SYNTHETIC STUDIES ON MARINEOSINS BASED ON A DIRECT COUPLING REACTION OF PYRROLE AND δ-LACTONE

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Abstract – A promising precursor of marineosins A and B, unusual macrocyclic pyrrole and spiroiminal alkaloids isolated from marine microorganism has been synthesized employing a direct coupling of pyrrole and δ-lactone.

INTRODUCTION

In 2008, Fenical et al. disclosed the isolation of marineosins A and B, structurally novel trans-fused macrocyclic framework, containing a spirocyclic tetrahydropyrans-dihydropyrrole iminal moiety and two pyrroles, from cultures of the marine Streptomyces sp. CNQ-617 (Figure 1).¹ The marineosins were found to exhibit significant anticancer activities toward human colon carcinoma (HCT-116) (IC₅₀ = 0.5 mM for marineosin A and IC₅₀ = 46 mM for marineosin B). Their intriguing molecular architectures and biological activities make marineosins attractive targets for synthesis, and the synthetic studies were reported by Lindsley et al.,² Snider et al.³ and Shi et al.⁴ Shi also reported the total synthesis of the proposed structure of marineosin A and its spectroscopic data differed from that reported for the natural product.⁵ Furthermore, Reynolds et al. reported the elucidation of the biosynthetic pathway for marineosins with the relevant gene cluster.⁶ Recently, Harran et al. disclosed an eight-step remarkable

Figure 1. Revised structure of marineosin A and original structure of marineosin A and B
synthesis of marineosin A, together with the stereochemical reassignment of marineosin A from 7R,8R to 7S,8R. Herein we report the formation of highly functionalized macrocyclic pyrrole core.

RESULTS AND DISCUSSION

Given the a-pyrrole-lactone structure, one of the most attractive and efficient approaches to marineosins is the direct coupling of a d-lactone and a pyrrole. In the course of our synthesis of marine natural products, ophiodilactones A and B, we were interested in direct oxidative coupling reactions of C-H and Ar-H bonds. Thus, the intramolecular direct coupling reaction of ophiodilactone A with Cu(II) catalyst under oxygen afforded ophiodilactone B in a good yield (Scheme 1). On the other hand, Baran et al. demonstrated the remarkably simple method for the direct coupling of the C-3 carbon of indoles or the C-2 carbon of pyrroles with the a-carbon of carbonyl compounds in the presence of Cu(II) (Scheme 2). It was proposed that the coupling proceeds through single-electron transfer of a metal-chelated complex to form a a-keto radical and subsequent nucleophilic attack of indoles or pyrroles to generate a radical anion involving the reduction of Cu(II) to Cu(0).

Taking into account these works, we selected direct pyrrole and d-lactone coupling for the key step for the synthesis of marineosins. Our synthetic plan makes a disconnection at the spiroiminal to give the methyl acetal 1 (Scheme 3). Methyl acetal 1 was considered to be accessible from tricyclic compound 2 through nucleophilic alkylation. From the retrosynthetic perspective, we envisioned pyrrole-lactone 3 as a precursor of 2 through ring-closing metathesis. We postulated that this precursor 3 could be accessed by a direct coupling of pyrrole 4 with lactone 5, based on Baran’s protocol. This approach is particularly appealing since two functionalized molecules could be unified stereo- and siteselectively without using protecting groups.
Pyrrole 4 was obtained from known \(N\)-benzenesulfonyl-pyrrole-2-carboxaldehyde 6\(^{11}\) shown in Scheme 4. Treatment of aldehyde 6 with 5-hexenylmagnesium bromide gave pyrrole alcohol 7, which was subjected to NaBH\(_4\) reduction under Muchowski's condition to afford 2-(6-heptenyl)pyrrole 4 in a good yield.\(^{12}\)

On the other hand, the required lactone 5 was synthesized in a stereoselective manner by 1,4-addition of a vinyl group to chiral pyranone 9 based on Ogasawara's protocol\(^{13}\) (Scheme 5). Thus, the coupling of commercially available (S)-propylene oxide with ethyl propiolate afforded compound 8 in 95% yield. Subsequent hydrogenation and lactone formation furnished chiral lactone 9 in 83% yields. The reaction of
9 with vinylmagnesium bromide and copper iodide furnished stereoselectively lactone 5 in 70% yield. Having 4 and 5 in hand, we explored their direct coupling (Scheme 6). Based on Baran’s protocol, the model reaction using simple pyrrole and lactone 5 with base and copper(II) 2-ethylhexanoate was initially investigated; however, the coupled product was not produced at all. After investigation under various conditions, we gratifyingly found that treatment of a mixture of 5 and 4 with LHMDS in the presence of copper(II) 2-ethylhexanoate at -60 °C for 3.5 h and then rt for 30 min furnished the desired product 3 in 15% yield with excellent stereoselectivity together with the recovered 4 in 49% yield and 5 in 49% yield. Although the yield of the product was not satisfying, it is important to note that the synthetic route to 3 avoid any protecting group manipulation.

Next our efforts focused on the formation of the macrocyclic framework and spirocyclic moiety of marineosins (Scheme 7). Ring-closing metathesis of 3 was found to be promoted cleanly by Grubbs 2nd catalyst in CH2Cl2 with high-dilution to deliver macrocyclic compound as a 1:2.2 E/Z-mixture, which was hydrogenated to afford 2 in 67% yield. The structure of 2 was confirmed by X-ray crystallographic analysis.14 Installation of a carbon chain to the d-lactone moiety was accomplished by the addition of the α-alkoxyorganolithium15 derived from the corresponding α-alkoxystannane to produce compound 10 in 79% yield. When 10 was exposed to acidic methanolysis conditions, methyl acetal 11 was obtained as a single isomer and subsequent removal of the benzylxymethyl group gave compound 12 in 72% yield. The methyl acetal in 11 was proved to be axial configuration by NOESY. Compound 12 was then converted to nitrile compounds 13a and 13b as a 2.2:1 diastereomeric mixture in 64% overall yield via aldehyde by TPAP oxidation followed by addition of lithium acetonitrile. Although we tried to clarify the stereochemistry of the resulting hydroxy group by modified Mosher’s method, efforts to assign the absolute configuration was unsuccessful due to no distinct difference between the ¹H-NMR spectra of the (R)- and (S)-MTPA esters of 13a. Methylation of major product 13a and subsequent partial hydrolysis of the nitrile group provided lactone 1 in 60% yield.
Scheme 7. Synthesis of macrocyclic compound 1

In conclusion, we have developed an effective route to macrocyclic compound 1, a promising precursor of marineosin A and B, which proceeds through direct coupling of the pyrrole and d-lactone moieties, ring-closing metathesis, and acetonitrile addition. The remaining tasks toward the total synthesis of marineosins are the installation of pyrrole and spiroamination which are currently under investigation.

