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SYNTHESIS OF *N*-METHYL UROCANATES OF HYDROXYDERIVATIVES OF ISOCEMBROL

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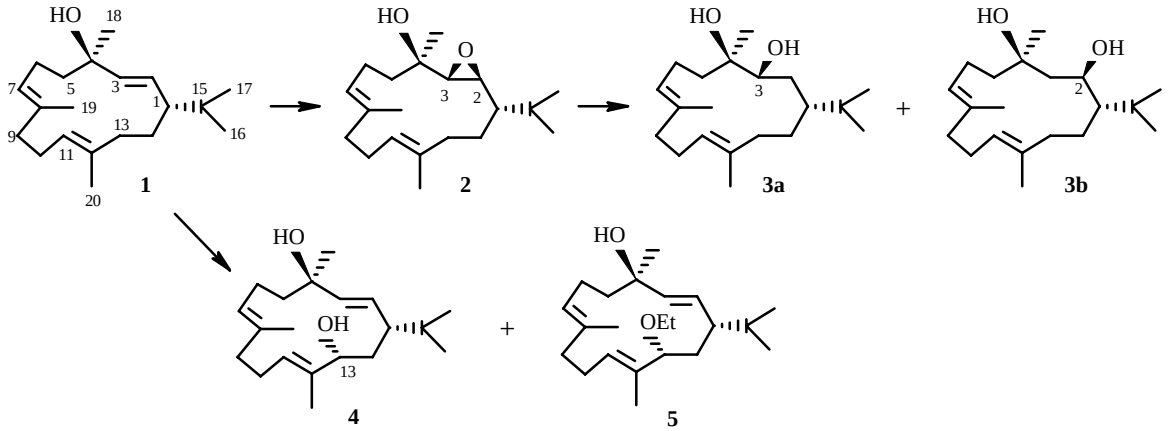
Alcohols were prepared by stereospecific hydroxylation of isocembrol and were esterified into N-*methylurocanates, proposed biomimetics of taxol.*

Keywords: isocembrol, diterpenoids, eleuthesoids, eleutherobin, sarcodictyin, urocanic acid

Urocanic [3-(4-imidazolyl)prop-2-enoic] acid exhibits multifaceted biological activity and is formed *in vivo* as a result of histidine metabolism [1]. Its *N*-methylderivative is the acid component in the diterpene esters eleutherobin and sarcodictyins, metabolites of soft coral *Eleutherobia* sp. and *Sarcodictyon roseum*, which exhibit a taxol-like mechanism of cytotoxic activity [2]. In creating a combinatory library of sarcodictyins, it was discovered that removal of the *N*-methylurocanic acid or replacing its imidazole ring by oxazole, thiazole, or benzene sharply affected its cytotoxic activity [3]. Valdivones, eleuthesides that are not *N*-methylurocanate esters [4], have not been demonstrated to have similar properties. On the other hand, an eleuthesoid containing a benzene ring instead of menthane retains its cytotoxic activity [5]. It may be that the biological properties of eleutherobin and sarcodictyin are unique because they are also *N*-methylurocanate esters, which makes it probable that other accessible taxol biomimetics exist.

Therefore, cembrane derivatives, which are proposed biogenetic precursors of eleuthesides [6], are promising diterpenoids for preparing *N*-methylurocanates. One of these derivatives, isocembrol (**1**), was isolated from Siberian cedar resin [7] and was studied for possible generation of the eleutheside carbon skeleton [8]. In contrast with this, we used hydroxy derivatives of isocembrol directly as the alcohols of *N*-methylurocanate esters.

We studied the possibility of introducing selectively a secondary hydroxyl into the molecule because esterification of the tertiary alcohol of **1** is problematical due to steric hindrances and competing elimination.



Scheme 1.

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Reaction of **1** and *t*-butylhydroperoxide (TBHP) in benzene in the presence of catalytic amounts of $VO(acac)_2$ produced regioselectively and stereospecifically epoxide **2**. The stereochemistry of **2** was established based on spectral data. Thus, the large SSCC $J_{1,2}$ = 9.1 Hz in the PMR spectra indicated that the oxirane ring had the β-orientation. The ^{13}C NMR spectra exhibited signals for C-2 and C-3 at 62.8 and 57.4 ppm, respectively.

