, *Lissoclinum voeltzkowi*.[1] This compound, which has an unusual vicinal *trans*-diequatorial dichloride, displayed extremely potent cytotoxic activity (IC_{50}=1 ng/mL against P388 leukaemia cell lines; 14 ng/mL against KB human carcinoma cell lines).[2] The isolation of chlorolissoclimide **2**[3] and the absolute configuration of dichlorolissoclimide **1**[4] were subsequently reported. In 2001, related compounds, the haterumaimides A–E, were isolated from an Okinawan *Lissoclinum* sp.[5] Subsequent papers described the isolation and biological activity of haterumaimide F–I (**3**–**6**),[6] haterumaimide J–K,[7] haterumaimide N–Q and semi-synthetic derivatives.[8] In addition, haterumaimide L–M and 3β-hydroxychlorolissoclimide have been isolated from *molluscs*, *Pleurobranchus albiguttatus*,[9] and *Pleurobranchus forskalii*,[9,10] which are known to feed on ascidians. From a structural viewpoint, the skeleton of this class of labdane diterpene alkaloid consists of a trans-decalin ring

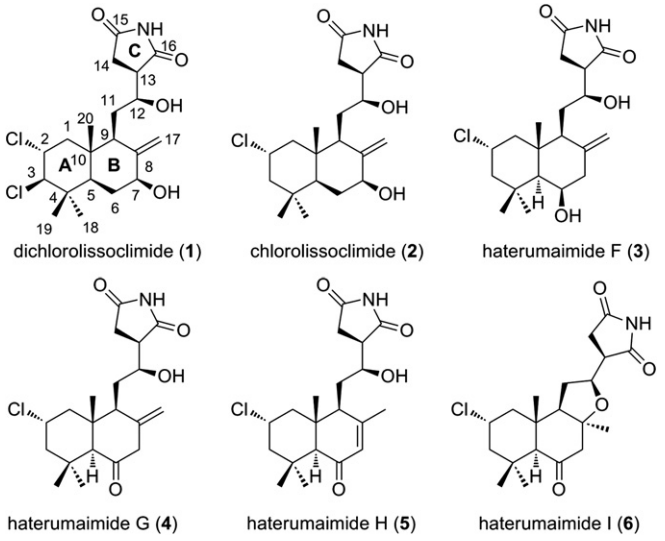


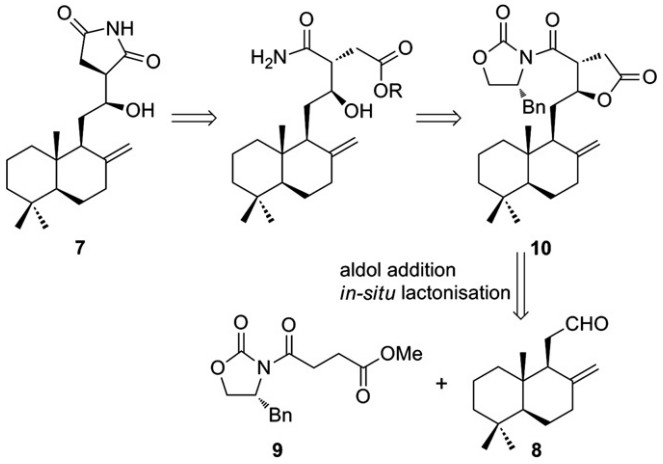
Fig. 1. Some examples of lissoclimides.

* Corresponding author. Tel.: +65 6799 8522; fax: +65 6316 6184; e-mail address: christina_chai@ices.a-star.edu.sg (C.L.L. Chai).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.09.031

subunit (rings A and B) and a rare chiral succinimide subunit (ring C) with seven to eight chiral centres. The biological mode of action of lissoclimides was unknown until 2006, when Robert and co-workers showed that dichlorolissoclimide **1** and chlorolissoclimide **2** were potent inhibitors of eukaryotic translation.[10]

As part of our ongoing natural product-based drug discovery activities, we were interested in the synthesis of the core structure **7**, which consists of the entire carboskeleton of the lissoclimide alkaloids (Scheme 1). The aim of the work reported herein is to develop a general asymmetric synthetic route for the installation of the chiral succinimide (ring C), which is applicable to the synthesis of the aforementioned natural products. To the best of our knowledge, no total syntheses of members of this class of compounds have been reported. The closest related study to our work is the recent publication of González and co-workers.[11] In their synthesis, nucleophilic addition of a succinimide anion to the aldehyde **8** yielded a diastereomeric mixture of compounds with the coveted core structure **7**.



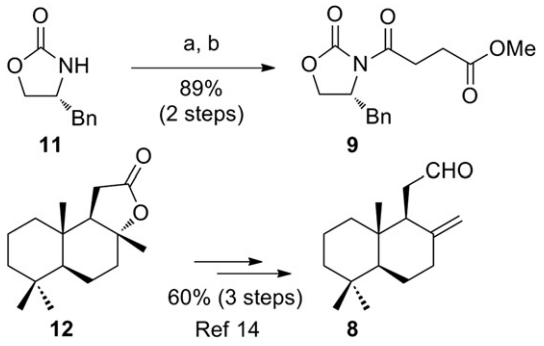
Scheme 1. Retrosynthetic analysis of the core structure **7** of the lissoclimides alkaloids.

2. Results and discussion

Retrosynthetically, the disconnection of the succinimido methanol moiety reveals that the two chiral centres of this rare motif could be obtained via an asymmetric aldol addition using a chiral auxiliary. The remaining chiral centres of the decalin moiety could be obtained from the chiral pool (Scheme 1). This synthetic sequence could then be achieved via an asymmetric aldol addition, in situ lactonisation followed by amidation and imidation. Interestingly, a procedure involving an asymmetric aldol addition followed by in situ lactonisation to give either the *syn*- or *anti*-aldol products was reported by Hajra and co-workers in 2007.[12] The diastereoselectivity was controlled by varying the addition sequence of the base and aldehyde, when chiral *N*-acyl-2-oxazolidinones containing additional γ/δ-chelating functional groups were used.