EXPERIMENTAL

General. Where appropriate, reactions were performed in flame-dried glassware under argon atmosphere. All extracts were dried over MgSO₄ and concentrated by rotary evaporation below 30 °C at 25 Torr unless otherwise noted. Commercial reagents and solvents were used as supplied with following exceptions. Acetonitrile (MeCN), N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), dichloromethane (CH₂Cl₂), pyridine, toluene, and triethylamine (NEt₃) were distilled from CaH₂. Ethyl acetate (AcOEt) was distilled from K₂CO₃. Thin-layer chromatography (TLC) was performed using precoated silica gel plates (0.2 or 0.5 mm thickness). Column chromatography was performed using silica gel (particle size 100-210 µm (regular), 40-50 µm (flash). Optical rotations were recorded on digital polarimeter at ambient temperature. Infrared spectra (FTIR) were measured on a Fourier transform infrared spectrometer. ¹H NMR (300 and 400 MHz) and ¹³C NMR (75 and 100 MHz) spectra were measured using CDCl₃, or C₆D₆ as solvent, and chemical shifts are reported as δ values in ppm based on
internal CHCl$_3$ (7.26 ppm, $^1$H; 77.0 ppm, $^{13}$C), C$_6$D$_6$ (7.13 ppm, $^1$H; 128.6 ppm, $^{13}$C). Mass (MS) and high resolution mass (HRMS) spectra were taken in EI, DART or ESI mode.

1-(1-(Phenylsulfonfyl)-1H-pyrrol-2-yl)hept-6-en-1-ol (7). To a mixture of magnesium turnings (2.24 g, 30.7 mmol) in Et$_2$O (6.0 mL) was added dropwise 6-bromo-1-hexene (0.20 mL, 1.50 mmol) and the mixture was stirred at 34 °C for 30 sec. The mixture was allowed to rt, and a solution of 6-bromo-1-hexene (3.90 mL, 29.2 mmol) in Et$_2$O (24.0 mL) was added dropwise over 30 min. Thus Grignard reagent (0.83 M in Et$_2$O) was prepared.

To the solution of compound 6 (1.00 g, 4.25 mmol) in THF (26 mL) was added the above-mentioned Grignard reagent (0.83 M in Et$_2$O, 14.9 mL, 12.3 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min and then at rt for 30 min. The mixture was neutralized by 2 mol/L HCl and extracted with AcOEt ($75 \text{ mL} \times 2$). Organic layers were washed with saturated aqueous NaHCO$_3$ (50 mL), brine (50 mL), dried, and concentrated. The residue was purified by flash chromatography (SiO$_2$ 70 g, hexane–AcOEt, 3:1) gave 7 (1.07 g, 3.36 mmol, 79%); a light red oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78 (d, $J = 8.0$ Hz, 2H), 7.61 (t, $J = 8.0$ Hz, 1H), 7.51 (t, $J = 8.0$ Hz, 2H), 7.31 (dd, $J = 3.2$, 1.6 Hz, 1H), 6.28-6.26 (m, 2H), 5.76 (ddt, $J = 17.2$, 10.4, 6.8 Hz, 1H), 4.97 (d, $J = 17.2$ Hz, 1H), 4.93 (d, $J = 10.4$ Hz, 1H), 4.81 (td, $J = 7.2$, 4.8 Hz, 1H), 2.71 (d, $J = 4.8$ Hz, 1H), 2.00 (q, $J = 7.2$ Hz, 2H), 1.85-1.75 (m, 2H), 1.42-1.26 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.7, 133.9, 129.5, 126.5, 123.5, 114.4, 112.4, 111.7, 65.2, 34.9, 33.6, 28.5, 25.5; FT-IR (neat) $\nu$ 3564, 2930, 1366, 1179, 1089, 726 cm$^{-1}$; MS (EI) $m/z$ 41, 55, 77, 96, 125, 141, 160, 178, 207, 236 (100), 256, 278, 302, 319 (M$^+$), 341; HRMS (EI) calcd for C$_{17}$H$_{21}$NO$_3$S (M$^+$) 319.1242, found 319.1250.

2-(Hept-6-enyl)-1H-pyrrole (4). To a mixture of NaBH$_4$ (0.98 g, 26.0 mmol) in 2-propanol (50 mL) was added dropwise a solution of 7 (1.65 g, 5.20 mmol) in 2-propanol (37 mL). The mixture was stirred at reflux for 26 h. To the reaction mixture was added water (50 mL) at 0 °C, and the mixture was extracted with (80 mL $\times 2$). Organic layers were washed with brine (50 mL) dried, and concentrated. The residue was purified by flash chromatography (SiO$_2$ 50 g, hexane–AcOEt, 15:1) gave 4 (746 mg, 4.57 mmol, 88%); a light red oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.82 (brs, 1H), 6.62 (brs, 1H), 6.12 (dd, $J = 5.6$, 3.0 Hz, 1H), 5.90 (s, 1H), 5.80 (ddt, $J = 17.2$, 10.4, 6.8 Hz, 1H), 4.98 (d, $J = 17.2$ Hz, 1H), 4.94 (d, $J = 10.4$ Hz, 1H), 2.57 (t, $J = 7.6$ Hz, 2H), 2.05 (dd, $J = 14.0$, 6.8 Hz, 2H), 1.61 (dt, $J = 7.6$, 7.6 Hz, 2H), 1.38 (brs, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.9, 132.7, 115.9, 114.3, 108.1, 104.8, 33.6, 29.4, 28.8, 28.6, 27.6; FT-IR (neat) $\nu$ 3385, 2930, 1366, 1089, 726 cm$^{-1}$; MS (EI) $m/z$ 41, 55, 77, 96, 125, 141, 160, 178, 207, 236 (100), 256, 278, 302, 319 (M$^+$), 341; HRMS (EI) calcd for C$_{11}$H$_{17}$N (M$^+$) 163.1361, found 163.1373.