The oxirane ring was opened by reacting **2** with $LiAlH_4$ in boiling THF or $(i\text{-}Bu)_2AlH$ in toluene at 75°C. In both instances the reaction occurred regioselectively and stereospecifically to produce β-alcohols **3a** and **3b** in 1:7 and 1:10 ratios, respectively. The structures of the isolated regioisomers **3a** and **3b** were confirmed by their spectral properties. Thus, the PMR spectrum of **3a** has two SSCC for H-3 with the C-2 protons. The two-dimensional 90° H—H COSY spectrum showed chemical shifts (CS) for the C-2 protons at 1.95 and 1.40 ppm. The proton with CS 1.95 ppm gave signals overlapping those of allylic protons and its SSCC could not be observed. The proton with CS 1.40 ppm was well observed and had a *trans*-SSCC of 8.9 Hz with H-3 and a *cis*-SSCC of 3.2 Hz with the C-1 proton. Thus, the C-3 hydroxyl was oriented in the direction opposite of the isopropyl. The ^{13}C NMR spectrum recorded in the JMOD regime had the signal for C-3 at 73.8 ppm with a negative amplitude, indicating that diol **3a** was a secondary alcohol.

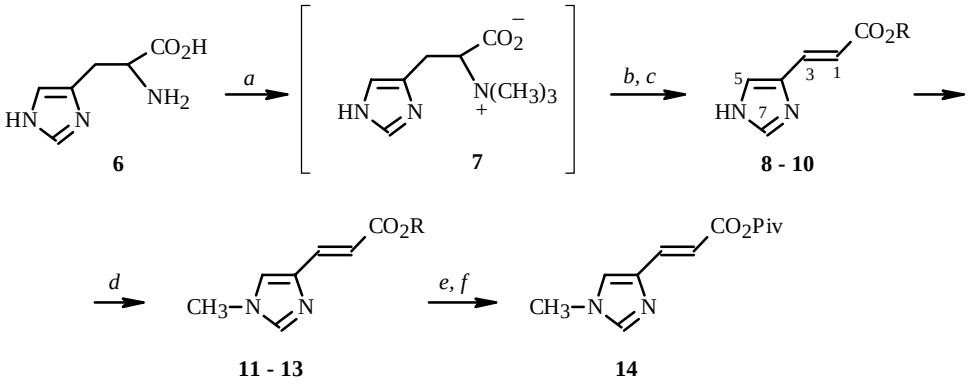
For regioisomer **3b**, double resonance established vicinal constants of 6.4 and 5.7 Hz for H-2 with the C-3 protons. The large $J_{2,1}$ = 10.7 Hz indicated that they were *trans*-diaxial, from which the *R*-configuration for C-2 was deduced.

Allylic oxidation of isocembrol by SeO_2 in boiling ethanol occurred regio- and stereospecifically. The reaction gave 30% yield of diol **4** (Scheme 1) and its esterification product **5** (35%).

The configuration of the new asymmetric center in **4** was established using PMR data. Thus, the signal for H-13 appeared at 3.74 ppm and gave a doublet—doublet signal with $J_{13,14}$ = 10.8 and $J_{14,1}$ = 1.7 Hz. The couplings were confirmed by double resonance. Thus, the stereochemistry of C-3 was also *S*-type.

The picture was analogous in the PMR spectrum of **5** with the single difference that the signals for H-13 were slightly shifted to 3.72 ppm with SSCC 10.6 and 4.3 Hz; H-14, 1.90 with SSCC 12.4, 10.7, and 1.6 Hz; and H-1, 2.48 with SSCC 9.4, 8.7, 5.3, and 1.6 Hz. The ethoxy quartet was observed at 3.22 ppm; the triplet, at 1.08 ppm. Thus, the structure of C-13 corresponded to the *S*-configuration also, as in **4**.

The *N*-methylurocanic acid was prepared by Hofman degradation of histidine (**6**) [9] with subsequent *N*-methylation of the methyl or ethyl ester of urocanic acid as before [10] and hydrolysis. The mixed anhydride **14** was synthesized as before [11] according to Scheme 2.