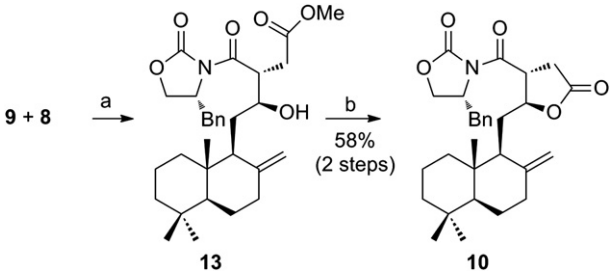
The oxazolidinone **9** was prepared by acylation of the chiral auxiliary **11** via its lithium amide,[13] followed by O-methylation (Scheme 2). After purification, the oxazolidinone **9** was obtained in 89% yield over two steps. Starting from commercially available (3a*R*)-(+)-sclareolide **12**, the aldehyde **8** was synthesised in 60% yield over three steps using reported procedures.[14]

With oxazolidinone **9** and aldehyde **8** in hand, a *syn*-selective aldol condensation was carried out under mild conditions with *n*-Bu_2BOTf/DIPEA in CH_2Cl_2 (Scheme 3).[12] As expected, after a standard workup with pH 7 phosphate buffer and 30% H_2O_2 in MeOH, the *syn*-aldol product lactone **10** was obtained as a single diastereoisomer in 30% isolated yield (for detailed studies related to the stereochemistry determination, see below). The yield of the desired lactone **10** could be improved by treatment of the crude



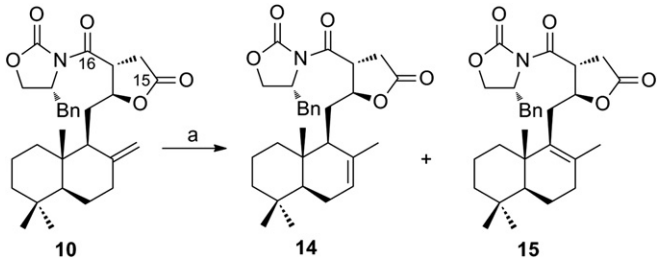
Scheme 2. Synthesis of the aldehyde **8** and chiral oxazolidinone **9**. (a) *n*-BuLi, succinic anhydride, THF, 0 °C to rt; (b) MeI, K_2CO_3, acetone, 40 °C.

reaction mixture obtained from the aldol reaction with *p*-TsOH (0.1 equiv) under reflux in CH_2Cl_2. This is to ensure complete lactonisation of the intermediate **13** and following this procedure, lactone **10** could be isolated as a single diastereomer with an improved yield of 58%.



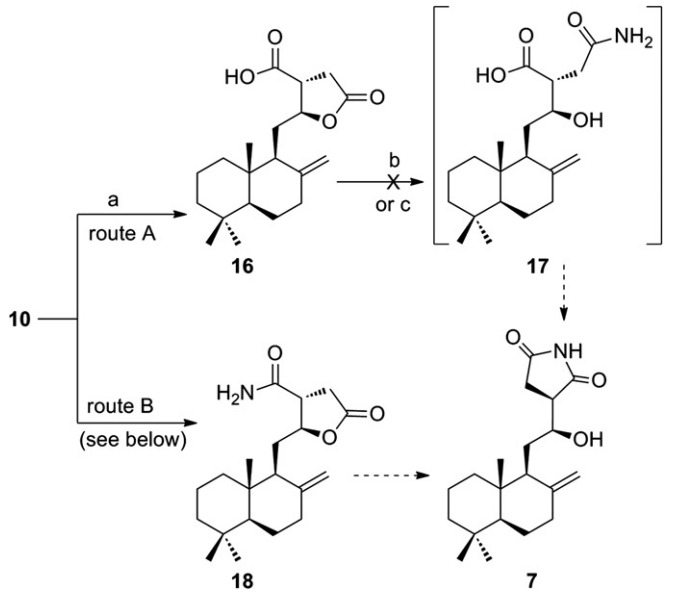
Scheme 3. Asymmetric aldol addition followed by lactonisation. (a) (i) *n*-Bu_2BOTf, DIPEA, CH_2Cl_2, −78 °C, (ii) pH 7 phosphate buffer, 30% H_2O_2, MeOH; (b) *p*-TsOH (cat.), CH_2Cl_2, reflux, 2 h.

Our efforts to improve the preparation of the lactone **10** revealed that with prolonged heating of crude **13** in CH_2Cl_2, the yield of **10** decreased significantly. The ^1H NMR spectra of isolated products suggested that the exocyclic double bond of **10** had migrated to the endocyclic positions. Indeed, when the pure compound **10** was treated with *p*-TsOH (0.1 equiv) in $CDCl_3$ at 90 °C for 3 h, complete isomerisation occurred (Scheme 4). A similar observation was also noted by Uddin and co-workers, when haterumaimide G (**4**) was treated with PPTS in MeOH at rt to give haterumaimide H (**5**).[6] These observations suggested the propensity of the double bond isomerisation in this class of compounds under acidic conditions.



Scheme 4. Migration of the exocyclic double bond into endocyclic positions. (a) *p*-TsOH (0.1 equiv), $CDCl_3$, 90 °C, 3 h.

We next investigated possible routes that could lead to the formation of succinimide ring C (Scheme 5). In route A, a LiOOH-mediated hydrolysis of compound **10** was carried out and this gave selectively the monocarboxylic acid **16** in 90% yield.[15] However, all attempts to transform this compound into the corresponding amide **17** with NH_3/H_2O or NH_3 gas followed by imidation in DMF at

