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Synthesis of hexahydrocarbazoles by cyclisation of 3-(but-3-enyl) indole derivatives

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ABSTRACT

A new cyclisation of 3-(but-3-enyl) indole derivatives that produces policyclic compounds with a hexahydrocarbazole structure is described. In this reaction three stereogenic centres are generated in one step, and this process can be considered as evidence of the biogenetic relationship between anominine and tubingensin A.

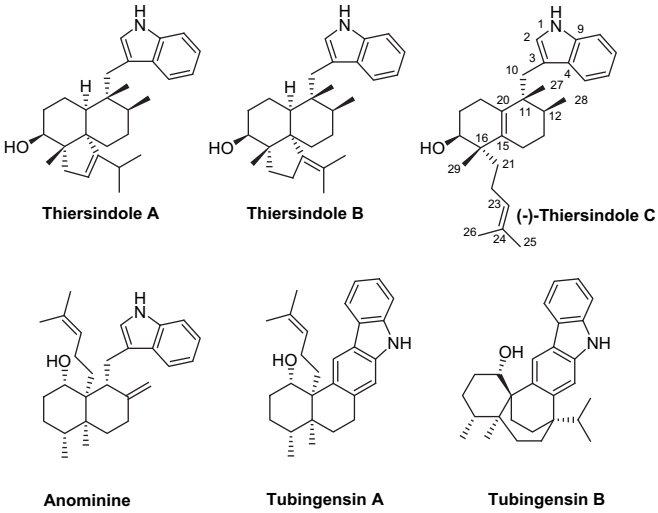
1. Introduction

Indole diterpene alkaloids isolated from fungi are very interesting natural compounds as a result of structural diversity and the bioactivity, which is often observed.[1] Tremorgenic,[2] antiinsect,[3] pollen growth inhibition,[4] antitumour[5] and antiviral activities[6] are the most frequently found.

Until now, more than one hundred indole diterpenes are known whose structure and biosynthesis have been fully established, although not many display the carbazole system present in tubingensins A and B.[6] The latter are diterpenes that show antiviral and antitumoural activity and have in their structure a 9*H*-octahydronaphto[2,1-*b*]carbazole ring system.

Recently our group has published the synthesis of (+)-thiersindole C[7] and preliminary studies towards the synthesis of thiersindoles A and B[8] are in progress. In this paper we will describe the discovery of a cyclisation reaction that, in one step, generates three new stereogenic centres with total stereoselection, to give a compound identified as a hexahydrocarbazole derivative. The development of methodologies for the synthesis of complex polycyclic systems present in natural products and analogues is an interesting goal; this reaction could be the keystone of just such as approach to the synthesis of analogues of tubingensin A.

Furthermore, our observation of this cyclisation strongly supports the hypothesis that anominine[9] is the biogenetic precursor of tubingensin A.



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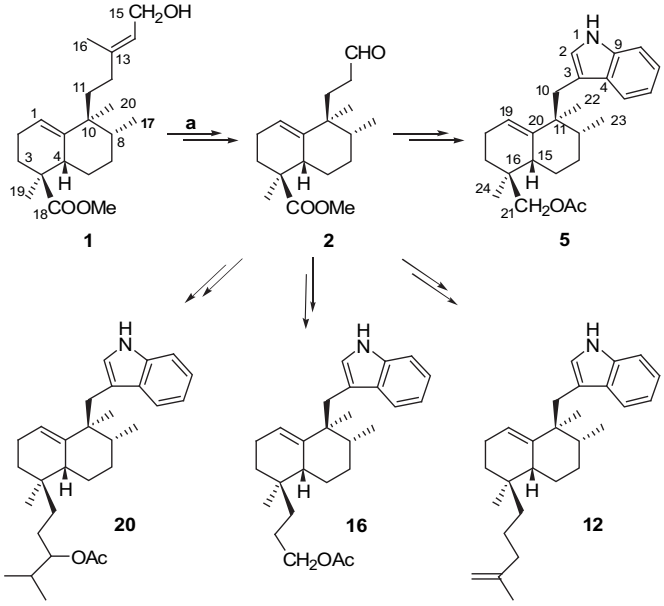
In this paper we describe this new cyclisation of 3(but-3-enyl) indole derivatives that leads to polycyclic hexahydrocarbazoles.

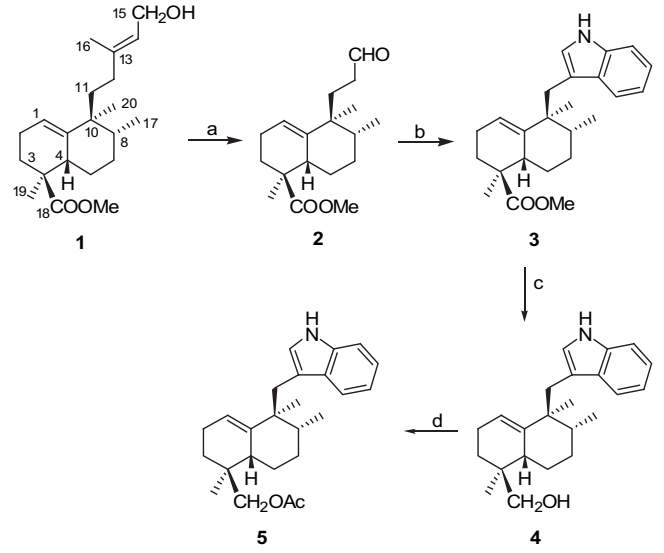
2. Results and discussion

The aim of this work is to study the cyclisation of indole derivatives giving rise to hexahydrocarbazoles that could be considered analogues of tubingensins. The indole derivatives **5**, **12**, **16** and **20**, all of which were obtained from compound **2**, Scheme 1, were selected as the starting materials for this study. Compound **2** was synthesised in six steps in 75% yield, from *ent*-halimic acid **1**,[7] and was an intermediate in the synthesis of thiersindole C.



Scheme 1. Aldehyde **2** for the synthesis of the starting material for the cyclisation. (a) Ref. 7.

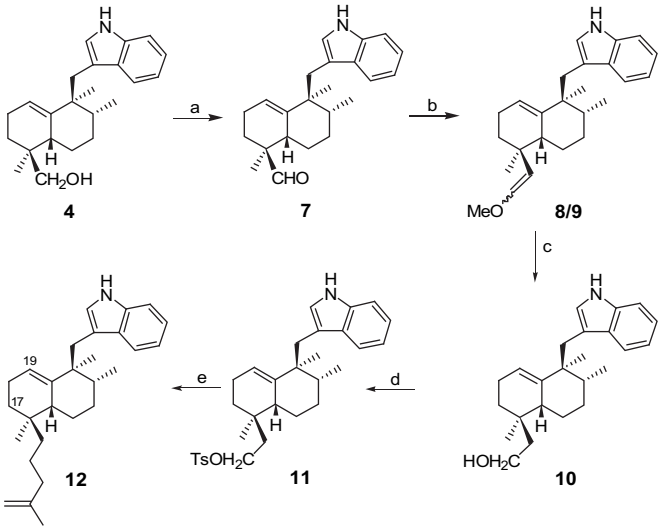
Next, the transformation of trinorderivative **2** into the various indole diterpenes will be described, starting in Scheme 2 with the synthesis of compound **5**.



Scheme 2. Reagents and conditions: (a) Ref. 7; (b) $PhNHNH_2$, HOAc, rt, 2 h, then 120 °C, 2 h, 95%; (c) LAH, Et_2O, 97%; (d) Ac_2O, Py, 95%.

For the introduction of the indole group Fischer methodology[10] was used. Thus, by reaction of **2** with phenylhydrazine in acetic acid for two hours at room temperature and then heating to 120 °C, the indole derivative **3** was obtained in an excellent yield. Reduction of **3** followed by acetylation gave compound **5**.

The starting material for the next cyclisation reaction, compound **12**, was obtained as shown in Scheme 3.