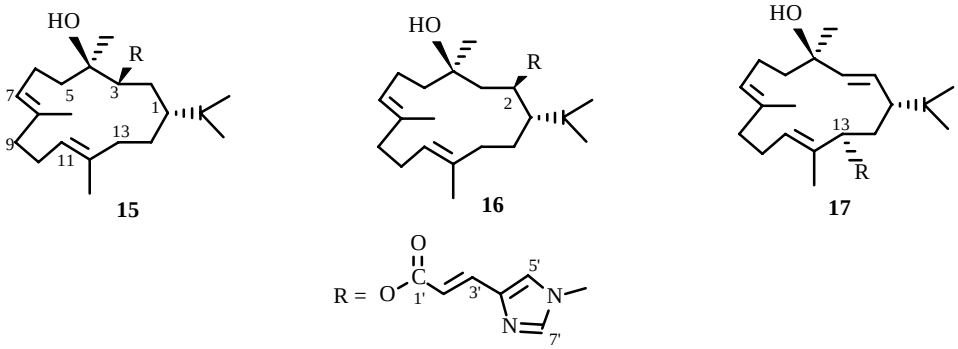
6 **7** **8 - 10** **11 - 13** **14**

8, 13: R = H; **9, 11:** R = CH_3; **10, 12:** R = C_2H_5

a. CH_3I, KOH, CH_3OH; *b.* 30% NaOH, boiled, **8** – 66%; *c.* MeOH or EtOH, H^+;
d. CH_3I, K_2CO_3, acetone; *e.* NaOH, THF-H_2O; *f.* PivCl, THF

Scheme 2.

An attempt to esterify **3a** by heating with *N*-methylurocanic acid in the presence of dicyclohexylcarbodiimide (DCC) [12] was unsuccessful. Nevertheless, **3b** and **4** were esterified into the urocanates **16** and **17** by this route in 25 and 31% yields, respectively.



Urocanate **15** could be prepared in 71% yield by alcoholysis of pivaloyl-*N*-methylurocanate by diol **3a**. Under these conditions the esterification proceeded with incomplete conversion in 38% yield.

The spectral properties of urocanates **15**, **16**, and **17** confirmed their structures and were composites of the CS of C and H atoms of *N*-methylurocanic acid and the corresponding diols with slight differences.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at working frequencies 300.13 (^{1}H) and 75.47 MHz (^{13}C). Published NMR spectra of **1** and its derivatives provided a basis for spectral identification of the products [13, 14]. ^{13}C NMR spectra were recorded with modulation of the C–H coupling constants, i.e., signals of CH_3– and CH groups were readily distinguished from CH_2 and quaternary C atoms. Spectra were also calculated using the ACD Labs program package. Melting points were determined on an S 30A/G Kofler block (GDR). Analytical TLC used PTSKh-AF-A Sorbfil plates (ZAO Sorbpolimer, Krasnodar). Optical rotation angles were measured on a Perkin—Elmer 3141 instrument.

(1*S*,2*S*,3*S*,4*R*)-2,3-Epoxycembra-7(*E*),11(*E*)-dien-4-ol (2). A mixture of **1** (0.540 g, 1.9 mmol) and a catalytic amount of $VO(acac)_2$ in benzene (10 mL) at 5°C was stirred for 5 min and treated with TBHP (0.58 g, 1.9 mmol, 29%) in toluene. The reaction mixture was brought to room temperature after 20 min. Three hours after the reaction was finished (TLC monitoring), EtOAc (50 mL) was added. The mixture was washed with $Na_2S_2O_5$ solution (3 × 10 mL) and water (2 × 10 mL) and dried over $MgSO_4$. Solvent was removed in a rotary evaporator. The solid was chromatographed over SiO_2 (petroleum ether:EtOAc, 6:1) to afford **2** (0.426 g, 75%), $C_{20}H_{34}O_2$, R_f 0.50 (petroleum ether:EtOAc, 3:1), mp 81-84°C, $[\alpha]_D^{20}$ +233.3° (*c* 0.03, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.94 (3H, d, J = 6.9, CH_3), 0.98 (3H, d, J = 6.9, CH_3), 1.28 (3H, s, CH_3), 1.32 (1H, m, CH), 1.52 (3H, s, CH_3), 1.64 (3H, s, CH_3), 1.71 (2H, m, CH_2), 1.90 (2H, m, CH_2), 2.10 (5H, m, CH, CH_2), 2.30 (4H, m, CH_2), 2.88 (1H, dd, J = 9.1, 2.4, H-2), 3.35 (1H, d, J = 2.4, H-3), 5.02 (1H, d, J = 10.1, H-7), 5.20 (1H, dd, J = 9.4, 4.4, H-11).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.9 (C-16), 14.4 (C-17), 18.0 (C-19), 20.3 (C-18), 22.1 (C-20), 22.8 (C-6), 23.9 (C-10), 24.3 (C-14), 30.0 (C-5), 36.4 (C-13), 39.4 (C-15), 39.7 (C-9), 44.1 (C-1), 57.4 (C-2), 62.8 (C-3), 69.8 (C-4), 126.0 (C-7), 126.8 (C-11), 133.0 (C-8), 133.6 (C-12).