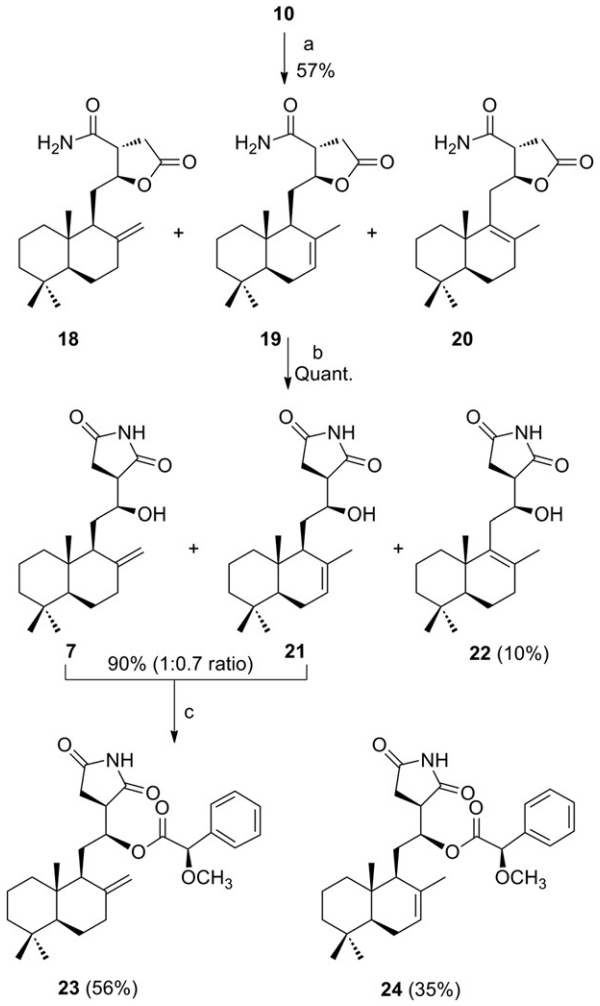


Scheme 5. Investigation of possible routes leading to the core structure **7**. (a) LiOH, H_2O_2, THF/H_2O, 0 °C to rt, 90%; (b) NH_4OH, DMF, 150 °C; (c) (i) NH_3 gas, rt, DMF; (ii) DMF, 150 °C.

high temperature were unsuccessful, giving only complex mixtures of highly polar products without any traces of compound **7**.[16] Investigation of route B was initiated by attempting to convert compound **10** into the corresponding amide **18**. The classical procedure for transamination of Evans' auxiliary using NH_4Cl/Me_3Al[17] was not suitable in this case, due to the lack of chemoselectivity between the ester and the 'imide-like' functional groups at C-15 and C-16 (as labelled in the Scheme 4), respectively. Fortunately, treating compound **10** with a large excess of ammonium acetate under microwave irradiation (MWI) at 150 °C for 15 min gave the amides **18**, **19** and **20** as a mixture of regioisomers in 5.3:3.7:1.0 ratio (as determined in the following step, see Scheme 6) in a combined yield of 57%.[18] Although the aforementioned isomerisation of the double bond had occurred, this unprecedented reaction provided a method for the transamination of chiral lactone **10**.

Imidation was achieved by treating the mixture of amides with sodium hydride giving a mixture of succinimides **7**, **21** and **22** in quantitative yield. Compound **22** was isolated in 10% yield by preparative LC-MS, whereas **7** and **21** were obtained as a 1:0.7 mixture of compounds in 90% isolated yield. The separation of these two isomers proved difficult, and only an analytically pure sample of compound **7** could be obtained. Subsequently, an esterification of the mixture with (*R*)-methoxyphenylacetic acid (MPA) was carried out, which facilitated the separation. Therefore, esters **23** and **24** were obtained in 56% and 35% isolated yields, respectively.

A series of 1D NOE difference experiments were carried out in order to establish the relative stereochemistry of the chiral centres generated during the aldol reaction. The observed NOE correlations of **10**, supported by conformation analysis (Fig. 2a),[19] strongly suggest a *syn*-aldol addition. Independently, the relative stereochemistries of compound **22**, 12*S** and 13*R** were proposed by a careful examination of NOE correlations of H-12/H-13, H-12/H-17, H-12/H-11α, H-12/H-14α, H-13/H-14α, H-11α/H-17, H-11β/H-20, H-11β/H-1eq, together with vicinal coupling constants of H-12 (ddd, *J*=10.8, 4.0, 2.4 Hz) and H-13 (ddd, *J*=8.8, 4.8, 2.4 Hz) and conformation analysis (Fig. 2b). In addition, comparison of these data with those from related compounds described in the literature[4,6,7] allowed us to confirm the relative stereochemistry of compounds **22** and **10**. This result is in good agreement with stereochemical outcomes as reported by the Evans group,[20] as well as Hajra and coworkers for aldol reaction using Evans' auxiliary.[12]



Scheme 6. Microwave-assisted amidation followed by imidation. (a) NH_4OAc, microwave irradiation (150 °C, 15 min); (b) (i) NaH, THF, rt, 30 min, (ii) MeOH, 0 °C. (c) EDC/DMAP, (*R*)-MPA acid, $CHCl_3$.

In order to determine the absolute stereochemistry of the chiral centres C-12 and C-13 resulting from the aldol addition step, compound **22** was derivatized as (*R*)-MPA ester **25** and (*S*)-MPA ester **26** (Fig. 3).[21] The ^{1}H NMR signals of these two compounds were assigned based on 2D NMR, and the obtained $\Delta\delta$ ($\delta^R-\delta^S$, ppm) values allowed us to confirm the 12*S* configuration of **22**. Based on the relative stereochemistry already deduced from NOE experiments, the *R* configuration of C-13 was assigned.

3. Conclusion

In summary, we have developed a useful synthetic strategy towards the synthesis of the chiral core structure of the lissoclimide class of anti-tumour agents. The rapid and straightforward synthetic route gave the desired core structure **7** in a reasonable yield (17.5% in four steps) from readily available **8**. It should be noted that in this reaction sequence, no protecting group was needed to access the alcohol group at C-12 of the core structure. These studies should pave the way for the total synthesis of dichlorolissoclimide **1** and its analogues.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 400 and Bruker Advance DRX-500 NMR instruments in $CDCl_3$ unless