Scheme 3. Reagents and conditions: (a) TPAP, NMO, molecular sieves, CH_2Cl_2, rt, 30 min, 95%; (b) $MeOCH_2PPh_3Cl$, NaHMDS, THF, −78 °C, 30 min, (**8**: 33%, **9**: 57%); (c) (i) *p*-TsOH, Me_2CO–H_2O, rt, 3 h; ii) $NaBH_4$, EtOH, 30 min, 36%; (d) TsCl, Py, rt, 90 min, 80%; (e) 2-methylallylmagnesium chloride, THF, 0 °C-rt, overnight, 58%.

Compound **12** is an analogue of (+)-thiersindole C, of which it is the 17-desoxy derivative with and olefin introduced at C-19. The synthesis was achieved following a similar scheme to that used for (+)-thiersindole C, that is, elongation of the side chain by one carbon atom via a Wittig and then introduction of the remaining four carbon atoms by substitution of an appropriate electrophile derived from this intermediate.

TPAP oxidation[11] of **4** gave aldehyde **7**, which upon reaction with $MeOCH_2PPh_3Cl$[12] gave the enol ether mixture **8**/**9**. The next sequence is the introduction of the four carbon atoms. Hydrolysis of **8**/**9** with *p*-toluensulfonic acid gives an unstable aldehyde, that was submitted to reduction with $NaBH_4$ to give the hydroxy derivative **10**.[13] Tosylation of **10** and substitution of the tosyl derivative **11** with 2-methylallylmagnesium chloride[14] gave, in good yield, the indole diterpene **12**, the analogue of thiersindole C.

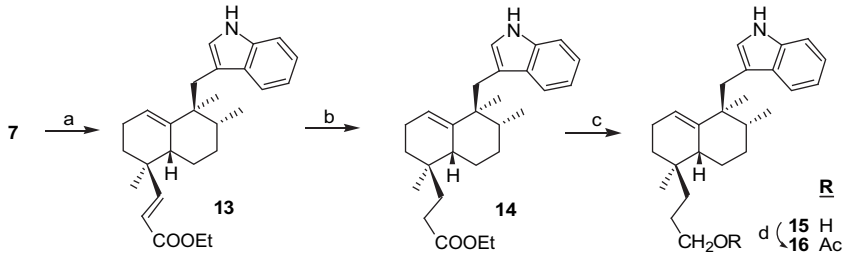
For the synthesis of the next starting material, **16,** the route shown in Scheme 4 was followed. Horner–Wadsworth–Emmons reaction of aldehyde **7** with $(EtO)_2P(O)CH_2COOEt$ in the presence of sodium hydride[15] gave **13**, which was chemoselectively hydrogenated with Wilkinson's catalyst $(Ph_3P)_3RhCl$ in the presence of Et_3SiH and HCl,[16] giving **14**. Reduction of the latter compound with LAH followed by acetylation of the hydroxyl derivative **15** produced **16**.

The final starting material for the cyclisation, the indole diterpene **20**, was synthesised starting from **15** (Scheme 5).

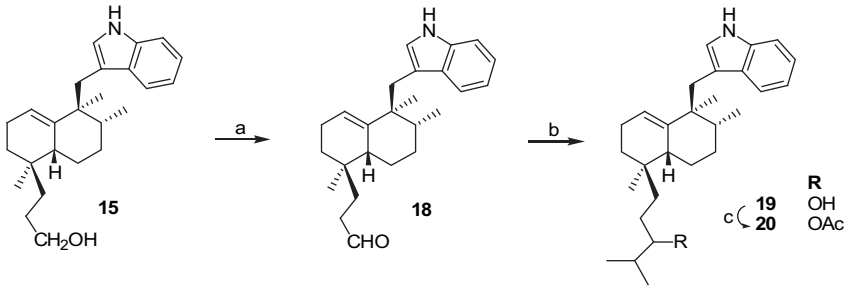
TPAP oxidation of **15** followed by addition of isopropylmagnesium chloride to the aldehyde **18** gave the hydroxy derivative **19**, which, on acetylation under the usual conditions led to the required compound **20**.

Once the starting materials, **5**, **12**, **16** and **20**, had been obtained the cyclisation reactions were tried on them in the presence of hydroiodic acid (Scheme 6).

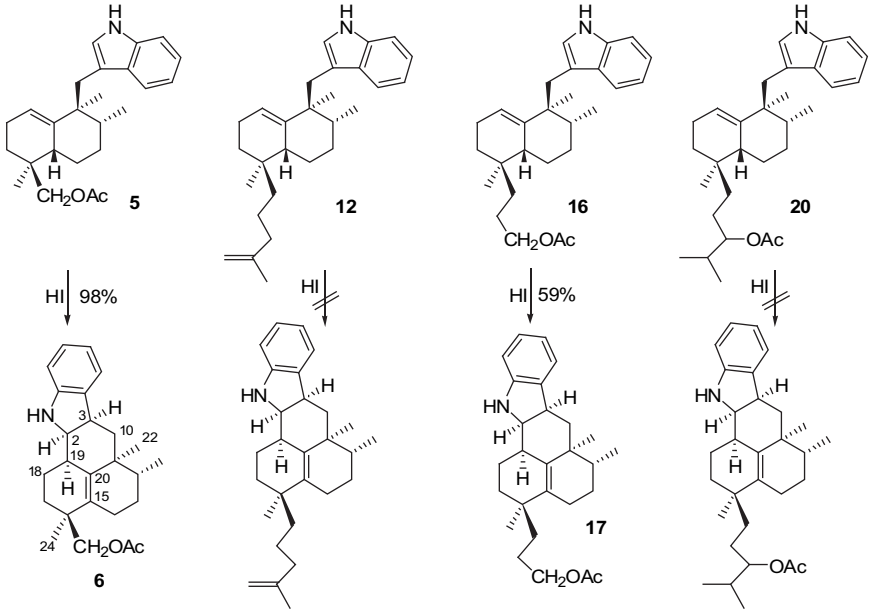
Treatment of **5** with HI at reflux in benzene gave a pentacyclic compound **6** (Scheme 6). The hexahydrocabazole structure for this compound was deduced from bidimensional NMR experiments, $^1H/^{13}C$ NMR (HMQC and HMBC). The upfield shifts of signals for H-2 and H-10 in ^1H NMR show that the indole group has been



Scheme 4. Reagents and conditions: (a) $(EtO)_2P(O)CH_2COOEt$, NaH, C_6H_6, 0 °C, 15 min, then, rt, 30 min, 73%; (b) $(Ph_3P)_3RhCl$, Et_3SiH, HCl, C_6H_6, 70 °C, 14 h, 99%; (c) LAH, Et_2O, 45 min, 93%; (d) Ac_2O, Py, rt, overnight, 94%.



Scheme 5. Reagents and conditions: (a) TPAP, NMO, molecular sieves, CH_2Cl_2, rt, 20 min, 90%; (b) *i*-PrMgCl, THF, rt, overnight, 44%; (c) Ac_2O, Py, rt, overnight, 98%.



Scheme 6. Cyclisation reactions with HI.