Ethyl (S)-5-hydroxyhex-2-ynoate (8). To a solution of ethyl propiolate (3.92 g, 40.0 mmol) in THF (100 mL) was added $n$-butyllithium (2.60 M in hexane, 15.4 mL, 40.0 mmol) at -78 °C, and the mixture was stirred for 30 min. To the reaction mixture were added dropwise (S)-(−)-propylene oxide (1.16 g, 20.0
and BF₃·OEt₂ (5.00 mL, 40.0 mmol) at -78 °C and stirring was continued for 2 h. The reaction was quenched with saturated aqueous NH₄Cl (80 mL) and the mixture was extracted with AcOEt (100 mL × 3). Organic layers were washed with brine (80 mL), dried, and concentrated. The residue was purified by column chromatography (SiO₂ 180 g, hexane–AcOEt, 5:1) gave 8 (2.95 g, 18.9 mmol, 95%); a brown oil; [α]D³³ +11.7 (c 0.84, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 4.23 (q, J = 7.2 Hz, 2H), 4.06 (sext, J = 6.0 Hz, 1H), 2.57-2.46 (m, 2H), 1.89 (brs, 1H), 1.33-1.29 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 153.7, 86.1, 74.6, 65.5, 61.8, 28.8, 22.3, 13.8; FT-IR (neat) ν 3416, 2979, 2233, 1699, 1238, 1066, 937, 752 cm⁻¹; MS (ESI) m/z 179 (100) [(M+Na)⁺]; HRMS (ESI) calcd for C₈H₁₂NaO₃ [(M+Na)⁺] 179.0684, found 179.0657.

(S)-5,6-Dihydro-6-methylpyran-2-one (9). To a solution of 8 (18.6 g, 118.8 mmol) in MeOH (238 mL) were added Lindlar catalyst (285.8 mg, 1.54 wt%) and quinoline (0.85 mL, 7.13 mmol) and the reaction mixture was stirred under H₂ atmosphere at rt for 27 h. The mixture was filtered through Celite and the cake was washed with Et₂O (200 mL × 3) and CH₂Cl₂ (150 mL × 3). The extracts were washed with 15% HCl (150 mL) and saturated aqueous NaHCO₃ (150 mL), and brine (150 mL), dried, and concentrated to give the crude alkene (17.6 g).

To a mixture of the crude alkene (17.6 g) in methanol (594 mL) was added dropwise concentrated HCl (100 mL) at 0 °C and the reaction mixture was stirred at rt for 90 min. To the mixture was added saturated aqueous NaHCO₃ (50 mL) at 0 °C, and the mixture was extracted with Et₂O (200 mL × 3) and CH₂Cl₂ (150 mL × 3). The extracts were washed with saturated aqueous NaHCO₃ (150 mL) and brine (150 mL), dried, and concentrated. The residue was purified by column chromatography (SiO₂ 350 g, hexane–AcOEt, 3:2) gave 9 (11.1 g, 98.8 mmol, 83%, 2 steps); a yellow oil; [α]D²⁸ +215.6 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 6.89 (ddd, J = 9.2, 6.0, 2.8 Hz, 1H), 6.03 (dd, J = 9.6, 2.4 Hz, 1H), 4.64-4.54 (m, 1H), 2.43-2.27 (m, 2H), 1.45 (d, J = 6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 164.5, 144.9, 121.2, 74.3, 30.9, 20.7; FT-IR (neat) v 2981, 1726, 1389, 1254, 1114, 1054, 816 cm⁻¹; MS (EI) m/z 43, 61, 68 (100), 88, 97, 112 (M⁺); HRMS (EI) calcd for C₆H₈O₂ (M⁺) 112.0524, found 112.0525.

(4S,6S)-Tetrahydro-6-methyl-4-vinylpyran-2-one (5). To a solution of copper(I) iodide (1.13 g, 5.94 mmol) in THF (150 mL) was added dropwise vinylmagnesium bromide (1.32 M in THF solution, 90.0 mL, 119 mmol) at -78 °C and the mixture was stirred for 15 min. To the mixture was added a solution of 9 (4.44 g, 39.6 mmol) in THF (48 mL), and the reaction mixture was stirred at that temperature for 2.5 h. The reaction was quenched with saturated aqueous NH₄Cl (200 mL) and the mixture was extracted with AcOEt (400 mL × 2). Organic layers were washed with H₂O (200 mL), brine (200 mL), dried, and concentrated. The residue was purified by column chromatography (SiO₂ 200 g, hexane–AcOEt, 5:1) gave 5 (3.90 g, 27.8 mmol, 70%); a yellow oil; [α]D²⁵ -43.1 (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.83 (ddd, J = 17.2, 10.8, 6.4 Hz, 1H), 5.13 (d, J = 10.8 Hz, 1H), 5.10 (d, J = 17.2 Hz, 1H), 4.55 (sext,
$J = 6.4$ Hz, 1H), 2.82-2.74 (m, 1H), 2.61 (dd, $J = 16.8, 6.0$ Hz, 1H), 2.46 (dd, $J = 17.2, 8.0$ Hz, 1H), 1.81 (t, $J = 6.4$ Hz, 2H), 1.38 (d, $J = 6.4$ Hz, 3H); $^1$C NMR (100 MHz, CDCl$_3$) δ 171.2, 139.3, 114.8, 73.4, 34.3, 33.7, 32.2, 21.0; FT-IR (neat) ν 2979, 1744, 1380, 1249, 1089, 922 cm$^{-1}$; MS (EI) m/z 43, 54 (100), 68, 81, 98, 112, 125, 140 (M$^+$); HRMS (EI) calcd for C$_8$H$_{12}$O$_2$ (M$^+$) 140.0837, found 140.0837.