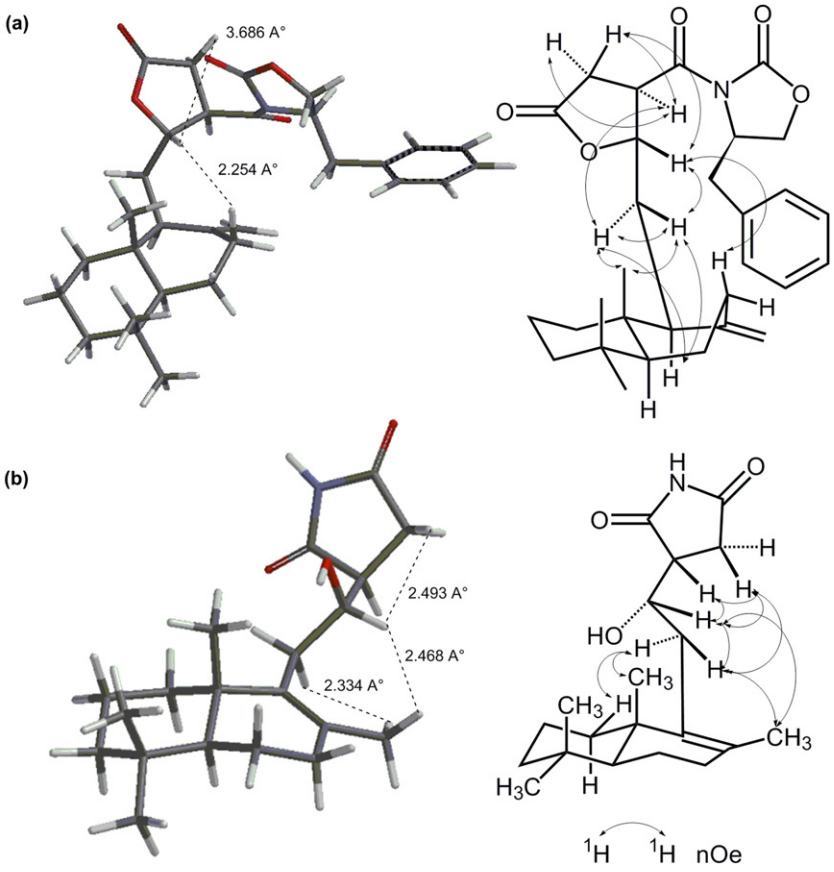


Fig. 2. Energy minimised conformations and selected spatial NOE correlation of: (a) the lactone **10**; (b) the succinimide **22**.

otherwise stated. Coupling constants are given in hertz and chemical shift are expressed as δ values in parts per million, using either TMS or the residual undeuterated solvent signal as reference. IR spectra were measured on a Bio-Rad FTS 3000MX FT-IR spectrometer as liquid film or as an evaporated film. Optical rotations were measured using a Jasco P-1030 polarimeter. Mass spectra were run by the electron impact (EI, 70 eV) mode on a Thermo Finnigan MAT XP95 mass spectrometer or by the electrospray ionization time-of-flight (ESI-TOF) mode on an Agilent 6210 mass spectrometer. Microwave reaction was carried out in sealed reactors in a Biotage Initiator™ Microwave Synthesiser with built-in temperature and pressure detectors. Solvents were taken from a Glass contour solvent purification system under nitrogen. Commercially available reagents were used as received. Flash column chromatography purification was carried out either manually or by using a Biotage SP1™ purification system by gradient elution. Preparative reversed-phase HPLC was performed either on a Gilson system complete with UniPoint software, 170 DAD detector, dual 306 pumps, 811C dynamic mixer, Gilson 202 fraction collector, and a Rheodyne 7125 injector with a 5 mL injection loop, or a Waters 2545 Binary Gradient Module with a 2996 PDA detector. Semi-preparative TLC was done using Merck silica gel 60 (F_{254}) pre-coated glass plates, 0.25 mm thickness.

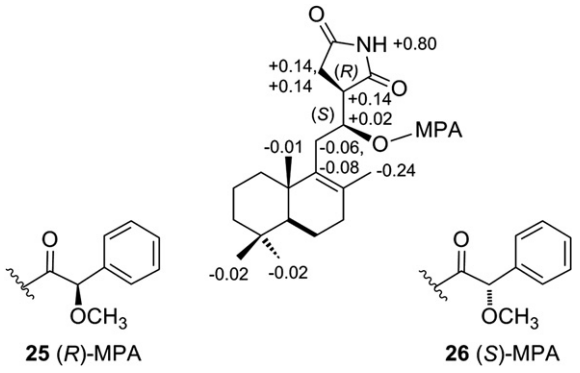


Fig. 3. $\Delta\delta^{RS}$ values ($\Delta\delta^{RS}=\delta^{R}-\delta^{S}$) of selected protons of (*R*)-MPA esters **25** and (*S*)-MPA ester **26**.

4.2. Synthesis

*4.2.1. (R)-Methyl 4-(4-benzyl-2-oxooxazolidin-3-yl)-4-oxobutanoate (**9**).* A solution of (*R*)-4-Benzyloxazolidin-2-one **11** (5.0 g, 28.22 mmol, 1 equiv) in dry THF (100 mL) was stirred at 0 °C for 15 min before *n*-BuLi (2.5 M, 12.4 mL, 31.04 mmol) was added to give an orange-coloured solution. Succinic anhydride (3.10 g, 31.04 mmol) was added and stirred for 15 h at rt. Saturated NH_4Cl (30 mL) was added to quench the reaction and a hard block of white gel was formed. HCl (2 M) solution was added until the pH of aqueous phase is acidic and the reaction mixture was extracted with CH_2Cl_2 (100 mL×3). The combined organic layers were washed with water (100 mL×2), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was directly submitted to methylation without further purification.

A suspension of K_2CO_3 (2.50 g, 180 mmol) in acetone (60 mL) was stirred for 30 min at 40 °C. The above crude oxazolidinone in acetone (20 mL) was added to the suspension. The reaction mixture was stirred for an additional 30 min before methyl iodide (25.6 g, 11.2 mL, 180 mmol) was added and stirred for another 15 h at 40 °C. The reaction mixture was filtered to remove K_2CO_3 and evaporated

under reduced pressure. The crude reaction mixture was dissolved in EtOAc (300 mL) and then washed with H_2O (100 mL×3). The organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue obtained was purified by silica gel chromatography and eluted with 10–50% EtOAc in hexane to provide the *title compound* **9** as a white solid (7.32 g, 89% after two steps). Mp 91.7–92.5 °C (lit.[2]: 90–92 °C). R_f (50% EtOAc/hexane) 0.43; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.35 (m, 5H), 4.68 (dddd, J=10.8, 9.5, 8.7, 3.1 Hz, 1H), 4.22 (dd, J=9.1, 8.7 Hz, 1H), 4.18 (dd, J=9.1, 3.1 Hz, 1H), 3.72 (s, 3H), 3.31–3.24 (m, 3H), 2.79 (dd, J=13.4, 9.5 Hz, 1H), 2.74–2.69 (m, 2H).