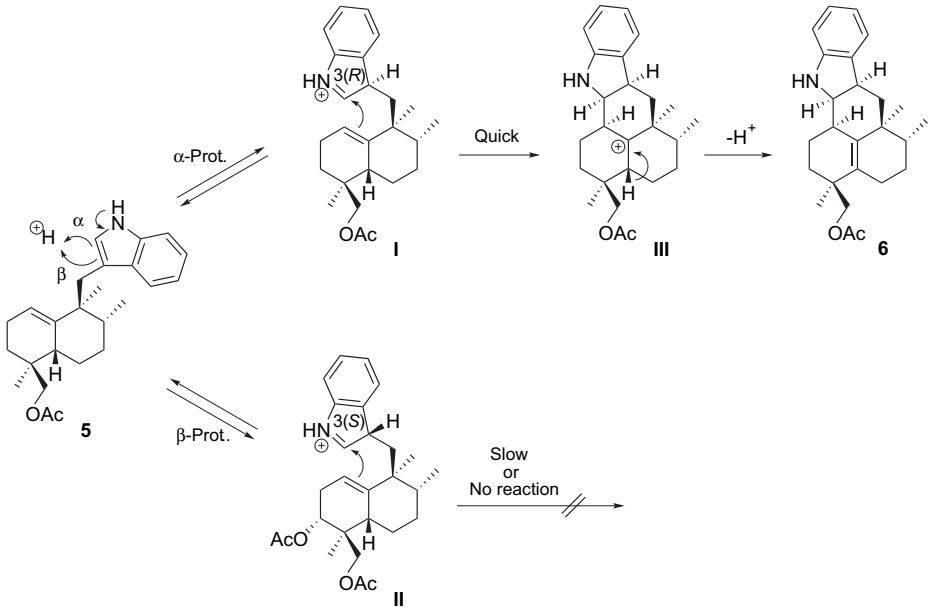
involved in the reaction. The shift of H-19 and the correlation of C-2 with H-18, indicate that a reaction of the ring double bond and the indole group has taken place, forming a new carbocyclic system between C-2 and C-19. Besides, in the ^{13}C NMR spectrum two quaternary carbons at 133.3 and 135.3 ppm, that showed a 1,3 relationship with H-24 and H-22, respectively, were observed, confirming the cyclisation at C-19 and the presence of a tetrasubstituted olefin $\Delta^{15(20)}$.

The cyclisation reaction is stereoselective and generates three new stereocentres in one step. NOEs from H-2 with H-3 and H-19, and from Me-22 with H-3 and H-19 permit the stereochemistry to be determined as 2*R*, 3*R*, 19*R* for the new stereocentres. So, hydrogens H-2, H-3 and H-19 are on the α side of the pentacyclic molecule.

Reaction of **16** with HI gave the hexahydrocarbazole **17**, as determined by spectroscopic analysis, that shows similar NOEs and correlations as for **6**.

Preliminary trials for the cyclisation of **12** and **20**, in acidic media, only gave complex mixtures, from which no could be isolated cyclisation product. It appears that for the cyclisation to hexahydrocarbazoles only substrates without any additional functionality that can be involved in the acidic media reaction can be used.

This result can be explained by a protonation of the indole group at C-3, that generates two stereoisomers, 3*R* and 3*S*, by protonation on the α side or β side of the molecule, respectively. Both intermediates **I** and **II** generated in the reaction are in equilibrium with the starting material. It seems that intermediate **I** can more



Scheme 7. Mechanism proposal for the cyclisation step.

easily adopt the conformation for the double bond attack than intermediate **II**. Once that the cyclisation has taken place a pentacyclic intermediate with a trisubstituted carbocation **III** is obtained, which loses a proton to give **6** (Scheme 7).

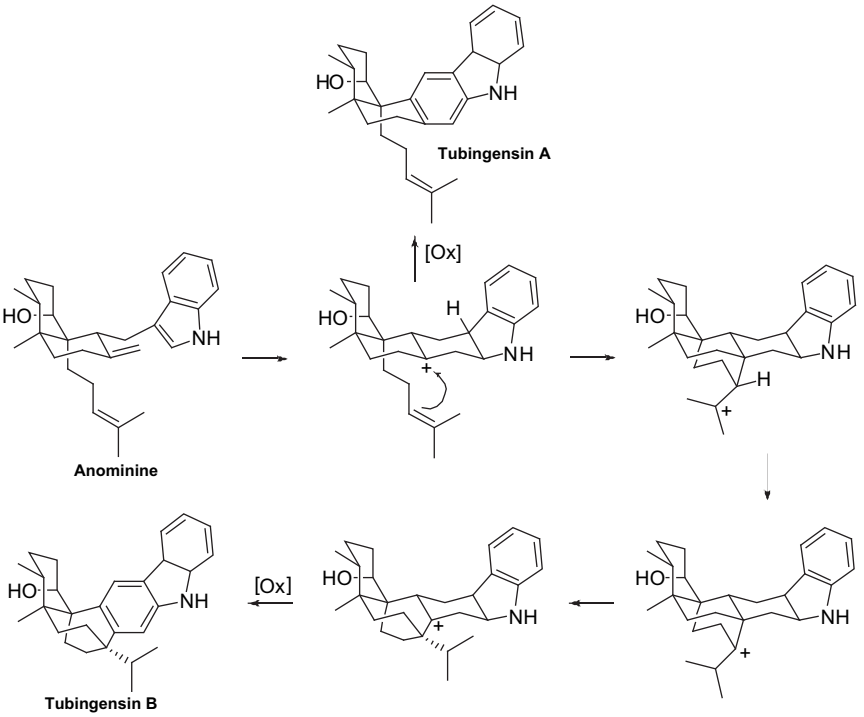
3. Conclusions

In conclusion, two compounds with a hexahydrocarbazole structure have been obtained (analogous to that of tubingensin A) by cyclisation of unsaturated 3-alkylindoles. This reaction would suggest anominine as a possible biogenetic precursor of tubingensin A and B (Scheme 8). This reaction can open a new route to the synthesis of anominine and tubingensin derivatives.

4. Experimental

4.1. General

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. IR spectra were recorded on an AVATAR 370 FTIR Thermo Nicolet spectrophotometers. ^{1}H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^{1}H and ^{13}C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ parts per million and coupling constants (J) are given in hertz. MS were performed using a VG-TS 250 spectrometer at 70 eV



Scheme 8. Anominine as biogenetic precursor of tubingensin A and B.

ionising voltage. Mass spectra are presented as *m*/*z* (% rel int.). HRMS were recorded on a VG Platform (Fisons) spectrometer using chemical ionisation (ammonia as gas) or Fast Atom Bombardment (FAB) technique. For some of the samples, QSTAR XL spectrometer was employed for electrospray ionisation (ESI). Optical rotations were determined on a Perkin–Elmer 241 polarimeter in 1 dm cells. Diethyl ether and THF were distilled from sodium, and dichloromethane was distilled from calcium hydride under argon atmosphere.

*4.1.1. Compound **3**.* To a solution of **2** (1.54 g, 5.27 mmol) in acetic acid (20 mL) was added phenylhydrazine (0.6 mL, 6.10 mmol) and the mixture was stirred at room temperature for 2 h, and at 130 °C for 2 h more. Then, the reaction mixture was diluted with EtOAc and washed with 6% aqueous $NaHCO_3$ and brine. Evaporation of the solvent after drying over Na_2SO_4 gave a residue, which was chromatographed on silica gel (Hex/EtOAc 95/5) to afford **3** (1.83 g, 95%).

R_f=0.58 (hexane/EtOAc 8:2); $[\alpha]_D^{22}$ −45.7 (*c* 0.81, $CHCl_3$); mp 129–132 °C; IR (film, cm^{-1}): 3399, 3052, 2949, 1727, 1457, 1434, 1379, 1255, 1232, 1198, 1112, 739; ^{1}H NMR *δ*: 8.01 (1H, br s, H-1), 7.63 (1H, d, *J*=7.6 Hz, H-5), 7.34 (1H, d, *J*=7.6 Hz, H-8), 7.16 (1H, t, *J*=7.6 Hz, H-7), 7.10 (1H, t, *J*=7.6 Hz, H-6), 6.94 (1H, s, H-2), 5.25 (1H, s, H-19), 3.72 (3H, s, –COO*Me*), 3.09 (1H, d, *J*=14.2 Hz, H_A-10), 2.98 (1H, d, *J*=14.2 Hz, H_B-10), 1.18 (3H, s, Me-24), 2.39–1.04 (10H, m), 0.88 (3H, s, Me-22), 0.83 (3H, d, *J*=6.8 Hz, Me-23); ^{13}C NMR *δ*: 179.2 (C-21), 141.4 (C-20), 135.6 (C-9), 129.5 (C-4), 123.3 (C-2), 121.5 (C-7), 120.2 (C-6), 119.7 (C-5), 119.2 (C-19), 113.6 (C-3), 111.0 (C-8), 52.1 (–COO*Me*), 45.4 (C-16), 44.7 (C-11), 38.9 (C-15), 37.9 (C-12), 35.2 (C-10), 31.9 (C-17), 28.7 (C-13), 23.6 (C-22), 22.9 (C-14), 23.0 (C-18), 16.3 (C-23), 18.8 (C-24); EIHRMS: calcd for $C_{24}H_{31}NO_2$ (M^+): 365.2353, found: 365.2355.