(1*S*,3*S*,4*R*)-Cembra-7(*E*),11(*E*)-dien-3,4-diol (3a) and (1*S*,2*R*,4*R*)-Cembra-7(*E*),11(*E*)-dien-2,4-diol (3b).

Method A. A solution of $LiAlH_4$ (0.071 g, 1.879 mmol) in THF (30 mL) was treated with **2** (0.575 g, 1.9 mmol) in THF (5 mL) and refluxed for 4 h. After the reaction was finished (TLC monitoring), the mixture was brought to room temperature. A solution of $NaHCO_3$ was slowly added until hydrogen evolution stopped. The aqueous layer was extracted with EtOAc (4 × 10 mL) and dried over $MgSO_4$. Solvent was removed in a rotary evaporator. The solid was chromatographed over SiO_2 (petroleum ether:EtOAc, 5:1) to afford **3a** (0.486 g, 84%) and **3b** (0.069 g, 12%).

Method B. A solution of **2** (0.09 g, 0.294 mmol) in toluene (5 mL) was treated dropwise with $(i\text{-Bu})_2AlH$ in toluene (0.5 mL, 0.7 mmol, 70%), heated at 75°C for 1 h, cooled to 0°C, and decomposed by adding successively water (5 mL) and HCl (5 mL, 1 N). The aqueous layer was extracted with EtOAc (4 × 10 mL). The organic layer was dried over $MgSO_4$. Solvent was removed in a rotary evaporator. The solid was chromatographed over SiO_2 (petroleum ether:EtOAc, 5:1) to afford **3a** (0.081 g, 88%), $C_{20}H_{36}O_2$, and **3b** (0.008 g, 8.5%), $C_{20}H_{36}O_2$.

3a. R_f 0.25 (petroleum ether:EtOAc, 3:1), $[\alpha]_D^{20}$ +107.7° (*c* 0.015, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.85 (3H, d, J = 6.9, CH_3), 1.90 (3H, d, J = 6.9, CH_3), 1.10 (3H, s, CH_3), 1.15-1.30 (4H, m, CH_2), 1.40 (1H, ddd, J = 10.7, $^3J_{3,2}$ = 8.9, $J_{1,2}$ = 3.2, H-2a), 1.40 (3H, s, CH_3), 1.5 (2H, m, H-10a, H-6a), 1.8 (1H, d, J = 6.9, 3.2, H-15), 1.9-2.0 (8H, m, CH_2), 2.1 (2H, m, H-10b, H-6b), 3.53 (1H, dd, J = 8.9, 1.6, H-3), 4.9 (1H, td, J = 7.0, 1.1, H-11), 5.18 (1H, t, J = 6.8, H-7).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.1 (C-18), 15.5 (C-19), 18.2 (C-16), 20.7 (C-17), 22.76 (C-20), 23.1 (C-6), 24.6 (C-10), 27.1 (C-14), 30.2 (C-15), 32.62 (C-5), 36.2 (C-9), 39.5 (C-13), 39.7 (C-2), 40.2 (C-1), 73.8 (C-3), 75.4 (C-4), 124.4 (C-7), 127.0 (C-11), 134.2 (C-8), 135.1 (C-12).