*4.2.2. (R)-4-Benzyl-3-((2S,3R)-5-oxo-2-(((1S,4aS,8aS)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)methyl)tetrahydrofuran-3-carbonyl)oxazolidin-2-one (**10**).* To a solution of **9** (1.90 g, 6.55 mmol) in dry CH_2Cl_2 (30 mL) was added a solution of n-Bu_2BOTf (1.0 M in CH_2Cl_2, 7.86 mL, 7.86 mmol) and DIPEA (1.70 mL, 9.82 mmol) and stirred for 15 min at 0 °C. The reaction mixture was cooled to −78 °C before the aldehyde **8**[14] (1.50 g, 6.41 mmol) in dry CH_2Cl_2 (15 mL) was added and stirred for another 1 h at −78 °C, followed by another 72 h at 0 °C. The reaction mixture was quenched with the addition of a pH 7 phosphate buffer solution (20 mL), 30% hydrogen peroxide (60 mL) and MeOH (20 mL) solution at 0 °C and stirred for 1 h. The reaction mixture was extracted with Et_2O (100 mL ×3). The combined organic layers was washed with water (50 mL×3), dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford a red-orange oil. The residue obtained, containing compound **13** as determined by ^{1}H NMR, was lactonised by refluxing the reaction mixture with p-TsOH (100 mg) in CH_2Cl_2 (300 mL) at 70 °C with a Soxhlet filled with calcium hydride for 2 h. The residue was purified by silica gel chromatography and eluted with 10–20% EtOAc in hexane to provide the *title compound* **10** as a viscous pale yellow oil (1.89 g, 58% after two steps). R_f (25% EtOAc/hexane) 0.31; $[\alpha]_D^{20}$ −35.15 (c 0.52, $CHCl_3$); IR (film) ν_{max} 2937, 2845, 1782, 1697, 1389, 1209, 1200, 1112, 1006, 890 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.17 (m, 5H), 4.95 (ddd, J=8.3, 5.6, 4.5 Hz, 1H), 4.85 (s, 1H), 4.68 (dddd, J=9.3, 7.2, 3.7, 3.4 Hz, 1H), 4.59 (s, 1H), 4.29 (dd, J=9.2, 7.2, 1H), 4.25 (dd, J=9.2, 3.7, 1H), 4.15 (ddd, J=9.3, 7.1, 5.6 Hz, 1H), 3.24 (dd, J=13.4, 3.4 Hz, 1H), 3.00 (dd, J=17.6, 9.3 Hz, 1H), 2.81 (dd, J=13.4, 9.3 Hz, 1H), 2.61 (dd, J=17.6, 7.1 Hz, 1H), 2.39 (ddd, J=12.7, 6.4, 4.1 Hz, 1H), 2.01–0.94 (m, 13H), 0.96 (s, 3H), 0.79 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 171.3, 152.9, 148.2, 134.5, 129.3, 129.0, 127.6, 106.9, 80.9, 66.7, 55.6, 55.3, 51.5, 44.6, 41.9, 39.6, 39.0, 38.0, 37.7, 33.5, 33.5, 32.9, 28.5, 24.2, 21.6, 19.2, 14.4. MS (ESI$^+$) m/z $[MH]^+$ 494; HRMS (ESI$^+$) m/z calcd for $C_{30}H_{39}NO_5Na$ $[M+Na]^+$ 516.2720, found 516.2714; calcd for $C_{30}H_{39}NO_5K$ $[M+K]^+$ 532.2460; found: 532.2459.

*4.2.3. (2S,3R)-5-Oxo-2-(((1S,4aS,8aS)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)methyl)tetrahydrofuran-3-carboxylic acid (**16**).* A solution of lactone **10** (120 mg, 0.24 mmol) in 4:1 THF/H_2O (5 mL) was treated at 0 °C with 30% H_2O_2 (198 μL, 1.92 mmol) followed by LiOH (7.2 mg, 0.3 mmol). The resulting mixture was stirred at rt for 3 h, and the excess of peroxide was quenched at 0 °C with 1.5 M aqueous Na_2SO_3. The mixture was then extracted with EtOAc (50 mL×3) and the organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure. The residue obtained was purified by silica gel chromatography and eluted with 2–5% MeOH in CH_2Cl_2 to provide the *title compound* **16** as a white amorphous solid (74 mg, 90%). R_f (10% MeOH/CH_2Cl_2) 0.36; $[\alpha]_D^{24}$ −7.37 (c. 2.35, $CHCl_3$). IR (film) ν_{max} 3435, 2928, 2850, 1777, 1766, 1641, 1585, 1414, 1385, 1262, 1202, 1018, 890, 803 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 (s, 1H), 4.72 (m, 1H), 4.63 (s, 1H), 2.90 (m, 1H), 2.81 (m, 1H), 2.71 (m, 1H), 2.39 (m, 1H), 1.99 (m, 2H), 1.79–0.98 (m, 11H), 0.88 (s, 3H), 0.80 (s, 3H), 0.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 176.6, 148.1, 107.0, 82.6, 55.3, 51.4, 42.0, 39.6, 39.0, 38.0, 33.6, 33.5, 31.8, 29.7, 29.4, 24.2, 21.7, 19.3, 14.4; HRMS (ESI$^-$) m/z calcd for $C_{20}H_{29}O_4$ $[M-H]^-$ 333.2071, found 333.2055.

*4.2.4. Microwave-assisted amidation of compound **10**.* Compound **10** (1.11 g, 2.252 mmol) and a large excess of NH_4OAc (7.77 g, 100.9 mmol) were submitted to microwave irradiation at 150 °C for 15 min without the use of any solvent. The reaction mixture was then cooled to rt, following which EtOAc (10 mL) was added. The solution was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue obtained was purified by silica gel chromatography and eluted with 20–100% EtOAc in hexane to provide a mixture of **18**/**19**/**20** (431 mg, combined yield 57%). Analytically pure samples of compounds **18** and **19** were obtained by reverse-phase HPLC (Luna Phenylhexyl C_{18} column, 5 μ, 21.2×150 mm; flow rate: 15 mL/min; mobile phase: acetonitrile in water with 0.1% formic acid; gradient: 40–46% (100 min)) to give **18** (rt 41 min) and **19** (rt 44 min).

*4.2.5. (2S,3R)-5-Oxo-2-(((1S,4aS,8aS)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)methyl)tetrahydrofuran-3-carboxamide (**18**).* Mp 179–179.5 °C; $[\alpha]_D^{20}$ −13.60 (c 0.22, $CHCl_3$); IR (film) ν_{max} 3381, 2928, 2867, 2360, 2237, 1778, 1678, 1458, 1423, 1383, 1365, 1292, 1224, 1149, 1023, 968, 889 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 (br s, 2H), 4.93 (s, 1H), 4.77 (td, J=7.9, 4.0 Hz, 1H), 4.66 (s, 1H), 2.92–2.72 (m, 3H), 2.44–1.12 (m, 14H), 0.89 (s, 3H), 0.81 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 173.3, 149.4, 108.4, 82.8, 56.7, 52.7, 48.0, 43.0, 40.8, 40.3, 39.1, 34.6, 34.5, 34.4, 29.9, 25.3, 22.6, 20.3, 15.4; HRMS (ESI$^+$) m/z calcd for $C_{20}H_{31}NO_3Na$ $[M+Na]^+$ 356.2196; found 356.2197.