*4.1.2. Compound **4**.* An ice cooled solution of **3** (316 mg, 0.87 mmol) in Et_2O (9 mL), was treated with LAH (33 mg, 0.87 mmol) and the mixture was stirred at room temperature for 1 h. Then, the reaction mixture was cooled back to 0 °C, wet Et_2O was added and the mixture was filtered. The resulting organic phase was dried over Na_2SO_4, filtered and evaporated to get **4** (283 mg, 97%).

R_f (hexane/EtOAc 7:3)=0.39; $[\alpha]_D^{22}$ −4.7 (*c* 0.94, $CHCl_3$); IR (film, cm^{-1}): 3415, 3052, 2925, 1457, 1378, 1040, 908, 737, 665; ^{1}H NMR *δ*: 7.99 (1H, br s, H-1), 7.61 (1H, dd, *J*=6.8 and 1.6 Hz, H-5), 7.33 (1H, dd, *J*=6.8 and 1.6 Hz, H-8), 7.15 (1H, td, *J*=6.8 and 1.6 Hz, H-7), 7.06 (1H, td, *J*=6.8 and 1.6 Hz, H-6), 6.95 (1H, d, *J*=2.2, H-2), 5.27 (1H, dd, *J*=4.0 and 3.0 Hz, H-19), 3.47 (1H, d, *J*=10.8 Hz, H_A-21), 3.31 (1H, d, *J*=10.8 Hz, H_B-21), 3.17 (1H, d, *J*=14.6 Hz, H_A-10), 2.86 (1H, d, *J*=14.6 Hz, H_B-10), 2.36–1.02 (10H, m), 0.93 (3H, s, Me-22), 0.86 (3H, s, Me-24), 0.84 (3H, d, *J*=7.0 Hz, Me-23); ^{13}C NMR *δ*: 142.0 (C-20), 135.8 (C-9), 129.4 (C-4), 123.1 (C-2), 121.5 (C-7), 120.5 (C-6), 113.5 (C-3), 119.6 (C-5), 119.2 (C-19), 111.1 (C-8), 70.1 (C-21), 44.9 (C-11), 38.4 (C-15), 37.5 (C-12), 36.9 (C-16), 34.9 (C-10), 29.6 (C-17), 29.5 (C-13), 23.9 (C-22), 23.2 (C-18), 22.7 (C-14), 20.3 (C-24), 16.2 (C-23); EIHRMS: calcd for $C_{23}H_{31}NONa$ (M^++Na): 360.2298, found: 360.2296.

*4.1.3. Compound **5**.* To a solution of **4** (890 mg, 2.64 mmol) in dry pyridine (3.3 mL), Ac_2O (3.3 mL) was added and the mixture was stirred at room temperature overnight. The reaction mixture was poured into ice-water and extracted with EtOAc. The organic layer was washed successively with 2 M aqueous HCl, 6% aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to afford a residue, which was purified by column chromatography (Hex/EtOAc 9/1) to afford **5** (293 mg, 95%).

R_f=0.49 (hexane/EtOAc 8:2); $[\alpha]_D^{22}$ −15.2 (*c* 0.97, $CHCl_3$); IR (film, cm^{-1}): 3409, 3052, 2926, 1740, 1458, 1376, 1242, 1035, 739, 666; ^{1}H NMR *δ*: 8.10 (1H, br s, H-1), 7.59 (1H, dd, *J*=7.0 and 1.6 Hz, H-5), 7.30 (1H, dd, *J*=7.0 and 1.6 Hz, H-8), 7.14 (1H, td, *J*=7.0 and 1.6 Hz, H-7), 7.08 (1H, td, *J*=7.0 and 1.6 Hz, H-6), 6.89 (1H, d, *J*=2.2, H-2), 5.29 (1H, dd, *J*=3.8 and 2.6 Hz, H-19), 3.93 (1H, d, *J*=10.6 Hz, H_A-21), 3.78 (1H, d, *J*=10.6 Hz, H_B-21), 3.12 (1H, d, *J*=14.8 Hz, H_A-10), 2.89 (1H, d, *J*=14.8 Hz, H_B-10), 1.97 (3H, s, -OOCMe), 2.33–1.01 (10H, m), 0.92 (3H, s, Me-22), 0.89 (3H, s, Me-24), 0.82 (3H, d, *J*=7.0 Hz, Me-23); ^{13}C NMR *δ*: 171.8 (–OO*C*Me), 141.8 (C-20), 135.9 (C-9), 129.4 (C-4), 122.9 (C-2), 121.6 (C-7), 120.4 (C-6), 119.5 (C-5), 119.2 (C-19), 113.4 (C-3), 111.1 (C-8), 71.3 (C-21), 44.8 (C-11), 38.4 (C-15), 38.1 (C-12), 35.4 (C-16), 34.9 (C-10), 29.6 (C-17), 29.2 (C-13), 23.7 (C-22), 23.2 (C-18), 22.6 (C-14), 21.1 (–OOC*Me*), 20.7 (C-24), 16.1 (C-23); EIHRMS: calcd for $C_{25}H_{33}NO_2Na$ (M^++Na): 402.2404, found: 402.2403.

*4.1.4. Compound **7**.* To a mixture of **4** (167 mg, 0.49 mmol), *N*-methylmorpholine-*N*-oxide (NMO) (232 mg, 1.72 mmol) and molecular sieves (248 mg, 500 mg/mmol) in anhydrous CH_2Cl_2 (1.1 mL) under Ar at room temperature, TPAP (9 mg, 0.025 mmol) was added and the mixture was stirred for 30 min. The reaction mixture was filtered through a pad of Celite and silica gel (CH_2Cl_2 and EtOAc). Evaporation of the solvent yielded the aldehyde **7** (157 mg, 95%).

R_f=0.39 (hexane/EtOAc 8:2); $[\alpha]_D^{22}$ −23.5 (*c* 0.026, $CHCl_3$); IR (film, cm^{-1}): 3415, 2922, 1718, 1457, 1093, 739; ^{1}H NMR *δ*: 9.46 (1H, s, H-21), 8.01 (1H, br s, H-1), 7.63 (1H, d, *J*=7.0 Hz, H-5), 7.33 (1H, d, *J*=7.0 Hz, H-8), 7.17 (1H, t, *J*=7.0 Hz, H-7), 7.11 (1H, t, *J*=7.0 Hz, H-6), 6.94 (1H, s, H-2), 5.32 (1H, t, *J*=1.5 Hz, H-19), 3.13 (1H, d, *J*=17.6 Hz, H-10_A), 3.00 (1H, d, *J*=17.6 Hz, H-10_B), 2.80 (1H, t, *J*=8.4 Hz, H-15), 2.20–1.18 (9H, m), 1.04 (3H, s, Me-24), 0.92 (3H, s, Me-22), 0.85 (3H, d, *J*=7.0 Hz, Me-23); ^{13}C NMR *δ*: 207.2 (C-21), 123.3 (C-2), 141.5 (C-20), 135.8 (C-9), 129.4 (C-4), 121.7 (C-7), 120.7 (C-6), 119.6 (C-5), 119.3 (C-19), 113.9 (C-3), 111.2 (C-8), 48.5 (C-16), 44.8 (C-11), 38.0 (C-15), 36.2 (C-12), 35.1 (C-10), 28.8 (C-17), 28.2 (C-13), 23.6 (C-22), 23.3 (C-18), 22.4 (C-14), 16.9 (C-24), 16.2 (C-23); EIHRMS: calcd for $C_{23}H_{29}NONa$ (M+Na): 358.2141, found: 358.2143.