(35,4R,6S)-3-(5-(Hept-6-enyl)-1H-pyrrol-2-yl)-tetrahydro-6-methyl-4-vinylpyran-2-one (3). To a solution of HMDS (0.96 mL, 4.5 mmol) in THF (5 mL) was added butyllithium (2.65 M in hexane, 1.66 mL, 4.4 mmol) at -78 °C and the mixture was stirred at 0 °C for 30 min. To this solution of LHMDS was added a solution of pyrrole 4 (489.8 mg, 3.0 mmol) and lactone 5 (140.2 mg, 1.0 mmol) in THF (3.0 mL), and the mixture was stirred at 40 °C for 30 min. To the mixture was added copper(II) 2-ethylhexanoate (700 mg, 2.0 mmol) and the reaction mixture was stirred at -60 °C for 3.5 h. After stirred at rt for 30 min, the reaction was quenched with 5% aqueous ammonia and extracted with AcOEt (10 mL × 3). The extracts were washed with H$_2$O (10 mL) and brine (10 mL), dried, and concentrated. The residue was purified by column chromatography (SiO$_2$ 30 g, hexane–AcOEt, 30:1 to 6:1) gave 3 (46.1 mg, 0.153 mmol, 15%; 21:1 diastereomeric mixture based on the $^1$H NMR spectrum) and recovered 4 (239 mg, 1.46 mmol, 49%) and lactone 5 (68.4 mg, 0.489 mmol, 49%).

3: a brown oil; [$\alpha$]$_D$ $^2$1 +22.0 (c 0.71, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 9.01 (brs, 0.08H), 8.51 (brs, 0.92H), 5.97-5.76 (m, 4H), 5.17 (d, $J = 16.0$ Hz, 1H), 5.14 (d, $J = 11.6$ Hz, 1H), 4.99 (dd, $J = 17.2, 1.6$ Hz, 1H), 4.93 (dd, $J = 10.4, 1.6$ Hz, 1H), 4.69-4.61 (m, 1H), 3.86 (d, $J = 4.4$ Hz, 0.07H), 3.76 (d, $J = 5.6$ Hz, 0.93H), 3.26-3.20 (m, 0.07H), 3.08 (dt, $J = 12.0, 5.6$ Hz, 0.93H), 2.55 (t, $J = 8.0$ Hz, 2H), 2.11-2.00 (m, 3H), 1.89 (dt, $J = 10.4, 4.0$ Hz, 1H), 1.61 (quint, $J = 8.0$ Hz, 2H) 1.45-1.33 (m, 7H); $^1$C NMR (100 MHz, CDCl$_3$) δ 172.5, 139.2, 139.0, 133.5, 124.1, 116.0, 114.3, 106.1, 104.6, 74.0, 42.8, 37.4, 35.4, 33.7, 29.4, 28.8, 28.7, 27.7, 21.3; FT-IR (neat) ν 3359, 2828, 1730, 1600, 1188, 1109, 913, 767 cm$^{-1}$; MS (EI) m/z 43, 58, 76, 104, 120, 147, 176, 203, 218, 232, 260, 272, 301 (M$^+$); HRMS (EI) calcd for C$_{19}$H$_{27}$NO$_2$ (M$^+$) 301.2042, found 301.2052.

(5-E or Z)-(35,4aS,15aS)-3-Methyl-3,4,4a,7,8,9,10,11-octahydro-12,15-epiminocycloundecac[6]pyran-1(15aH)-one. To the solution of 3 (45.2 mg, 0.15 mmol) in degassed CH$_2$Cl$_2$ (150 mL) was added 2nd generation Grubbs catalyst (12.8 mg, 15.0 μmol) and the mixture was stirred under reflux for 1 day. After stirring under air for 4 h, the mixture was concentrated and purified by flash chromatography (SiO$_2$ 5 g, hexane–AcOEt, 3:1 to 1:1) to afford macrocyclic E-alkene (9.1 mg, 33.3 μmol, 22%) and Z-alkene (20.1 mg, 73.5 μmol, 49%).

**E-alkene**: a white solid; [$\alpha$]$_D$ $^{21}$ -47.4 (c 0.29, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.54 (brs, 1H), 6.18 (s, 1H), 5.83 (s, 1H), 5.28-5.15 (m, 2H), 4.67-4.58 (m, 1H), 3.59 (d, $J = 12.4$ Hz, 1H), 2.65 (dt, $J = 15.2, 5.6$ Hz, 1H), 2.57-2.45 (m, 2H), 2.05-1.84 (m, 4H), 1.56-1.26 (m, 7H), 1.08 (quint, $J = 6.8$ Hz, 1H), 0.89-0.76 (m, 1H); $^1$C NMR (100 MHz, CDCl$_3$) δ 171.8, 133.7, 131.9, 130.9, 124.5, 107.4, 107.1, 72.7,
44.6, 43.6, 35.9, 29.5, 26.9, 26.0, 22.6, 21.1; FT-IR (neat) ν 3332, 2927, 1711, 773 cm⁻¹; MS (EI) m/z 43, 55, 69, 81, 93, 120, 149, 158, 187, 200, 228, 229, 256, 273 (100, M⁺), 293; HRMS (EI) calcd for C₁₇H₂₃NO₂ (M⁺) 273.1729, found 273.1727.

Z-alkene: a yellow solid; [α]D²¹ +18.9 (c 0.30, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.26 (brs, 0.89H), 7.66 (brs, 0.11H), 5.94-5.81 (m, 1H), 5.76-5.69 (m, 1H), 5.55 (dd, J = 15.2, 9.6 Hz, 0.11H), 5.26-5.15 (td, J = 10.4, 3.6 Hz, 1H), 5.10 (t, J = 10.4 Hz, 0.89H), 4.83-4.63 (m, 1H), 3.93 (d, J = 5.2 Hz, 0.11H), 3.62 (d, J = 12.4 Hz, 0.89H), 3.31-3.22 (m, 1H), 2.77-2.36 (m, 2H), 2.29-1.92 (m, 3H), 1.80 (dt, J = 14.0, 4.8 Hz, 1H), 1.68-0.68 (m, 8H), 0.40 (quint, J = 8.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 174.0, 133.5, 132.3, 129.9, 124.3, 109.2, 105.9, 72.9, 44.5, 36.8, 35.3, 31.9, 29.2, 27.5, 27.2, 26.1, 25.7, 21.1, 20.9, 19.4; FT-IR (neat) ν 3361, 2929, 1724, 1209 cm⁻¹; MS (EI) m/z 43, 58, 93, 106, 120, 132, 149, 186, 187, 228, 229, 272, 273 (100, M⁺), 301, 303; HRMS (EI) calcd for C₁₇H₂₃NO₂ (M⁺) 273.1729, found 273.1727.