*4.2.6. (2S,3R)-5-Oxo-2-(((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methyl)tetrahydrofuran-3-carboxamide (**19**).* Mp 167–168 °C $[\alpha]_D^{20}$ −53.85 (c 0.18, $CHCl_3$); IR (film) ν_{max} 3382, 2928, 2867, 2361, 2238, 1778, 1678, 1459, 1423, 1383, 1364, 1292, 1224, 1149, 1022, 968, 889 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (br s, 2H), 5.46 (s, 1H), 4.85 (dd, J=13.2, 6.5 Hz, 1H), 2.92–2.77 (m, 3H), 2.02–0.95 (m, 12H), 1.72 (s, 3H), 0.89 (s, 3H), 0.87 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 173.2, 134.3, 124.5, 84.4, 51.2, 51.0, 48.4, 43.1, 40.8, 37.8, 34.6, 34.1, 34.0, 33.7, 24.7, 23.4, 22.8, 19.7, 14.4; MS (ESI$^+$) m/z $[M+Na]^+$ 356.59; MS (ESI$^-$) m/z $[M-H]^-$ 352.52.

*4.2.7. Procedure for the formation of succinimides starting from the isomeric mixture **18**/**19**/**20**.* To a solution of the mixture of compounds **18**, **19** and **20** (50 mg, 0.15 mmol) in THF (2 mL) was added NaH (13.8 mg, 0.345 mmol, 60% in mineral oil) at 0 °C followed by stirring at rt for 30 min. The reaction mixture was quenched with the addition of MeOH (5 mL) and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography eluted with 3% MeOH in CH_2Cl_2 to provide a mixture of **7**/**21**/**22** as an inseparable mixture (50 mg, quant.). Purification using reverse phase HPLC-MS (Luna Phenylhexyl C_{18} column, 5 μ, 21.2×250 mm; flow rate: 20 mL/min; mobile phase: acetonitrile in water with 0.1% formic acid; gradient: 40% (10 min), 40–60% (30 min), 80% (5 min)) gave the mixture **7**/**21** (45 mg, rt 28.1 min) in 1:0.7 ratio (determined by ^{1}H NMR spectroscopy) and the pure compound **22** (5 mg, 10%, rt 29.9) as a white amorphous solid. The mixture of compounds **7** and **21** was further purified by using normal phase HPLC (IA column, 5 μ, 20×250 mm; flow rate: 20 mL/min; mobile phase: isopropanol in hexane; gradient: 5% (2 min), 5–20% (30 min), 20% (20 min)) to give the analytically pure compound **7** (4 mg) as a white amorphous solid.

*4.2.8. (R)-3-((S)-1-Hydroxy-2-((1S,4aS,8aS)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)ethyl)pyrrolidine-2,5-dione (**7**).* $[\alpha]_D^{20}$ +40.45 (c 0.71, $CHCl_3$); IR (film) ν_{max} 3470, 3193, 2928, 2845, 1775, 1713, 1456, 1363, 1261, 1186, 1090, 1037 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.73 (br s, 1H), 4.95 (s, 1H), 4.68 (s, 1H), 4.37 (m, 1H), 2.95–2.85 (m, 2H), 2.69 (dd, J=17.6, 8.0 Hz, 1H), 2.43 (ddd, J=12.8, 4.4, 2.8 Hz, 1H), 2.00 (dt, J=12.8, 4.8 Hz, 1H), 1.92 (br s, 1H), 1.79–1.07 (m, 12H), 0.89 (s, 3H), 0.81 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 176.3, 149.0, 107.3, 69.5, 55.6, 53.9, 46.8, 42.0, 39.2, 38.2, 33.6, 33.5, 29.7, 29.4, 29.1, 24.3, 21.6, 19.3, 14.4; HRMS (ESI^+) m/z calcd for $C_{20}H_{31}NO_3Na$ $[M+Na]^+$ 356.2196; found 356.2195.

*4.2.9. (R)-3-((S)-1-Hydroxy-2-((4aS,8aS)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)ethyl)pyrrolidine-2,5-dione (**22**).* $[\alpha]_D^{20}$ +9.90 (c 0.31, $CHCl_3$); IR (film) ν_{max} 3464, 3229, 2927, 2867, 1774, 1709, 1707, 1459, 1359, 1264, 1190, 1097, 1039, 947 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 4.38 (ddd, J=10.8, 4.0, 2.4 Hz, 1H), 2.98 (dd, J=17.2, 4.8 Hz, 1H), 2.92 (ddd, J=8.8, 4.8, 2.4 Hz, 1H), 2.73 (dd, J=17.2, 8.8 Hz, 1H), 2.32 (dd, J=14.0, 10.8 Hz, 1H), 2.18 (dd, J=14.0, 4.0 Hz, 1H), 2.00–2.15 (m, 2H), 1.89 (br s, 1H), 1.80 (m, 1H), 1.41–1.73 (m, 5H), 1.65 (s, 3H), 1.23–1.12 (m, 3H), 0.98 (s, 3H), 0.90 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 176.9, 135.4, 131.9, 69.0, 51.4, 47.4, 41.5, 39.1, 37.7, 33.7, 33.3, 33.24, 33.20, 29.9, 21.7, 20.9, 20.3, 18.9, 18.8; HRMS (ESI^+) m/z calcd for $C_{20}H_{31}NO_3Na$ $[M+Na]^+$ 356.2196; found 356.2193.

4.3. General procedure for the MPA esters

To a solution of the appropriate succinimides, methoxyphenylacetic acid (MPA) and 4-dimethylamino pyridine (DMAP) in either $CDCl_3$ or $CHCl_3$, was added *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl) at rt. The solution was then stirred for 24 h and the solvents evaporated to give the crude mixture.