*4.1.5. Compounds **8**/**9**.* To a suspension of methoxymethyltriphenylphosphonium chloride (812 mg, 2.36 mmol) in THF (4.7 mL) at −78 °C under Ar atmosphere, 0.6 M NaHMDS in toluene (4.0 mL, 2.4 mmol) was added dropwise and the mixture was stirred for 30 min. Then a solution of **7** (263 mg, 0.78 mmol) in THF (4.0 mL) was added dropwise and the resulting mixture was stirred for 30 min. After that it was allowed to warm up to room temperature, quenched with aqueous saturated NH_4Cl and extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. The residue obtained after removing the solvent was purified by column chromatography (Hex/EtOAc 95/5) to afford the mixture **8** (99 mg, 33%) and **9** (171 mg, 57%).

*4.1.5.1. Compound **8**.* R_f=0.34 (hexane/EtOAc 9:1); $[\alpha]_D^{22}$ −282.5 (*c* 0.02, $CHCl_3$); IR (film, cm^{-1}): 3415, 2929, 1649, 1455, 1379, 1210, 1097, 740; ^{1}H NMR *δ*: 7.95 (1H, br s, H-1), 7.63 (1H, d, *J*=7.0 Hz, H-5), 7.33 (1H, d, *J*=7.0 Hz, H-8), 7.16 (1H, t, *J*=7.0 Hz, H-7), 7.10 (1H, t, *J*=7.0 Hz, H-6), 6.98 (1H,br s, H-2), 5.74 (1H, d, *J*=7.4 Hz, H-22), 5.25 (1H, t, *J*=1.8 Hz, H-19), 4.22 (1H, d, *J*=7.4 Hz, H-21), 3.53 (3H, s, –O*Me*), 3.06 (1H, d, *J*=14.6 Hz, H-10_A), 2.96 (1H, d, *J*=14.6 Hz, H-10_B), 2.57 (1H, m, H-15), 2.15–1.10 (9H, m), 1.10 (3H, s, Me-24), 0.89 (3H, s, Me-22), 0.83 (3H, d, *J*=7.0 Hz, Me-23); ^{13}C NMR *δ*: 145.6 (C-22), 142.2 (C-20), 135.8 (C-9), 123.2 (C-2), 129.6 (C-4), 121.5 (C-7), 120.7 (C-5), 119.7 (C-6), 119.2 (C-19), 117.1 (C-21), 113.9 (C-3), 111.0 (C-8), 59.8 (–O*Me*), 44.7 (C-11), 42.8 (C-15), 38.4 (C-12), 36.8 (C-16), 34.9 (C-10), 32.6 (C-17), 29.3 (C-13), 23.5 (C-18), 23.4 (C-14), 23.1 (C-27), 22.4 (C-29)16.3 (C-28); EIHRMS: calcd for $C_{25}H_{33}NONa$ (M+Na): 386.2454, found: 386.2456.

*4.1.5.2. Compound **9**.* R_f=0.30 (hexane/EtOAc 9:1); $[\alpha]_D^{22}$ −47.4 (*c* 0.03, $CHCl_3$); IR (film, cm^{-1}): 3415, 2929, 1649, 1455, 1379, 1210, 1097, 740; ^{1}H NMR *δ*: 8.01 (1H, br s, H-1), 7.62 (1H, d, *J*=7.2 Hz), 7.34 (1H, d, *J*=7.2 Hz, H-8), 7.17 (1H, t, *J*=7.2 Hz, H-7), 7.10 (1H, t, *J*=7.2 Hz, H-6),

6.93 (1H, br s, H-2), 6.30 (1H, d, *J*=12.8 Hz, H-22), 5.30 (1H, br s, H-19), 4.91 (1H, d, *J*=12.8 Hz, H-21), 3.54 (3H, s, –O*Me*), 3.02 (1H, d, *J*=14.0 Hz, H-10$_A$), 2.96 (1H, d, *J*=14.0 Hz, H-10$_B$), 2.57 (1H, m, H-15), 2.15–1.12 (9H, m), 0.98 (3H, s, Me-24), 0.91 (3H, s Me-22), 0.83 (3H, d, *J*=7.0 Hz, Me-23); ^{13}C NMR δ: 145.9 (C-22), 141.8 (C-20), 135.8 (C-9), 129.5 (C-4), 123.2 (C-2), 121.6 (C-7), 120.6 (C-5), 119.7 (C-6), 119.2 (C-19), 115.1 (C-21), 113.7 (C-3), 111.1 (C-8), 56.4 (–O*Me*), 44.6 (C-11), 43.4 (C-15), 37.8 (C-12), 36.9 (C-16), 35.5 (C-10), 29.0 (C-17), 28.7 (C-13), 23.9 (C-27), 23.2 (C-18), 20.7 (C-29), 22.2 (C-14), 16.3 (C-28); EIHRMS: calcd for $C_{25}H_{33}NONa$ (M+Na): 386.2454, found: 386.2456.

4.1.6. Compound ***10***. To a solution of the mixture **8/9** (39 mg, 0.11 mmol) in acetone/H_2O 98:2 (3.6 mL), *p*-toluenesulfonic acid (7 mg, 0.035 mmol) was added at room temperature and the mixture was stirred for 3 h. It was quenched by adding water and extracted with Et_2O. The organic layer was washed with a 6% aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. The residue obtained after removing the solvent was purified by column chromatography (Hex/EtOAc 8/2) to afford **10** (14 mg, 36%).

R_f=0.21 (hexane/EtOAc 7:3); $[\alpha]_D^{22}$ −8.21 (*c* 0.03, $CHCl_3$); IR (film, cm^{-1}): 3583, 3414, 2925, 1456, 1380, 1092; ^{1}H NMR δ: 7.98 (1H, br s, H-1), 7.61 (1H, dd, *J*=7.0 and 1.8 Hz, H-5), 7.34 (1H, dd, *J*=7.0 and 1.8 Hz, H-8), 7.17 (1H, dt, J=7.0 and 1.8 Hz, H-7), 7.10 (1H, dt, *J*=7.0 and 1.8 Hz, H-6), 6.96 (1H, d, *J*=2.6 Hz, H-2), 5.32 (1H, br s, H-19), 3.68 (1H, ddd, *J*=11.0, 7.0 and 7.0 Hz, H-22$_A$), 3.64 (1H, ddd, *J*=11.0, 7.0 and 7.0 Hz, H-22$_B$), 3.08 (1H, d, *J*=14.6 Hz, H-10$_A$), 2.92 (1H, d, *J*=14.6 Hz, H-10$_B$), 2.15–1.05 (12H, m), 0.93 (3H, s, Me-27), 0.87 (3H,s, Me-29), 0.82 (3H, d, *J*=7.0 Hz, Me-28); ^{13}C NMR δ: 142.2 (C-20), 135.8 (C-9), 129.5 (C-4), 123.0 (C-2), 121.7 (C-7), 120.3 (C-6), 119.7 (C-5), 119.3 (C-19), 113.7 (C-3), 111.1 (C-8), 59.9 (C-22), 44.7 (C-11), 42.9 (C-21), 41.9 (C-15), 38.1 (C-12), 35.0 (C-10), 33.9 (C-16), 32.3 (C-17), 29.3 (C-13), 23.8 (C-27), 23.1 (C-18), 23.0 (C-29), 22.8 (C-14), 16.2 (C-28); EIHRMS: calcd for $C_{24}H_{33}NONa$ (M+Na): 374.2454, found: 374.2467.

4.1.7. Compound ***11***. To a solution of **10** (16 mg, 0.045 mmol) in pyridine (0.22 mL) was added TsCl (29 mg, 0.152 mmol) and the mixture was stirred at room temperature for 1 h and 30 min. The reaction mixture was poured into ice-water and extracted with Et_2O. The extracts were washed successively with 2 M aqueous HCl, 6% aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. Filtration, and evaporation of the solvent gave **11** (19 mg, 80%).