3b. R_f 0.30 (petroleum ether:EtOAc, 3:1), $[\alpha]_D^{20}$ -40.4° (*c* 0.02, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.72 (3H, d, J = 6.9, CH_3), 0.90 (3H, d, J = 6.9, CH_3), 1.10 (3H, s, CH_3), 1.30 (2H, m, CH_2), 1.45 (1H, m, CH), 1.54 (1H, m, CH_2), 1.62 (6H, s, CH_3, CH_3), 1.67-1.70 (3H, m, CH, CH_2), 1.80 (1H, m, H-1), 1.90-2.28 (6H, m, CH, CH_2), 2.33 (1H, m, CH_2), 2.50 (1H, m, CH_2), 3.10 (1H, s, OH), 3.30 (1H, ddd, J = 10.7, 6.4, 5.7, H-2), 5.02 (1H, br.s, H-7), 5.07 (1H, br.s, H-11).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.51 (CH_3), 15.76 (CH_3), 17.50 (CH_3), 20.68 (CH_3), 22.37 (CH_3), 23.89 (C-6), 24.03 (C-10), 27.01 (C-15), 27.92 (C-14), 34.35 (C-5), 36.95 (C-9), 37.81 (C-13), 39.73 (C-1), 39.83 (C-3), 73.74 (C-4), 76.92 (C-2), 125.77 (C-11), 126.33 (C-7), 134.74 (C-8), 136.35 (C-12).

(1*S*,4*R*,13*S*)-Cembra-2(*E*),7(*E*),11(*E*)-trien-4,13-diol (4) and (1*S*,4*R*,13*S*)-Ethoxycembra-2(*E*),7(*E*),11(*E*)-trien-4-ol (5). A solution of **1** (0.220 g, 0.759 mmol) in EtOH (80%, 15 mL) was boiled gently for 2 h and treated with SeO_2 (0.084 g, 0.766 mmol) in EtOH (80%, 5 mL). After the reaction was finished (TLC monitoring), the mixture was brought to room temperature and filtered to remove precipitated Se. The filtrate was evaporated. The solid was dissolved in EtOAc (25 mL), washed with water (2 × 10 mL), and dried over $MgSO_4$. Solvent was removed in a rotary evaporator. The solid was chromatographed over SiO_2 (petroleum ether:EtOAc, 7:1) to afford **4** (0.062 g, 30%), $C_{20}H_{36}O_2$ and **5** (0.071 g, 35%), $C_{20}H_{36}O_2$.

4. R_f 0.22 (petroleum ether:EtOAc, 5:1), $[\alpha]_D^{20}$ +56.1° (*c* 0.01, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.85 (3H, d, J = 6.8, CH_3), 0.88 (3H, d, J = 6.8, CH_3), 0.90-1.18 (2H, m, CH, CH_2), 1.24 (3H, s, CH_3), 1.24-1.43 (3H, m, CH, CH_2), 1.48 (3H, s, CH_3), 1.54 (3H, s, CH_3), 1.65-1.90 (3H, m, CH_2), 1.90 (1H, ddd, J = 12.8, 10.8, 1.7, H-14), 2.15 (2H, m, CH_2), 2.25 (1H, m, CH_2), 2.35 (1H, dddd, J = 8.7, 8.6, 8.5, 1.7, H-1), 3.30 (1H, br.s, OH), 3.74 (1H, dd, J = 10.8, 4.4, H-13), 5.10 (2H, m H-7, H-11), 5.12 (1H, dd, J = 15.7, 8.9, H-2), 5.52 (1H, dd, J = 15.7, H-3).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 9.19 (C-16), 14.89 (C-17), 19.57 (C^4-CH_3), 19.95 (C-15), 22.15 (C-6), 23.25 (C-10), 27.88 (C^{12}-CH_3), 33.00 (C^8-CH_3), 35.14 (C-14), 38.64 (C-9), 42.79 (C-5), 45.73 (C-1), 72.30 (C-4), 77.57 (C-13), 128.77 (C-11), 128.89 (C-7), 129.10 (C-2), 131.75 (C-8), 134.35 (C-12), 137.62 (C-3).

5. R_f 0.30 (petroleum ether:EtOAc, 5:1), $[\alpha]_D^{20}$ +40.5° (*c* 0.046, $CHCl_3$).

PMR spectrum (CCl_4:C_6D_6, δ, ppm, J/Hz): 0.80 (3H, d, J = 6.9, CH_3), 0.83 (3H, d, J = 6.9, CH_3), 0.86 (1H, m, CH), 1.08 (3H, t, J = 7.0, CH_3), 1.15 (3H, s, CH_3), 1.16 (1H, m, CH), 1.25 (1H, m, CH_2), 1.44 (2H, m, CH_2), 1.48 (3H, s, CH_3), 1.50 (3H, m, CH_3) 1.9 (1H, ddd, J = 12.4, 10.6, 1.6, H-14), 2.15 (1H, m, CH_2), 2.48 (1H, dddd, J = 9.4, 8.7, 5.3, 1.6, H-1), 3.22 (2H, q, J = 6.9, CH_2), 3.72 (1H, dd, J = 10.6, 4.3, H″-13), 5.08 (1H, dd, J = 16.0, 5.3, H-2), 5.12 (2H, m, H-7, H-11), 5.33 (1H, d, J = 16.0, H-3).