*4.3.1. Synthesis of (R)-MPA esters **23** and **24**.* Following the general procedure for MPA esters, the mixture of compounds **7** and **21** (in 1/0.7 ratio, 10 mg, 0.03 mmol), (*R*)-MPA (10 mg, 0.06 mmol), DMAP (0.5 mg, 0.004 mmol) in $CHCl_3$ (3 mL) were reacted with EDC·HCl (19.5 mg, 0.1 mmol). The crude mixture was purified first by silica gel chromatography eluted with 20% EtOAc in hexane to give the mixture of (*R*)-esters (in 1:0.7 ratio, 14.4 mg, quant.). This mixture was further purified by using normal phase preparative HPLC (OD column, 5 μ, 20×250 mm; flow rate: 20 mL/min; mobile phase: isopropanol in hexane; gradient: 5% (2 min), 5–20% (30 min), 20% (20 min)) to provide compound **23** (8 mg, 56%) and compound **24** (5 mg, 35%) as colourless foams.

*4.3.1.1. (R)-((S)-1-((R)-2,5-Dioxopyrrolidin-3-yl)-2-((1S,4aS,8aS)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)ethyl) 2-methoxy-2-phenylacetate (**23**).* $[\alpha]_D^{20}$ 29.52 (c 2.0, $CHCl_3$); IR (film) ν_{max} 3169, 2928, 2850, 1748, 1719, 1643, 1456, 1352, 1177, 1111, 1012, 903, 755, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (br s, 1H), 7.36 (m, 5H), 5.52 (m, 1H), 4.92 (s, 1H), 4.90 (s, 1H), 3.40 (s, 3H), 3.03 (ddd, J=8.4, 6.4, 2.4 Hz, 1H), 2.69 (d, J=8.4 Hz, 1H), 2.67 (d, J=6.4 Hz, 1H), 2.37 (ddd, J=12.8, 3.6, 2.0 Hz, 1H), 1.92–1.67 (m, 4H), 1.63–0.98 (m, 10H), 0.90 (s, 3H), 0.78 (s, 3H), 0.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 175.4, 169.2, 146.3, 136.1, 128.74, 128.67 (2C), 126.8 (2C), 108.5, 82.6, 72.3, 57.5, 55.7, 55.6, 44.0, 41.9, 39.6, 39.1, 38.0, 33.55, 33.51, 29.9, 25.9, 24.1, 21.6, 19.2, 14.2; HRMS (ESI^+) m/z calcd for $C_{29}H_{39}NO_5Na$ $[M+Na]^+$ 504.2720; found 504.2713.

*4.3.1.2. (R)-((S)-1-((R)-2,5-Dioxopyrrolidin-3-yl)-2-((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)ethyl) 2-methoxy-2-phenylacetate (**24**).* $[\alpha]_D^{20}$ −2.33 (c 2.3, $CHCl_3$); IR (film) ν_{max} 3249, 2924, 2849, 1747, 1714, 1712, 1456, 1349, 1178, 1104, 754, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (br s, 1H), 7.36 (m, 5H), 5.56 (m, 1H), 5.41 (br s, 1H), 4.71 (s, 1H), 3.39 (s, 3H), 3.15 (ddd, J=7.2, 5.1, 2.1 Hz, 1H), 2.70 (d, J=7.2 Hz, 2H), 1.96 (m, 1H), 1.82 (m, 1H), 1.74 (s, 3H), 1.60–1.36 (m, 8H), 1.13 (m, 2H), 0.86 (s, 3H), 0.85 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 175.4, 169.3, 136.0, 133.4, 128.8, 128.7 (2C), 126.8 (2C), 123.3, 82.6, 73.5, 57.5, 49.92, 49.87, 43.9, 42.0, 39.6, 36.7, 33.0, 32.9, 30.3, 29.3, 23.7, 22.2, 21.7, 18.7, 13.4; HRMS (ESI^+) m/z calcd for $C_{29}H_{39}NO_5Na$ $[M+Na]^+$ 504.2720; found 504.2714.

*4.3.2. Synthesis of (R)- and (S)-MPA esters of compound **22**. 4.3.2.1. (R)-((S)-1-((R)-2,5-Dioxopyrrolidin-3-yl)-2-((4aS,8aS)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl) ethyl) 2-methoxy-2-phenylacetate (**25**).* Following the general procedure for MPA esters, compound **22** (2.0 mg, 0.006 mmol), (*R*)-MPA (2 mg, 0.012 mmol), DMAP (0.05 mg, 0.0004 mmol) in $CDCl_3$ (0.5 mL) were reacted with EDC·HCl (7.8 mg, 0.04 mmol). The crude mixture was purified first by silica gel chromatography eluted with 20% EtOAc in hexane then by preparative TLC eluted with 25% EtOAc in hexane to provide the (*R*)-MPA ester **25** as a white foam in 75% yield (2.7 mg). R_f (50% EtOAc/hexane) 0.62; $[\alpha]_D^{20}$ 59.75 (c 1.05, $CHCl_3$); IR (film) ν_{max} 3270, 2925, 2848, 1748, 1715, 1712, 1636, 1456, 1352, 1262, 1174, 1099, 1028, 800, 737, 699, 607; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (br s, 1H), 7.38–7.34 (m, 5H), 5.68 (ddd, J=8.8, 7.2, 2.4, 1H), 4.67 (s, 1H), 3.37 (s, 3H), 3.05 (ddd, J=8.4, 6.0, 2.4, 1H), 2.76 (d, J=6.0 Hz, 1H), 2.75 (d, J=8.4 Hz, 1H), 2.42 (dd, J=14.4, 8.8 Hz, 1H), 2.13 (dd, J=14.4, 7.2 Hz, 1H), 1.91–1.73 (m, 3H), 1.40 (s, 3H), 1.68–1.26 (m, 7H), 1.19–1.11 (m, 1H), 0.94 (s, 3H), 0.87 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 175.4, 169.4, 135.9, 134.3, 130.9, 128.8, 128.7 (2C), 127.1 (2C), 82.7, 72.6, 57.4, 50.8, 45.2, 41.5, 38.5, 37.2, 33.3, 30.9, 30.6, 30.3, 29.7, 21.8, 20.9, 20.4, 18.9, 18.8; HRMS (ESI^+) m/z calcd for $C_{29}H_{39}NO_5Na$ $[M+Na]^+$ 504.2720; found 504.2737.