(3S,4aS,15aS)-3-Methyl-3,4,4a,5,6,7,8,9,10,11-decahydro-12,15-epiminocyclo[undeca[c]pyran-1(15aH)-one (2). To a mixture of E-alkene and Z-alkene (137 mg, 502 μmol) in EtOH (20 mL) was added palladium/C (54.8 mg, 40 wt%) and the mixture was stirred under atmospheric hydrogen at rt for 22 h. The reaction mixture was filtered through Celite and concentrated. The residue was purified by preparative TLC (hexane–AcOEt, 5:1) to give 2 (127 mg, 461 μmol, 92%); a light yellow solid; Mp 155-156 °C (decomp); [α]D²⁴ -45.6 (c 1.00, CHCl₃); ¹H NMR (400 MHz, 0.9 mg/0.6 mL CDCl₃) δ 7.89 (brs, 1H), 5.94 (t, J = 2.8 Hz, 1H), 5.79 (t, J = 2.8 Hz, 1H), 4.65-4.58 (m, 1H), 3.50 (d, J = 12.0 Hz, 1H), 2.64 (ddd, J = 14.4, 5.2, 5.2 Hz, 1H), 2.50 (ddd, J = 14.4, 9.2, 5.2 Hz, 1H), 2.11-2.00 (m, 2H), 1.69 (ddd, J = 13.6, 4.4, 4.4 Hz, 1H), 1.59-1.50 (m, 4H), 1.41 (d, J = 6.0 Hz, 3H) 1.31-1.22 (m, 5H), 0.92-0.77 (m, 2H), 0.50-0.40 (m, 1H); ¹H NMR (400 MHz, 13.5 mg/0.6 mL CDCl₃) δ 8.54 (brs, 1H), 5.90 (t, J = 2.8 Hz, 1H), 5.71 (t, J = 2.8 Hz, 1H), 4.64-4.56 (m, 1H), 3.46 (d, J = 12.4 Hz, 1H), 2.38-2.22 (m, 3H), 2.15 (ddd, J = 14.0, 10.0, 10.0 Hz, 1H), 1.67 (ddd, J = 14.0, 4.8, 4.8 Hz, 1H), 1.61-1.04 (m, 12H), 0.88-0.73 (m, 2H), 0.42-0.31 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 175.8, 134.4, 124.0, 109.9, 105.0, 73.3, 45.6, 38.2, 33.0, 31.9, 27.9, 27.1, 25.4, 24.6, 24.2, 24.1, 21.0; FT-IR (neat) ν 3353, 2926, 1723, 1209, 758 cm⁻¹; MS (EI) m/z 43, 58, 93, 106, 120, 132, 149, 186, 187, 228, 229, 272, 273 (100, M⁺), 301, 303; HRMS (EI) calcd for C₁₇H₂₃NO₂ (M⁺) 275.1885, found 275.1874.

(3S,4S,6S)-6-Methyl-2-(((benzyloxy)methoxy)methyl)-3,4,5,6-tetrahydro-1H,2H-1(2,5)-pyrrola-2(3,4)-pyranacyclonaphan-2-ol (10). To a solution of (benzyloxymethoxy)methyltributylstannane (1.17 g, 2.66 mmol) in THF (5.0 mL) was added n-butyllithium (2.76 M in hexane, 0.964 mL, 2.66 mmol) at -78 °C and mixture was stirred for 5 min. To this mixture was added 2 (122 mg, 443 μmol) in THF (3.9 mL) and the mixture was stirred at -78 °C for 1 h. To the reaction mixture was added saturated aqueous NH₄Cl (10 mL) and extracted with AcOEt (20 mL × 3). The residue was purified by flash chromatography (SiO₂ 10 g, hexane–AcOEt, 5:1) to afford 10 (150 mg, 351 μmol, 79%); [α]D²⁰ +11.6 (c
0.58, CHCl3); 1H NMR (400 MHz, CDCl3) δ 8.21 (brs, 1H), 7.35-7.26 (m, 5H), 5.80 (t, J = 2.8 Hz, 1H), 5.73 (t, J = 2.8 Hz, 1H), 4.81-4.76 (m, 2H), 4.65-4.56 (m, 2H), 4.26 (sext, J = 6.8 Hz, 1H), 3.66 (d, J = 10.0 Hz, 1H), 3.61 (brs, 1H), 3.54 (d, J = 10.0 Hz, 1H), 4.81-4.76 (m, 2H), 4.65-4.56 (m, 2H), 4.26 (sext, J = 6.8 Hz, 1H), 3.66 (d, J = 10.0 Hz, 1H), 3.61 (brs, 1H), 3.54 (d, J = 10.0 Hz, 1H), 2.69 (ddd, J = 14.8, 4.0, 4.0 Hz, 1H), 2.51 (ddd, J = 14.8, 11.2, 4.0 Hz, 1H), 2.37 (d, J = 11.6 Hz, 1H), 2.27-2.19 (m, 1H), 1.74-1.61 (m, 3H), 1.49 (d, J = 6.8 Hz, 3H), 1.40-1.26 (m, 5H), 1.21-1.08 (m, 2H), 0.93-0.79 (m, 3H), 0.51-0.46 (m, 1H); 13C NMR (100 MHz, CDCl3) δ 137.5, 132.7, 128.7, 128.4, 127.9, 127.7, 109.5, 105.0, 97.5, 95.4, 74.6, 69.6, 69.3, 47.0, 38.7, 30.5, 28.4, 27.4, 27.1, 25.4, 24.8, 24.7, 24.6, 22.8; FT-IR (neat) ν 3462, 2925, 1724, 1586, 1456, 1114, 1044, 765, 699, 576 cm⁻¹; MS (ESI) m/z 450 (100) [(M+Na)+]; HRMS (ESI) calcd for C26H37NNaO4 [(M+Na)+] 450.2620, found 450.2583.