^{13}C NMR spectrum (CCl_4:C_6D_6, δ, ppm): 9.28 (CH_3), 15.0 (C-19), 16.13 (C-16), 20.13 (C-6), 21.49 (C-10), 23.10 (C-18), 23.15 (C-20), 33.63 (C-14), 35.49 [$\underline{C}(CH_3)_2$], 38.59 (C-9), 43.07 (C-5), 45.94 (C-1), 57.02 (CH_2O), 75.80 (C-4), 77.01 (C-13), 128.05 (C-11), 129.57 (C-7), 131.08 (C-8), 134.76 (C-12).

(*E*)-3-(1*H*-Imidazol-4-yl)-2-propenoic Acid (8). A solution of histidine (**6**, 2.0 g, 13 mmol) in methanol (5 mL) was placed in a round-bottomed flask equipped with a reflux condenser and two dropping funnels, cooled to 0-5°C, stirred, and treated simultaneously with KOH (2.0 g, 34 mmol, 25%) in methanol and CH_3I (2.0 mL, 34 mmol, 50%) in methanol. After 1 h when the pH of the reaction mixture was neutral, the mixture was brought to room temperature and treated with another portion of KOH (1.0 g, 17 mmol, 25%) in methanol and CH_3I (1.2 mL, 17 mmol, 50%) in methanol. When the pH of the solution again became neutral, methanol was removed in a rotary evaporator. The solid was dissolved in aqueous NaOH (30%) and refluxed for 5 h. The mixture was neutralized by HCl (5 M) and evaporated. The solid was extracted with EtOH. Recrystallization from EtOH afforded urocanic acid (**8**, 1.17 g, 66%), $C_6H_6N_2O_2$, R_f 0.40 (EtOH), mp 210-212°C.

PMR spectrum [$(CD_3)_2SO$, δ, ppm, J/Hz]: 6.30 (1H, d, J = 15.6, H-2), 7.38 (1H, d, J = 15.6, H-3), 7.41 (1H, s, H-5), 7.75 (1H, s, H-7).

^{13}C NMR spectrum [$(CD_3)_2SO$, δ, ppm]: 116.34 (C-2), 123.2 (C-7), 134.44 (C-3), 136.3 (C-4), 139.56 (C-5), 169.8 (C=O).

(*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-2-propenoic Acid (13). The ethyl ester **12** (0.720 g, 4.02 mmol) in THF:H_2O (20 mL, 1:1) was treated with NaOH (0.164 g, 4.10 mmol) and stirred at room temperature for 24 h. The mixture was neutralized with HCl (2.06 mL, 2 M, 4.12 mmoL). Solvent was removed in a rotary evaporator. The solid was chromatographed over SiO_2 (EtOH:EtOAc, 1:5) to afford **13** (0.546 g, 90%), $C_6H_6N_2O_2$, R_f 0.45 (EtOH), mp 235-237°C.

PMR spectrum (CD_3OD, δ, ppm): 3.35 (s, N–CH_3), 4.90 (d, H-2), 5.90 (s, H-5), 5.97 (d, H-3), 6.23 (s, H-7).

^{13}C NMR spectrum (CD_3OD, δ, ppm): 34.26 (N–CH_3), 118.41 (C-2), 124.74 (C-3), 136.29 (C-7), 137.98 (C-4), 140.80 (C-5), 171.45 (C=O).