*4.3.2.2. (S)-((S)-1-((R)-2,5-Dioxopyrrolidin-3-yl)-2-((4aS,8aS)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl) ethyl) 2-methoxy-2-phenylacetate (**26**).* Following the general procedure for MPA esters, **22** (1.0 mg, 0.003 mmol), (*S*)-MPA (2 mg, 0.012 mmol), DMAP (0.05 mg, 0.0004 mmol) in $CDCl_3$ (0.5 mL) were reacted with EDC (7.8 mg, 0.04 mmol). The crude mixture was purified first by silica gel chromatography, eluted with 20% EtOAc in hexane then by preparative TLC eluted with 25% EtOAc in hexane to provide (*S*)-MPA ester **26** was obtained in 44% yield (0.8 mg). R_f (50% EtOAc/hexane) 0.65; $[\alpha]_D^{20}$ +7.02 (c 1.05, $CHCl_3$); IR (film) ν_{max} 2960, 2925, 1755, 1715, 1713, 1659, 1462, 1282, 1177, 1097, 1022, 866, 801, 700, 615 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.32 (m, 5H), 6.72 (br s, 1H), 5.66 (ddd, J=8.0, 5.2, 2.0 Hz, 1H), 4.60 (s, 1H), 3.38 (s, 3H), 2.89 (ddd, J=8.5, 5.8, 2.6 Hz, 1H), 2.62 (d, J=5.8 Hz, 1H), 2.61 (d, J=8.5 Hz, 1H), 2.48 (dd, J=14.4, 9.6 Hz, 1H), 2.21 (dd, J=14.4, 5.2 Hz, 1H), 2.00 (m, 2H), 1.78 (m, 1H), 1.67–1.15 (m, 11H), 0.97 (s, 3H), 0.89 (s, 3H), 0.84 (s, 3H); HRMS (ESI^+) m/z calcd for $C_{29}H_{39}NO_5Na$ $[M+Na]^+$ 504.2720; found 504.2716. The small quantity compound **26** obtained (0.8 mg) did not allow us to record a full ^{13}C NMR spectrum.

Acknowledgements

We thank the Agency for Science, Technology and Research (A*STAR) of Singapore and MerLion Pharmaceuticals Pte Ltd for funding this project, Prof. Brian Cox (AstraZeneca, Macclesfield, UK) and Prof. Richard J. K. Taylor (Department of Chemistry, University of York) for helpful discussions. We also thank Dr. Paul Bernardo (ICES) for preliminary studies, Ms. Xu Jin (ICES) and the Chemical Synthesis Laboratory (ICES) for HPLC support.

Supplementary data

^{1}H and ^{13}C NMR spectra for compounds **10**, **16**, **18**, **19**, **7**, **22**–**25** and ^{1}H NMR spectrum of **26** are provided. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.09.031. These data include MOL files and

InChiKeys of the most important compounds described in this article.

References and notes

1. Malochet-Grivois, C.; Cotelle, P.; Biard, J.-F.; Henichart, J. P.; Debitus, C.; Roussakis, C.; Verbist, J.-F. *Tetrahedron Lett.* **1991**, *32*, 6701.
2. (a) Malochet-Grivois, C.; Roussakis, C.; Robillard, N.; Biard, J. F.; Riou, D.; Debitus, C.; Verbist, J.-F. *Anticancer Drug Des.* **1992**, *7*, 493; (b) Roussaki, C.; Charrier, J.; Riou, D.; Biard, J.-F.; Malochet-Grivois, C.; Meflah, K.; Verbist, J.-F. *Anticancer Drug Des.* **1994**, *9*, 119.
3. Biard, J.-F.; Malochet-Grivois, C.; Roussakis, C.; Cotelle, P.; Henichart, J. P.; Debitus, C.; Verbist, J.-F. *Nat. Prod. Lett.* **1994**, *4*, 43.
4. Toupet, L.; Biard, J.-F.; Verbist, J.-F. *J. Nat. Prod.* **1996**, *59*, 1203.
5. Uddin, M. J.; Kokubu, S.; Suenaga, K.; Ueda, K.; Uemura, D. *Heterocycles* **2001**, *54*, 1039.
6. Uddin, M. J.; Kokubu, S.; Ueda, K.; Suenaga, K.; Uemura, D. *J. Nat. Prod.* **2001**, *64*, 1169.
7. Uddin, M. J.; Kokubu, S.; Ueda, K.; Suenaga, K.; Uemura, D. *Chem. Lett.* **2002**, *31*, 1028.
8. Uddin, M. J.; Ueda, K.; Siwu, E. R. O.; Kita, M.; Uemura, D. *Bioorg. Med. Chem.* **2006**, *14*, 6954.
9. Fu, X.; Palomar, A. J.; Hong, E. P.; Schmitz, F. J.; Valeriote, F. A. *J. Nat. Prod.* **2004**, *67*, 1415.
10. Robert, F.; Gao, H. Q.; Donia, M.; Merrick, W. C.; Hamann, M. T.; Pelletier, J. *RNA* **2006**, *12*, 717.
11. González, M. A.; Romero, D.; Zapata, B.; Betancur-Galvis, L. *Lett. Org. Chem.* **2009**, *6*, 289.
12. Hajra, S.; Giri, A. K.; Karmakar, A.; Khatua, S. *Chem. Commun.* **2007**, 2408.
13. Stoncius, A.; Nahrwold, M.; Sewald, N. *Synthesis* **2005**, *11*, 1829.
14. Boukouvalas, J.; Wang, J.-X.; Marion, O.; Ndzi, B. *J. Org. Chem.* **2006**, *71*, 6670.
15. (a) Kim, H.-C.; Park, O.-S. *Tetrahedron: Asymmetry* **2008**, *19*, 896; (b) Evans, D. A.; Briton, T. G.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.
16. For examples of succinimide formation starting from succinic acid derivatives with ammonia, see: (a) Obniska, J.; Kaminski, K.; Skrzynska, D.; Pichor, J. *Eur. J. Med. Chem.* **2009**, *44*, 2224; (b) Miller, C. A.; Long, M. L. *J. Am. Chem. Soc.* **1953**, *75*, 373.
17. (a) Chibale, K.; Warren, S. *Tetrahedron Lett.* **1991**, *32*, 6645; (b) Evans, D. A.; Sjogren, E. B.; Dow, B. J. *Tetrahedron Lett.* **1986**, *27*, 4957.
18. Attempts to recrystallise either **18** or **19** obtained in small quantities after HPLC separation for X-ray analysis in order to determine the stereochemistry, were unsuccessful.
19. The energy minimised conformations were obtained using the MMFF94 force field, Spartan 04 version for Windows; Wavefunction, Inc.
20. (a) Evans, D. A.; Bartrolo, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127; (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.
21. Latypov, S. K.; Seco, J. M.; Quio, E.; Riguera, R. *J. Org. Chem.* **1996**, *61*, 8569.