(2R,3S,4S,6S)-2-Methoxy-6-methyl-2-(((benzyloxy)methoxy)methyl)-3,4,5,6-tetrahydro-1H,2H-1(2,5)-pyrrola-2(3,4)-pyranacyclonaphane (11). To a solution of 10 (152 mg, 356 µmol) in MeOH (7.1 mL) was added CSA (1.4 mg, 0.0356 mmol), and the mixture was stirred at rt for 15 min. To the mixture was added saturated aqueous NaHCO3 (5 mL) and extracted with CH2Cl2 (10 mL × 3). Organic extracts were washed with brine (5 mL), dried over anhydrous K2CO3, and concentrated. The residue was purified by flash chromatography (SiO2 5 g, hexane–AcOEt, 9:1) to afford 11 (132 mg, 298 µmol, 84%); a brown oil; [α]D²⁰ -3.8 (c 0.21, CHCl3); 1H NMR (400 MHz, CDCl3) δ 8.08 (brs, 1H), 7.36-7.23 (m, 5H), 5.85 (t, J = 2.8 Hz, 1H), 5.72 (t, J = 2.8 Hz, 1H), 4.80-4.77 (m, 2H), 4.64-4.57 (m, 2H), 4.31-4.25 (m, 1H), 3.61 (d, J = 10.0 Hz, 1H), 3.48 (d, J = 10.0 Hz, 1H), 3.32 (s, 3H), 2.82 (d, J = 12.4 Hz, 1H), 2.71 (ddd, J = 14.8, 4.4, 4.4 Hz, 1H), 2.51 (ddd, J = 14.8, 11.2, 4.4 Hz, 1H), 2.17-2.08 (m, 1H), 1.68-1.62 (m, 4H), 1.44 (d, J = 7.2 Hz, 3H), 1.39-1.21 (m, 4H), 1.18-1.05 (m, 2H), 0.91-0.73 (m, 3H), 0.54-0.45 (m, 1H); 13C NMR (100 MHz, CDCl3) δ 137.9, 132.3, 129.1, 128.3, 128.0, 127.6, 109.5, 105.0, 100.7, 95.2, 69.8, 69.4, 69.3, 49.1, 46.1, 38.5, 30.8, 28.4, 27.3, 26.9, 25.5, 24.8, 24.7, 24.6, 21.6; FT-IR (neat) ν 3467, 2925, 1724, 1586, 1456, 1114, 1044, 765, 699, 576 cm⁻¹; MS (ESI) m/z 432, 450, 464 (100) [(M+Na)+]; HRMS (ESI) calcd for C27H39NNaO4 [(M+Na)+] 464.2777, found 464.2826.

3-Hydroxy-3-((2R,3S,4S,6S)-2-methoxy-2-methyl-2,2,2,2-tetrahydro-1H,2H-1(2,5)-pyrrola-2(3,4)-pyranacyclonaphan-2-yl)propanenitrile (12). To the mixture of lithium dispersion (30% in oil, 150 mg, 6.42 mmol) in THF (3.7 mL) was added naphthalene (827 mg, 6.42 mmol) and the mixture was stirred at rt for 1 h. The mixture was allowed to cool to -50 °C and a solution of 11 (63.9 mg, 145 µmol) in THF (1.2 mL) was added. After stirring at that temperature for 8.5 h, the reaction was quenched with saturated aqueous NH4Cl (10 mL) and the mixture was extracted with AcOEt (20 mL × 3). Organic extracts were washed with brine (10 mL) and dried, and concentrated. The residue was purified by flash chromatography (SiO2 7 g, hexane–AcOEt, 6:1) to afford 12 (40.1 mg, 125 µmol, 86%); a yellow oil; [α]D²⁰ +26.1 (c 0.96, CHCl3); 1H NMR (400 MHz, CDCl3) δ 8.12 (brs, 1H), 5.90 (t, J = 2.8 Hz, 1H), 5.73 (t, J = 2.8 Hz, 1H), 4.24-4.17 (m, 1H), 3.59-3.53 (m, 2H), 3.35 (s, 3H), 2.71 (ddd, J = 15.2, 4.4, 4.4 Hz,
1H), 2.57 (d, \( J = 12.0 \) Hz, 1H), 2.50 (ddd, \( J = 15.2 \) Hz, 3H), 1.43 (d, \( J = 6.8 \) Hz, 3H), 1.38-1.23 (m, 4H), 1.18-1.06 (m, 2H), 0.90-0.72 (m, 3H), 0.54-0.43 (m, 1H); 13C NMR (100 MHz, CDCl₃) δ 133.4, 128.4, 109.4, 105.4, 99.8, 69.5, 65.4, 49.2, 48.1, 38.7, 30.6, 28.3, 27.2, 25.4, 24.8, 24.7, 24.6, 21.5; FT-IR (neat) ν 3466, 2924, 2855, 1453, 1371, 1136, 1056, 765, 491 cm⁻¹; MS (ESI) m/z 312, 344 (100) [(M+Na)+]; HRMS (ESI) calcd for C₁₉H₃₁NNaO₃ [(M+Na)+] 344.2202, found 344.2251.