(1*S*,3*S*,4*R*)-3-[1″-Methyl-1″*H*-imidazol-4″-yl]-(*E*)-ethenylcarbonyloxy]-cembra-7(*E*),11(*E*)-dien-4-ol (15). A solution of **3a** (0.115 g, 0.373 mmol) in CH_2Cl_2 (1 mL) was treated with Et_3N (0.78 mL, 5.595 mmol) and 4-DMAP (0.045 g, 0.373 mmol). The solution was cooled to 0°C and treated with a solution of pivaloyl *N*-methylurocanate (15 mL, 3.112 mmol, 0.2 M) in CH_2Cl_2. The mixture was brought to room temperature and stirred for 5 d. After the reaction was finished (TLC monitoring), the mixture was diluted with saturated $NaHCO_3$ solution, extracted with CH_2Cl_2 (3 × 10 mL), and dried over $MgSO_4$. Solvent was removed in a rotary evaporator. The solid was chromatographed over SiO_2 (EtOAc) to afford **15** (0.114 g, 71%), $C_6H_6N_2O_2$ R_f 0.25 (EtOAc), $[\alpha]_D^{20}$ +11.5° (*c* 0.066, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.74 (3H, d, CH_3), 0.83 (3H, d, CH_3), 1.12 (3H, s, C^4-CH_3), 1.15-1.30 (2H, m, CH_2), 1.45-1.60 (2H, m, CH_2), 1.55 (3H, s, C^{12}-CH_3), 1.60 (3H, s, C^8-CH_3), 1.85 (1H, ddd, J = 14.2, 8.3, 5.6, H-2), 1.95-2.30 (13H, m, CH, CH_2), 2.5 (1H, br.s, OH), 3.68 (3H, s, N–CH_3), 4.75 (1H, s, H-7′), 5.02 (1H, t, J = 7.0, H-7), 5.07 (1H, dd, J = 8.3, 2.7, H-3), 5.38 (1H, t, J = 7.3, H-11), 6.58 (1H, d, J = 15.6, H-2′), 7.07 (1H, s, H-5′), 7.55 (1H, d, J = 15.6, H-3′).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.78 (C^{19}-CH_3), 14.88 (C^{17}-CH_3), 16.92 (C^{16}-CH_3), 21.11 (C^{20}-CH_3), 21.77 (C-6), 24.08 (C^{18}-CH_3), 24.17 (C-10), 25.67 (C-14), 29.0 (C-15), 33.54 (N–CH_3), 35.60 (C-9), 35.69 (C-5), 38.87 (C-13), 39.24 (C-1), 39.31 (C-2), 75.21 (C-4), 78.15 (C-3), 116.13 (C-2′), 122.55 (C-3′), 124.83 (C-11), 126.56 (C-7), 133.73 (C-8), 134.33 (C-12), 136.36 (C-7′), 138.44 (C-4′), 139.13 (C-5′), 168.30 (C=O).

(1*S*,3*S*,4*R*)-2-[1″-Methyl-1″*H*-imidazol-4″-yl]-(*E*)-ethenylcarbonyloxy]-cembra-7(*E*),11(*E*)-dien-4-ol (16). A solution of **3b** (0.169 g, 0.548 mmol) in $CHCl_3$ (50 mL) was treated with **13** (0.248 g, 1.644 mmol), DCC (0.451 g, 2.192 mmol), and 4-DMAP (0.334 g, 2.740 mmol). The mixture was heated on an oil bath at 65°C for 7 d, diluted with saturated NH_4Cl solution, extracted with CH_2Cl_2 (3 × 10 mL), and dried over $MgSO_4$. Solvent was removed in a rotary evaporator. The solid was chromatographed over SiO_2 (EtOAc) to afford **16** (0.060 g, 25%), $C_6H_6N_2O_2$, R_f 0.30 (EtOAc), $[\alpha]_D^{20}$ -2.20° (*c* 0.050, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.78 (3H, d, J = 6.8, CH_3), 0.88 (3H, d, J = 6.8, CH_3), 1.21 (3H, s, CH_3), 1.61 (3H, s, CH_3), 1.62 (3H, s, CH_3), 1.30 (2H, m, CH_2), 1.48 (2H, m, CH_2), 1.70 (2H, m, CH_2), 1.80 (1H, m, CH), 1.93 (1H, ddt, J = 8.7, 7.0, 3.6, H-1), 2.12 (6H, m, CH_2), 2.30 (1H, ddd, CH_2), 3.70 (3H, s, N–CH_3), 4.95 (1H, J = 8.7, 5.7, 2.8, H-2), 5.05 (1H, dd, H-11), 5.26 (1H, m, H-7), 6.52 (1H, d, J = 15.6, H-11), 7.07 (1H, s, H-5′), 7.45 (1H, s, H-7′), 7.55 (1H, d, J = 15.7, H-2′).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.36 (C^{18}-CH_3), 15.94 (C^{19}-CH_3), 18.16 (C^{16}-CH_3), 19.60 (C^{17}-CH_3), 22.57 (C-6), 24.55 (C-10), 24.78 (C^{20}-CH_3), 27.61 (C-14), 28.91 (C-15), 30.44 (C-5), 33.47 (N–CH_3), 37.14 (C-9), 37.97 (C-13), 39.04 (C-3), 39.48 (C-1), 75.64 (C-4), 76.48 (C-2), 115.98 (C-2′), 122.54 (C-3′), 124.19 (C-11), 126.24 (C-7), 135.4 (C-8), 135.61 (C-12), 135.93 (C-7′), 138.40 (C-4′), 139.11 (C-5′), 167.32 (C=O).