R_f=0.41 (hexane/EtOAc 9:1); $[\alpha]_D^{22}$ −21.1 (*c* 0.01, $CHCl_3$); IR (film, cm^{-1}): 3422, 1655; ^{1}H NMR δ: 8.00 (1H, s, H-1), 7.75 (2H, d, *J*=8.4 Hz, H-2′ and H-6′), 7.57 (1H, d, *J*=7.0 Hz, H-5), 7.34 (1H, d, *J*=7.0 Hz, H-8), 7.28 (2H, d, *J*=8.4 Hz, H-3′ and H-4′), 7.16 (1H, t, *J*=7.0 Hz, H-7), 7.09 (1H, t, *J*=7.0 Hz, H-6), 6.91 (1H, d, *J*=2.0 Hz, H-2), 5.29 (1H, t, *J*=2.8 Hz, H-19), 4.08 (2H, m, H-22), 2.97 (1H, d, *J*=14.4 Hz, H-10$_A$), 2.88 (1H, d, *J*=14.4 Hz, H-10$_B$), 2.38 (3H, s, *Me*C$_6$H$_4$SO$_3$–), 2.18–1.03 (12H, m), 0.90 (3H, s, Me-27), 0.81 (3H, s, Me-29), 0.79 (3H, d, *J*=7.0 Hz, Me-28).

4.1.8. Compound ***12***. To a solution of **11** (23 mg, 0.045 mmol) in tetrahydrofuran (0.22 mL) cooled at 0 °C under Ar atmosphere 0.5 M in THF 2-methylpropenylmagnesium chloride (3.15 mL, 1.55 mmol) was added and the mixture stirred at room temperature overnight. Then, the solution was cooled back to 0 °C, quenched with saturated NH_4Cl aqueous solution and extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. The residue was chromatographed on silica gel (Hex/EtOAc 98/2) to yield **12** (10 mg, 58%).

R_f=0.74 (hexane/EtOAc 95:5); $[\alpha]_D^{22}$ −22.6 (*c* 0.01, $CHCl_3$); IR (film, cm^{-1}): 3412, 2958, 1458, 1383, 1261, 1094; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (1H, br s, H-1), 7.61 (1H, d, *J*=7.6 Hz, H-5), 7.33 (1H, d, *J*=7.6 Hz, H-8), 7.15 (1H, t, *J*=7.6 Hz, H-7), 7.11 (1H, t, *J*=7.6 Hz, H-6), 6.93 (1H, s, H-2), 5.27 (1H, s, H-19), 4.71 (1H, s, H-25$_A$), 4.68 (1H, s, H-25$_B$), 3.05 (1H, d, *J*=14.5 Hz, H-10$_A$), 2.93 (1H, d, *J*=14.5 Hz, H-10$_B$), 2.18–1.10 (14H, m), 1.98 (2H, t, *J*=6.6 Hz, H-23), 1.71 (3H, s, Me-26), 0.88 (3H, s, Me-27), 0.83 (3H, s, Me-29), 0.81 (3H, d, *J*=7.0 Hz, Me-28); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.3 (C-24), 143.2 (C-20), 135.5 (C-9), 129.3 (C-4), 122.7 (C-2), 121.3 (C-7), 120.2 (C-6), 119.4 (C-5), 118.9 (C-19), 113.6 (C-3), 110.9 (C-8), 109.6 (C-25), 44.4 (C-11), 41.7 (C-15), 40.0 (C-21), 38.7 (C-23), 38.0 (C-12), 34.2 (C-16), 34.1 (C-10), 31.5 (C-17), 29.0 (C-13), 23.4 (C-27), 22.8 (C-14), 22.6 (C-18), 22.4 (C-26), 22.2 (C-29), 21.5 (C-22), 15.9 (C-28).

4.1.9. Compound ***13***. To a mixture of NaH (365 mg 60% in mineral oil, 15.22 mmol) and benzene (6.0 mL) cooled at 0 °C, methyl diethylphosphonoacetate (1.8 mL) was added under argon atmosphere and the resulting solution was stirred at room temperature 15 min. Then a solution of **7** (298 mg, 0.89 mmol) in benzene (3.0 mL) was added via canula and the mixture was stirred 30 min at room temperature. Then it was quenched with saturated NH_4Cl aqueous solution and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated to give a crude oil, which was chromatographed on silica gel (Hex/EtOAc 9/1) to afford **13** (265 mg, 73%).

R_f=0.47 (hexane/EtOAc 8:2); $[\alpha]_D^{22}$ −66.2 (*c* 0.06, $CHCl_3$); IR (film, cm^{-1}): 3413, 3054, 2925, 1702, 1644, 1456, 1379, 1307, 1184, 1095, 1036, 739; ^{1}H NMR δ: 8.19 (1H, br s, H-1), 7.63 (1H, d, *J*=7.0 Hz, H-5), 7.32 (1H, d, *J*=7.0 Hz, H-8), 7.12 (1H, d, J=14.0 Hz, H-21), 7.12 (1H, t, *J*=7.0 Hz, H-7), 7.08 (1H, t, *J*=7.0 Hz, H-7), 6.91 (1H, d, *J*=2.2 Hz, H-2), 5.87 (1H, d, *J*=14.0 Hz, H-22), 5.32 (1H,br s, H-19), 4.28 (2H, c, *J*=7.0 Hz, –O*CH*$_2$CH$_3$), 3.06 (1H, d, *J*=14.2 Hz, H-10$_A$), 2.93 (1H, d, *J*=14.2 Hz, H-10$_B$), 2.40–1.08 (10H, m), 1.34 (3H, t, *J*=7.0 Hz, –OCH$_2$*CH*$_3$), 1.06 (3H, s, Me-29), 0.91 (3H, s, Me-27), 0.85 (3H, d, *J*=7.0 Hz, Me-28); ^{13}C NMR δ: 167.8 (C-23), 159.5 (C-21), 141.2 (C-20), 135.9 (C-9), 129.5 (C-4), 123.5 (C-2), 121.5 (C-7), 120.7 (C-6), 119.6 (C-5), 119.2 (C-19), 118.2 (C-22), 113.3 (C-3), 111.2 (C-8), 60.6 (-O*CH*$_2$CH$_3$), 44.9 (C-11), 41.6 (C-15), 38.9 (C-16), 37.9 (C-12), 35.3 (C-10), 33.4 (C-17), 28.9 (C-13), 22.9 (C-14), 22.9 (C-18), 23.9 (C-27), 20.0 (C-29), 16.3 (C-28), 14.6 (–OCH$_2$*CH*$_3$); EIHRMS: calcd for $C_{27}H_{35}NO_2Na$ (M+Na): 428.5600, found (M+Na) 428.2568.

4.1.10. Compound ***14***. To a solution of **13** (147 mg, 0.36 mmol) and Wilkinson's catalyst $(Ph_3P)_3RhCl$ (53 mg, 0.057 mmol) in benzene (3.6 mL) under Ar atmosphere was added Et_3SiH (0.6 mL, 3.6 mmol) and the mixture was stirred at 70 °C for 14 h. Then it was allowed to cool to room temperature and it was quenched with 2 M aqueous HCl. Water was added and the solution was extracted with EtOAc. The organic layer was washed with 6% aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated to give a residue that was chromatographed on silica gel (Hex/EtOAc 95/5) to yield **14** 145 mg (99%).

R_f=0.51 (hexane/EtOAc 8:2); $[\alpha]_D^{22}$ −22.9 (*c* 0.08, $CHCl_3$); IR (film, cm^{-1}): 3412, 2922, 1718, 1457, 1096; ^{1}H NMR δ: 8.07 (1H, br s, H-1), 7.60 (1H, d, *J*=7.6 Hz, H-5), 7.31 (1H, d, *J*=7.6 Hz, H-8), 7.16 (1H, t, *J*=7.6 Hz, H-7), 7.10 (1H, t, *J*=7.6 Hz, H-6), 6.93 (1H, d, *J*=2.0 Hz, H-2), 5.31 (1H, br s, H-19), 4.17 (2H, c, *J*=7.0 Hz, –O*CH*$_2$CH$_3$), 3.07 (1H, d, *J*=14.4 Hz, H-10$_A$), 2.93 (1H, d, *J*=14.4 Hz, H-10$_B$), 2.38–1.08 (14H, m), 1.26 (3H, t, *J*=7.0 Hz, –OCH$_2$*CH*$_3$), 0.94 (3H, s, Me-29), 0.85 (3H, s, Me-27), 0.83 (3H, d, *J*=7.0 Hz, Me-28); ^{13}C NMR δ: 175.0 (C-23), 142.1 (C-20), 135.9 (C-9), 129.5 (C-4), 123.2 (C-2), 121.6 (C-7), 120.4 (C-6), 119.6 (C-5), 119.2 (C-19), 113.6 (C-3), 111.1 (C-8), 60.6 (–O*CH*$_2$CH$_3$), 44.8 (C-11), 41.6 (C-15), 38.2 (C-12), 35.0 (C-10), 35.0 (C-21), 34.2 (C-16), 31.5 (C-17), 29.4 (C-22), 29.2 (C-13), 22.9 (C-14), 23.7 (C-27), 23.1 (C-18), 22.2 (C-29), 16.2 (C-28), 14.5 (–OCH$_2$*CH*$_3$); EIHRMS: calcd for $C_{27}H_{37}NO_2Na$ (M+Na): 430.2717, found: 430.2700.