(2R,3S,4S,6S)-2-Methoxy-6-methyl-3,4,5,6-tetrahydro-1H,2H-1(2,5)-pyrrola-2(3,4)-pyranacyclonaphane-2-carboaldehyde. To a solution of 12 (62.4 mg, 194 μmol) in CH₂Cl₂ (19.4 mL) and acetonitrile (2.0 mL) were added 4A -MS (93.6 mg) prepared by heating at 200 °C in vacuo and N-methylmorpholine N-oxide (52.5 mg, 398 μmol) and TPAP (27.3 mg, 77.6 μmol). The reaction mixture was stirred at rt for 2 h, and the mixture was filtered through Celite and concentrated. The residue was purified by flash chromatography (SiO₂ 3 g, hexane–AcOEt, 6:1) to afford aldehyde (44.3 mg, 139 μmol, 74%); a colorless oil; [α]₁⁹D +7.8 (c 0.78, CHCl₃); 1H NMR (400 MHz, CDCl₃) δ 9.37 (s, 1H), 8.12 (brs, 1H), 5.76 (t, \( J = 2.8 \) Hz, 1H), 5.72 (t, \( J = 2.8 \) Hz, 1H), 4.41-4.34 (m, 1H), 3.38 (s, 3H), 2.76 (ddd, \( J = 14.8 \) Hz, 1H), 2.52 (ddd, \( J = 14.8 \), 11.2, 4.8 Hz, 1H), 2.48 (d, \( J = 12.0 \) Hz, 1H), 2.20-2.11 (m, 1H), 1.75-1.56 (m, 5H), 1.46 (d, \( J = 6.8 \) Hz, 1H), 1.38-1.25 (m, 3H), 1.18-1.07 (m, 2H), 0.91-0.75 (m, 3H), 0.54-0.45 (m, 1H); 13C NMR (100 MHz, CDCl₃) δ 199.2, 133.6, 126.0, 110.0, 105.4, 100.4, 69.8, 51.5, 46.2, 38.3, 30.3, 28.4, 27.2, 27.1, 25.4, 24.8, 24.7, 24.5, 21.2; FT-IR (neat) ν 3468, 2926, 2854, 1745, 1446, 1376, 1133, 1040, 767 cm⁻¹; MS (ESI) m/z 260, 288, 342 (100) [(M+Na)+]; HRMS (ESI) calcd for C₁₉H₂₉NNaO₃ [(M+Na)+] 342.2045, found 342.2023.

3-Hydroxy-3-((2R,3S,4S,6S)-2-methoxy-6-methyl-3,4,5,6-tetrahydro-1H,2H-1(2,5)-pyrrola-2(3,4)-pyranacyclonaphane-2-yl)propanenitrile (13a and 13b). A mixture of N,N-diisopropylamine (114 μL, 812 μmol) in THF (0.7 mL) was added n-butyllithium (2.76 M in hexane, 294 μL, 812 μmol) and the mixture was stirred at 0 °C for 15 min. To this LDA solution was added MeCN (49.5 μL, 948 μmol) at -78 °C and stirring was continued for 45 min. To the mixture was added the above-mentioned aldehyde (17.3 mg, 54.2 μmol) in THF (1.5 mL) and the mixture was stirred for 1 h. To the mixture was added saturated aqueous NH₄Cl (5 mL) and extracted with AcOEt (10 mL × 3). Organic extracts were washed with brine (10 mL), dried, and concentrated. The residue was purified by flash chromatography (preparative TLC, hexane–AcOEt, 3:1) to afford 13a (11.7 mg, 32.4 μmol, 60%) and 13b (5.2 mg, 14.4 μmol, 27%).

13a: a brown oil; [α]₁⁹D -14.1 (c 0.59, CHCl₃); 1H NMR (400 MHz, CDCl₃) δ 8.02 (brs, 1H), 5.84 (t, \( J = 2.8 \) Hz, 1H), 5.72 (t, \( J = 2.8 \) Hz, 1H), 4.29-4.21 (m, 1H), 3.99 (ddd, \( J = 9.6 \), 4.4, 3.2 Hz, 1H), 3.39 (s, 3H), 2.76-2.57 (m, 3H), 2.55-2.48 (m, 2H), 2.38 (dd, \( J = 16.4 \), 3.2 Hz, 1H), 2.09-1.99 (m, 1H), 1.72-1.50 (m, 5H), 1.40 (d, \( J = 6.8 \) Hz, 3H), 1.33-1.26 (m, 3H), 1.20-1.06 (m, 2H), 0.88-0.71 (m, 3H), 0.38-0.29 (m,
1H; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 133.4, 127.7, 118.5, 110.3, 105.5, 100.3, 71.7, 69.7, 49.9, 44.5, 38.1, 29.6, 28.4, 27.9, 27.8, 25.7, 24.7, 24.5, 24.3, 21.3, 20.7; FT-IR (neat) $\nu$ 3463, 2923, 2854, 2251, 1722, 1452, 1140, 1082, 1023, 769, 546, 415 cm$^{-1}$; MS (ESI) $m/z$ 329, 351, 352, 383 (100) [(M+Na)$^+$]; HRMS (ESI) calcd for C$_{21}$H$_{32}$N$_2$NaO$_3$ [(M+Na)$^+$] 383.2311, found 383.2300.

13b: a colorless powder; $[\alpha]_D$ +7.9 (c 0.12, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.12 (brs, 1H), 5.90 (t, $J$ = 2.8 Hz, 1H), 5.74 (t, $J$ = 2.8 Hz, 1H), 4.23-4.17 (m, 1H), 4.00 (td, $J$ = 9.2, 4.0 Hz, 1H), 3.41 (s, 3H), 2.73-2.66 (m, 2H), 2.58 (dd, $J$ = 16.4, 9.2 Hz, 1H), 2.50 (ddd, $J$ = 14.4, 11.2, 4.0 Hz, 1H), 2.41 (d, $J$ = 12.0 Hz, 1H), 2.19 (d, $J$ = 9.2 Hz, 1H), 2.15-2.08 (m, 1H), 1.74-1.63 (m, 3H), 1.53-1.47 (m, 3H), 1.53-1.47 (m, 1H), 1.40 (d, $J$ = 6.8 Hz, 1H), 1.36-1.08 (m, 6H), 0.94-0.76 (m, 3H), 0.45-0.35 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 134.7, 126.4, 118.2, 110.4, 105.9, 99.5, 71.0, 69.5, 49.0, 44.7, 38.4, 29.8, 27.8, 27.5, 25.4, 24.7, 24.5, 24.5, 22.5, 21.4; FT-IR (neat) $\nu$ 3463, 2927, 2857, 2251, 1725, 1457, 1274, 1137, 1033, 770 cm$^{-1}$; MS (DART) $m/z$ 320, 329, 361 (100) [(M+H)$^+$]; HRMS (DART) calcd for C$_{21}$H$_{33}$N$_2$O$_3$ [(M+H)$^+$] 361.2491, found 361.2512.