(1*S*,3*S*,4*R*)-13-[1″-Methyl-1″*H*-imidazol-4″-yl]-(*E*)-ethenylcarbonyloxy]-cembra-2(*E*),7(*E*),11(*E*)-trien-4-ol (17).

Method A. A solution of **4** (0.115 g, 0.373 mmol) in CH_2Cl_2 (1 mL) was treated with Et_3N (0.78 mL, 5.595 mmol) and 4-DMAP (0.045 g, 0.373 mmol), cooled to 0°C, and treated with pivaloyl *N*-methylurocanate (15 mL, 3.112 mmol, 0.2 M) in CH_2Cl_2. The mixture was brought to room temperature and stirred for 5 d. After the reaction was finished (TLC monitoring), the mixture was diluted with saturated $NaHCO_3$ solution, extracted with CH_2Cl_2 (3 × 10 mL), and dried over $MgSO_4$. Solvent was removed in a rotary evaporator. The solid was chromatographed over SiO_2 (EtOAc) to afford **17** (0.114 g, 71%).

Method B. A solution of **4** (0.238 g, 0.778 mmol) in $CHCl_3$ (70 mL) was treated with **13** (0.352 g, 2.330 mmol), DCC (0.640 g, 3.108 mmol), and 4-DMAP (0.474 g, 3.885 mmol). The mixture was heated on an oil bath at 65°C for 6 d, diluted with saturated NH_4Cl solution, extracted with CH_2Cl_2 (3 × 10 mL), and dried over $MgSO_4$. Solvent was removed in a rotary

evaporator. The solid was chromatographed over SiO_2 (EtOAc) to afford **17** (0.131 g, 38%), $C_6H_6N_2O_2$, R_f 0.25 (EtOAc), $[\alpha]_D^{20}$ +11.5° (*c* 0.066, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.78 (3H, d, J = 6.8, CH_3), 0.88 (3H, d, J = 6.8, CH_3), 1.20-1.30 (3H, m, CH, CH_2), 1.45 (3H, m, CH_3), 1.58 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.62 (2H, m, CH_2), 1.70 (2H, m, CH_2), 1.82 (1H, m, CH_2), 1.95 (1H, ddd, ^2J = 12.0, ^3J = 10.9, 1.7, H-14), 2.0-2.20 (4H, m, CH_2), 2.25 (1H, m, CH_2), 2.50 (1H, dddd, J = 9.0, 8.3, 7.5, 1.7, H-1), 3.70 (3H, s, N–CH_3), 4.83 (1H, m, H-2), 5.13 (1H, m, J = 10.9, 4.7, H-13), 5.38 (1H, dd, J = 15.7, 8.3, H-2), 5.30 (1H, m, H-7), 5.40 (1H, m, H-11), 6.65 (1H, d, J = 15.7, H-1′), 7.06 (1H, s, H-5′), 7.45 (1H, s, H-7′), 7.55 (1H, d, J = 15.7, H-2′).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 10.05 (C^{20}-CH_3), 12.65 (C^{19}-CH_3), 19.35 (C^{16}-CH_3), 19.78 (C^{17}-CH_3), 21.98 (C-6), 23.71 (C-10), 27.67 (C^{18}-CH_3), 32.61 (C-9), 33.08 (C-15), 33.30 (N–CH_3), 37.97 (C-14), 47.67 (C-5), 45.20 (C-1), 72.09 (C-4), 79.43 (C-13), 116.31 (C-2′), 122.03 (C-2), 128.33 (C-7), 128.85 (C-11), 130.18 (C-12), 130.70 (C-3′), 131.31 (C-8), 135.48 (C-7′), 138.0 (C-3), 138.30 (C-4′), 138.86 (C-5′), 166.54 (C=O).

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