4.1.11. Compound ***15***. An ice cooled solution of **14** (116 mg, 0.285 mmol) in dry Et_2O (2.9 mL) was treated with $LiAlH_4$ (50 mg, 1.31 mmol) and the mixture was stirred at room temperature for

45 min. Then, the solution was cooled back to 0 °C, wet Et_2O was added and the mixture was filtered. The resulting organic phase was dried over Na_2SO_4, filtered and evaporated affording **15** (97 mg, 93%).

R_f=0.36 (hexane/EtOAc 7:3); $[\alpha]_D^{22}$ −3.3 (*c* 0.08, $CHCl_3$); IR (film, cm^{-1}): 3416, 2954, 1456, 1060, 739; ^1H NMR δ: 8.18 (1H, br s, H-1), 7.63 (1H, d, *J*=7.0 Hz, H-5), 7.32 (1H, d, *J*=7.0 Hz, H-8), 7.17 (1H, t, *J*=7.0 Hz, H-7), 7.10 (1H, t, *J*=7.0 Hz, H-6), 6.94 (1H, br s, H-2), 5.32 (1H, br s, H-19), 3.55 (2H, t, *J*=7.0 Hz, H-23), 3.10 (1H, d, *J*=14.6 Hz, H-10_A), 2.91 (1H, d, *J*=14.6 Hz, H-10_B), 2.28–1.10 (15H, m), 0.93 (3H, s, Me-29), 0.84 (3H, d, *J*=7.0 Hz, Me-28), 0.83 (3H, s, Me-27); ^{13}C NMR δ: 142.3 (C-20), 135.8 (C-9), 129.5 (C-4), 123.1 (C-2), 121.6 (C-7), 120.3 (C-6), 119.6 (C-5), 119.2 (C-19), 113.6 (C-3), 111.1 (C-8), 64.2 (C-23), 44.7 (C-11), 41.9 (C-15), 38.4 (C-12), 36.1 (C-21), 34.5 (C-10), 34.1 (C-16), 31.5 (C-17), 29.5 (C-13), 27.2 (C-22), 23.8 (C-18), 23.3 (C-27), 23.0 (C-29), 22.8 (C-14), 16.2 (C-28); EIHRMS: calcd for $C_{25}H_{35}NONa$ (M+Na): 388.2611, found: 388.2595.

*4.1.12. Compound **16**.* To a solution of **15** (41 mg, 0.113 mmol) in dry pyridine (0.3 mL), acetic anhydride (0.3 mL) was added and the mixture was stirred overnight at room temperature. The reaction mixture was poured into ice-water and extracted with EtOAc. The organic layer was washed successively with aqueous 2 M HCl, aqueous 6% $NaHCO_3$ and brine and the resulting solution was then dried over Na_2SO_4 and evaporated to yield **16** (43 mg, 94%).

R_f=0.36 (hexane/EtOAc 7:3); $[\alpha]_D^{22}$ −3.3 (*c* 0.08, $CHCl_3$); IR (film, cm^{-1}): 3413, 2927, 1735, 1457, 1383, 1244, 1052, 739; ^1H NMR δ: 8.06 (1H, br s, H-1), 7.61 (1H, d, *J*=7.0 Hz, H-5), 7.34 (1H, d, *J*=7.0 Hz, H-8), 7.17 (1H, t, *J*=7.0 Hz, H-7), 7.12 (1H, t, *J*=7.0 Hz, H-6), 7.05 (1H, s, H-2), 5.29 (1H, br s, H-19), 4.03 (2H, t, *J*=6.6 Hz, H-23), 3.11 (1H, d, *J*=14.4 Hz, H-10_A), 2.90 (1H, d, *J*=14.4 Hz, H-10_B), 2.15–1.20 (14H, m), 2.05 (3H, s, CH_3COO–), 0.94 (3H, s, Me-29), 0.84 (3H, s, Me-27), 0.82 (3H, d, *J*=6.8 Hz, Me-28); ^{13}C NMR δ: 171.6 (Me*COO*–), 142.2 (C-20), 135.8 (C-9), 129.5 (C-4), 123.0 (C-2), 121.6 (C-7), 120.4 (C-6), 119.6 (C-5), 119.2 (C-19), 113.6 (C-3), 111.1 (C-8), 65.6 (C-23), 44.8 (C-11), 42.0 (C-15), 38.5 (C-12), 36.1 (C-21), 34.9 (C-10), 34.2 (C-16), 31.2 (C-22), 29.9 (C-17), 29.4 (C-13), 23.7 (C-27), 23.3 (C-18), 23.0 (C-14), 22.6 (*Me*COO–), 21.3 (C-29), 16.2 (C-28).

*4.1.13. Compound **18**.* To a mixture of **15** (63 mg, 0.173 mmol), *N*-methylmorpholine-*N*-oxide (NMO) (69 mg, 0.51 mmol) and molecular sieves (110 mg, 500 mg/mmol) in anhydrous CH_2Cl_2 (1.1 mL) under Ar at room temperature, TPAP (3 mg, 0.01 mmol) was added and the mixture was stirred for 20 min. The reaction mixture was filtered through a pad of Celite and silica gel and washed with CH_2Cl_2 and EtOAc. Evaporation of the solvent yielded the aldehyde **18** (56 mg, 90%).

^1H NMR δ: 9.67 (1H, br s, H-23), 8.07 (1H, br s, H-1), 7.60 (1H, d, *J*=7.0 Hz, H-5), 7.32 (1H, d, *J*=7.0 Hz, H-8), 7.15 (1H, t, *J*=7.0 Hz, H-7), 7.09 (1H, t, *J*=7.0 Hz, H-6), 6.94 (1H, br s, H-2), 5.33 (1H, br s, H-19), 3.12 (1H, d, *J*=14.0 Hz, H-10_A), 2.90 (1H, d, *J*=14.0 Hz, H-10_B), 2.40–1.10 (14H, m), 0.95 (3H, s, Me-29), 0.82 (3H, d, *J*=6.8 Hz, Me-28), 0.81 (3H, s, Me-27).

*4.1.14. Compound **19**.* To a solution of **18** (25 mg, 0.07 mmol) in tetrahydrofuran (0.4 mL) cooled at 0 °C under Ar atmosphere 2.0 M in THF, isopropenylmagnesium chloride (1.8 mL, 3.6 mmol) was added and the mixture stirred at room temperature overnight. It was cooled back to 0 °C, quenched with saturated NH_4Cl aqueous solution and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give a residue that was chromatographed on silica gel (Hex/EtOAc 98/2) to yield **19** (13 mg, 44%).