3-Methoxy-3-((2S,3S,4S,6S)-2-methoxy-6-methyl-3,4,5,6-tetrahydro-1H,2H-1(2,5)-pyrrola-2(3,4)-pyranacyclonaphan-2-yl)propanenitrile. To a solution of 13a (22.2 mg, 61.6 $\mu$mol) in THF (3.1 mL) was added sodium hydride (60% in mineral oil, 7.4 mg, 185 $\mu$mol) and stirred for 30 min. To this mixture was added MeI (52.4 mg, 370 $\mu$mol) and stirring was continued at rt for 2.5 h. To the mixture was added saturated aqueous NH$_4$Cl (5 mL) and extracted with AcOEt (10 mL $\times$ 3). Organic extracts were washed with brine (10 mL), dried, and concentrated. The residue was purified by flash chromatography (SiO$_2$ 1 g, hexane–AcOEt, 8:1) to afford methoxy compound (18.6 mg, 49.7 $\mu$mol, 81%); a brown oil; $[\alpha]_D$ -26.6 (c 0.19, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.93 (brs, 1H), 5.82 (t, $J$ = 2.8 Hz, 1H), 5.70 (t, $J$ = 2.8 Hz, 1H), 4.22 (sext, $J$ = 6.8 Hz, 1H), 3.59-3.56 (m, 4H), 3.34 (s, 3H), 2.84 (d, $J$ = 12.4 Hz, 1H), 2.65 (ddd, $J$ = 14.8, 6.0, 4.0 Hz, 1H), 2.51 (ddd, $J$ = 14.8, 10.4, 4.0 Hz, 1H), 2.34 (dd, $J$ = 17.6, 10.0 Hz, 1H), 2.12 (dd, $J$ = 17.6, 2.4 Hz, 1H), 2.02-1.93 (m, 1H), 1.71-1.61 (m, 2H), 1.56-1.44 (m, 3H), 1.37 (d, $J$ = 6.8 Hz, 3H), 1.33-1.05 (m, 5H), 0.91-0.69 (m, 3H), 0.32-0.23 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 133.0, 128.2, 119.4, 110.3, 105.3, 101.6, 81.5, 68.8, 60.9, 49.0, 42.8, 38.0, 29.7, 28.5, 28.0, 27.9, 25.8, 24.8, 24.5, 24.2, 21.4, 19.7; FT-IR (neat) $\nu$ 3466, 3386, 2926, 2248, 1457, 1373, 1268, 1115, 1026, 915, 770, 734 cm$^{-1}$; MS (ESI) $m/z$ 397 (100) [(M+Na)$^+$]; HRMS (ESI) calcd for C$_{22}$H$_{34}$N$_2$O$_3$ [(M+Na)$^+$] 397.2491, found 397.2512.

3-Methoxy-3-((2R,3S,4S,6S)-2-methoxy-6-methyl-3,4,5,6-tetrahydro-1H,2H-1(2,5)-pyrrola-2(3,4)-pyranacyclonaphan-2-yl)propanamide (1). To the mixture of methoxy compound (11.8 mg, 31.5 $\mu$mol) in DMSO (1.3 mL) were added 30% H$_2$O$_2$ (320 $\mu$L, 3.15 mmol) and K$_2$CO$_3$ (87.1 mg, 630 $\mu$mol), and the mixture was stirred at 60 °C for 11.5 h and at 80 °C for 3 h. To this mixture were added 30% H$_2$O$_2$ (320 $\mu$L, 3.15 mmol) and K$_2$CO$_3$ (87.1 mg, 630 $\mu$mol), and stirring was continued for 3.5 h. To the
mixture was added H$_2$O (5 mL), extracted with Et$_2$O (10 mL × 3). Organic extracts were washed with brine (5 mL), dried, and concentrated. The residue was purified by flash chromatography (SiO$_2$ 0.8 g, hexane–AcOEt, 2:1 to 1:2) to afford 1 (9.2 mg, 23.4 μmol, 74%); [α]$_D^{19}$ -10.5 (c 0.72, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.02 (brs, 1H), 5.80 (t, $J$ = 2.8 Hz, 1H), 5.68 (t, $J$ = 2.8 Hz, 1H), 5.56 (brs, 1H), 5.27 (brs, 1H), 4.22 (sext, $J$ = 6.8 Hz, 1H), 3.75 (dd, $J$ = 9.2, 2.8 Hz, 1H), 3.49 (s, 3H), 3.34 (s, 3H), 2.84 (d, $J$ = 11.6 Hz, 1H), 2.65 (ddd, $J$ = 14.8, 6.0, 4.0 Hz, 1H), 2.50 (ddd, $J$ = 14.8, 10.8, 4.0 Hz, 1H), 2.10-1.98 (m, 3H), 1.69-1.60 (m, 2H), 1.57-1.41 (m, 3H), 1.38 (d, $J$ = 6.8 Hz, 3H), 1.35-1.23 (m, 3H), 1.18-1.04 (m, 2H), 0.89-0.68 (m, 3H), 0.34-0.23 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 174.5, 132.5, 129.3, 109.7, 104.9, 102.9, 82.1, 68.5, 60.3, 48.8, 43.3, 38.2, 37.6, 29.7, 28.6, 28.1, 27.9, 25.8, 24.8, 24.6, 24.2, 21.5; FT-IR (neat) ν 3464, 3340, 3199, 2925, 2854, 1674, 1442, 1336, 1113, 1020, 911, 733 cm$^{-1}$; MS (ESI) m/z 242, 301, 329, 351, 383, 385, 413, 415 (100) [(M+Na)$^+$]; HRMS (ESI) calcd for C$_{22}$H$_{36}$N$_2$NaO$_4$ [(M+Na)$^+$] 415.2573, found 415.2622.

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SUPPORTING INFORMATION
$^1$H and $^{13}$C NMR spectra of new compounds are available.

REFERENCES AND NOTES
14. The crystallographic data (CCDC 1936764) can be obtained free of charge from the Cambridge Crystallographic Data centre via www.ccdc.cam.ac.uk/data_request/cif.