R_f=0.29 (hexane/EtOAc 75:25); $[\alpha]_D^{22}$ −10.9 (*c* 0.04, $CHCl_3$); IR (film, cm^{-1}): 3411, 2927, 1458, 1384, 1092; ^1H NMR δ: 8.03 (1H,br s, H-1), 7.61 (1H, d, *J*=7.0 Hz, H-5), 7.32 (1H, d, *J*=7.0 Hz, H-8), 7.19 (1H, t, *J*=7.0 Hz, H-6), 7.13 (1H, t, *J*=7.0 Hz, H-7), 6.97 (1H, s, H-2), 5.31 (1H, br s, H-19), 3.25 (1H, m, H-23), 3.10 (1H, d, *J*=14.2 Hz, H-10_A), 2.92 (1H, d, *J*=14.2 Hz, H-10_B), 2.15–1.10 (14H, m), 0.93 (3H, s, Me-29), 0.89 (6H, d, *J*=6.6 Hz, Me-25 and Me-26), 0.83 (3H, s, Me-29), 0.83 (3H, d, *J*=7.0 Hz, Me-28); ^{13}C NMR δ: 142.3 (C-20), 135.8 (C-9), 129.5 (C-4), 123.1 (C-2), 121.6 (C-7), 120.4 (C-6), 119.6 (C-5), 119.2 (C-19), 113.8 (C-3), 111.0 (C-8), 77.9 (C-23), 44.7 (C-11), 42.1 (C-15), 38.3 (C-12), 36.3 (C-21), 34.9 (C-10), 34.2 (C-16), 33.3 (C-24), 31.5 (C-17), 29.4 (C-22), 28.3 (C-13), 23.8 (C-27), 23.3 (C-18), 23.0 (C-14), 22.7 (C-29), 19.3 (C-25), 17.2 (C-26), 16.2 (C-28); EIHRMS: calcd for $C_{28}H_{41}NONa$ (M+Na): 430.3080, found: 430.3083.

*4.1.15. Compound **20**.* To a solution of **19** (19 mg, 0.05 mmol) in dry pyridine (1.0 mL), acetic anhydride (1.0 mL) was added and the mixture was stirred for 13 h at room temperature. The reaction mixture was poured then into ice-water and extracted with EtOAc. The organic layer was washed successively with aqueous 2 M HCl, aqueous 6% $NaHCO_3$ and brine. It was then dried over Na_2SO_4 filtered and evaporated to yield **20** (22 mg, 98%).

R_f=0.47 (hexane/EtOAc 9:1); IR (film, cm^{-1}): 3399, 2923, 1720, 1459, 1384, 1246, 1093; ^1H NMR δ: 8.37 (1H, br s, H-1), 7.59 (1H, d, *J*=7.0 Hz, H-5), 7.33 (1H, d, *J*=7.0 Hz, H-8), 7.14 (1H, t, *J*=7.0 Hz, H-6), 7.08 (1H, t, *J*=7.0 Hz, H-7), 6.90 (1H, br s, H-2), 5.21 (1H, br s, H-19), 4.81 (1H, m, H-23), 4.65 (1H, m, H-23′), 3.30 (1H, d, *J*=14.4 Hz, H-10_A), 2.74 (1H, d, *J*=14.4 Hz, H-10_B), 2.15–1.10 (14H, m), 2.09 (3H, s, –OOC*Me*), 2.00 (3H, s, –OOC*Me*′), 0.92 (3H, d, *J*=6.6 Hz, Me-25), 0.90 (3H, s, Me-29), 0.89 (3H, d, *J*=6.6 Hz, Me-26), 0.84 (3H, s, Me-27), 0.83 (3H, d, *J*=6.8 Hz, Me-28); EIHRMS: calcd for $C_{30}H_{43}NO_2Na$ (M+Na): 472.3186 found: 472.3171.

*4.1.16. Compound **6**.* To a solution of **5** (920 mg, 2.43 mmol) in benzene (140 mL) was added 57% aqueous HI (0.5 mL) and the mixture was stirred at 85 °C for 45 min. The reaction mixture was diluted with Et_2O and washed with 10% aqueous $NaHSO_3$, 6% aqueous $NaHCO_3$ and brine. Evaporation of the solvent after drying over Na_2SO_4 gave **6** (910 mg, 98%).

$[\alpha]_D^{22}$ +51.3 (*c* 0.52, $CHCl_3$); IR (film, cm^{-1}): 3368, 2929, 1739, 1610, 1464, 1371, 1242, 1036, 738, 667; ^1H NMR (400 MHz) δ: 7.07 (1H, d, *J*=7.4 Hz, H-5), 7.01 (1H, t, *J*=7.4 Hz, H-7), 6.70 (1H, t, *J*=7.4 Hz, H-6), 6.64 (1H, d, *J*=7.4 Hz, H-8), 4.08 (1H, d, *J*=10.8 Hz, H_A-21), 3.99 (1H, d, *J*=10.8 Hz, H_B-21), 3.77 (1H, dd, *J*=6.0 and 4.6 Hz, H-2), 3.11 (1H, dt, *J*=12.2 and 6.0 Hz, H-3), 2.71–2.64 (1H, m, H-19), 2.03 (3H, s, –OOCMe), 2.15–1.18 (11H, m), 1.03 (3H, s, Me-22), 1.02 (3H, s, Me-24), 0.84 (3H, d, *J*=6.4 Hz, Me-23); ^{13}C NMR δ: 171.4 (–OO*C*Me), 149.9 (C-9), 135.7 (C-4), 135.3 (C-20), 133.3 (C-15), 127.1 (C-7), 123.1 (C-5), 118.7 (C-6), 110.0 (C-8), 70.0 (C-21), 66.6 (C-2), 41.8 (C-10), 40.2 (C-12), 38.5 (C-3), 38.5 (C-16), 38.0 (C-11), 33.6 (C-19), 31.7 (C-17), 27.0 (C-13), 25.7 (C-14), 23.5 (C-18), 23.0 (C-24), 21.0 (–OOC*Me*), 18.1 (C-22), 16.2 (C-23); EIHRMS: calcd for $C_{25}H_{34}NO_2$ (M^++H) 380.2584, found: 380.2574.

*4.1.17. Compound **17**.* To a solution of **16** (43 mg, 0.106 mmol) in benzene (7.0 mL) was added 57% aqueous HI (0.02 mL) and the mixture was stirred at 85 °C for 2 h. The reaction mixture was diluted with Et_2O and washed with 10% aqueous $NaHSO_3$, 6% aqueous $NaHCO_3$ and brine. Evaporation of the solvent after drying over Na_2SO_4 gave a residue, which was chromatographed on silica gel (Hex/EtOAc 95/5) to afford **17** (25 mg, 59%).

R_f=0.61 (hexane/Et OAc8:2); $[\alpha]_D^{22}$ +80.3 (*c* 0.02, $CHCl_3$); IR (film, cm^{-1}): 3368, 2924, 1736, 1482, 1383, 1244, 1040; ^1H NMR (400 MHz, C_6D_6) δ: 7.21 (1H, br s, H-1), 7.13 (1H, d, *J*=7.2 Hz, H-5), 7.12 (1H, t, *J*=7.2 Hz, H-7), 6.87 (1H, t, *J*=7.2 Hz, H-6), 6.60 (1H, d, *J*=7.2 Hz, H-8), 4.05 (2H, m, H-23), 3.47 (1H, dd, *J*=6.0 and 4.0 Hz, H-2), 3.00 (1H, dt, *J*=12.0 and 6.0 Hz, H-3), 2.46 (1H, br s, H-19), 2.10–1.10 (15H, m), 1.73 (3H, s, *Me*COO–), 1.00 (3H, s, Me-29), 0.96 (3H, s, Me-27), 0.82 (3H, d, *J*=6.8 Hz, Me-28); ^{13}C NMR (100 MHz, C_6D_6) δ: 169.9 (Me*COO*–), 150.5 (C-9), 135.9 (C-4), 135.3 (C-20), 134.0 (C-15), 127.1 (C-7), 123.3 (C-5), 118.2 (C-6), 110.2 (C-8), 67.2 (C-2), 65.0

(C-23), 42.5 (C-10), 40.6 (C-12), 39.0 (C-3), 38.1 (C-16), 37.0 (C-11), 36.1 (C-21), 33.1 (C-19), 32.3 (C-17), 27.2 (C-13), 25.8 (C-14), 25.8 (C-27), 23.7 (C-22), 23.5 (C-18), 20.3 (*Me*COO–), 17.6 (C-29), 16.2 (C-28).

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