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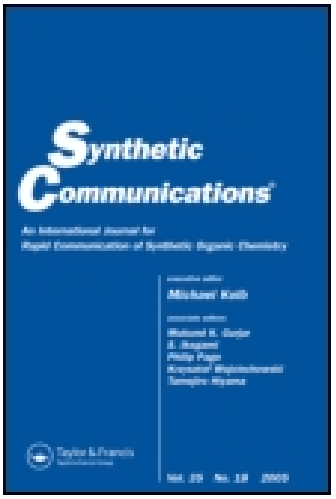

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Stereoselective Synthesis of (+)-Nephrosteranic Acid by Ring-Closing Metathesis and Its Biological Evaluation

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STEREOSELECTIVE SYNTHESIS OF (+)-NEPHROSTERANIC ACID BY RING-CLOSING METATHESIS AND ITS BIOLOGICAL EVALUATION

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A simple and efficient approach to (+)-nephrosteranic acid from dodecanol as a starting material is described, employing Sharpless asymmetric epoxidation, ring-closing metathesis, and Gilman addition of a vinyl group as key steps. These key reactions allow fast access to trisubstituted γ-butyrolactone. The molecule synthesized exhibits potent antifungal, antibacterial, and cytotoxic activities against all the tested strains.

Keywords: Antimicrobial activity; chemoselective reduction; Gilman 1,4 addition; paraconic acids; ring-closing metathesis; sharpless asymmetric epoxidation

INTRODUCTION

Lichens, the natural source of paraconic acids, are successful alliances between fungi and algae. Each is doing what it does best and thriving as a result of natural cooperation/symbiosis. They live as one organism, both inhabiting the same body, and produce a variety of substances friendly to the environment and human health, except for few poisonous examples. Screening and isolation of molecules from suitable lichen symbionts or medicinal plants has resulted in a great number of paraconic acids with antineoplastic, antibiotic, and antibacterial[1] properties, which prompted many researchers to devise new synthetic routes toward these natural products. The diversity of their biogenetic origin suggests that the structure may be one of the key elements in their biosynthesis.[2] Paraconic acids are naturally occurring γ-butyrolactones, having a carboxylic acid in the 3-position as their characteristic functionality (Fig. 1). Consequently, a number of syntheses have been developed, leading to a variety of paraconic acids either in racemic[3] or

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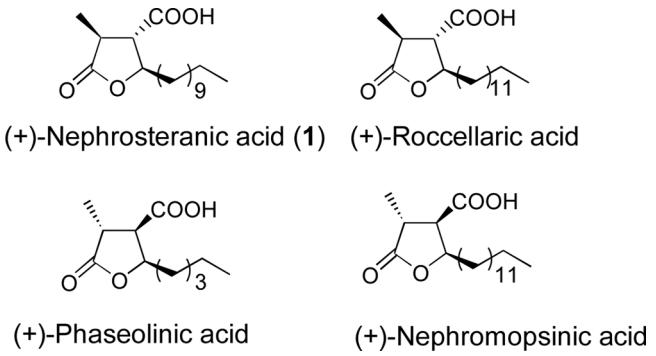
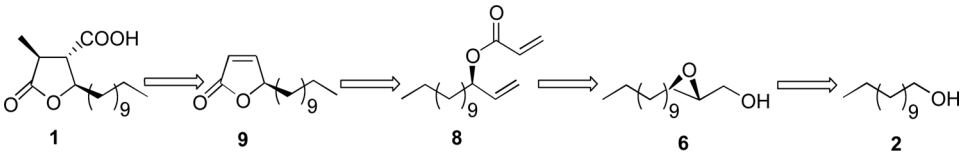


Figure 1. Paraconic acids.



Scheme 1. Retrosynthesis of (+)-nephrosteranic acid.

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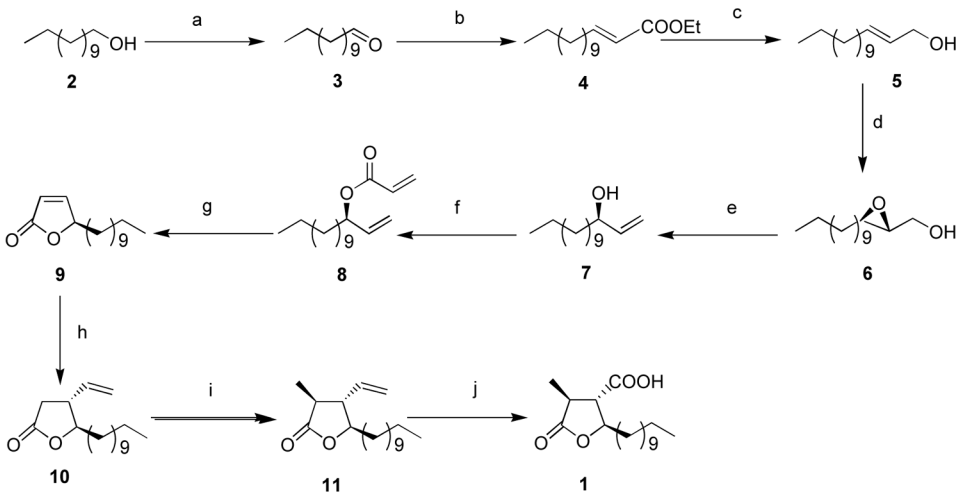
in enantiopure form and using starting materials from chiral pool,[4] chiral auxillaries,[5] or asymmetric methodology.[6] Surprisingly, (+)-nephrosteranic acid **1**[7] with 11-carbon alkyl chain at the γ-position has been the least often prepared of the common members of this important group of natural products. As part of our ongoing program toward synthesis of biologically active compounds,[8] we became interested in developing a simple and flexible route to stereoselective synthesis of (+)-nephrosteranic acid, employing Sharpless asymmetric epoxidation as the source of chirality, ring-closing metathesis (RCM) to build the carbon framework, and Gilman addition of vinyl group as key steps. The retrosynthetic analysis of (+)-nephrosteranic acid (Scheme 1) indicates compound **9** is the key intermediate, which is derived from bis-olefin **8** upon RCM. Olefin **8** could be envisaged as deriving from asymmetric epoxide **6**, which would be prepared from inexpensive dodecanol **2**.

RESULTS AND DISCUSSION

The formal synthesis of target molecule (+)-nephrosteranic acid was initiated from commercially available dodecanol **2**, which was subjected to pyridinumchlorochromate (PCC) oxidation to give dodecanal **3** in 95% yield (Scheme 2). Compound **3** was subjected to a two-carbon homologation by means of Wittig reaction[9] using ethoxycarbonylmethylenetriphenylphosphorane. The reaction was carried out in refluxing benzene for 2 h, which gave a mixture of *trans* and *cis* conjugated ester in 88:12 ratio. The *trans* compound **4** was purified and then subjected to chemoselective reduction[10] using LAH/$AlCl_3$ in anhydrous ether to afford allyl alcohol **5** in



Scheme 2. (a) PCC, DCM, rt, 3 h, 95%; (b) $Ph_3P{=}CHCO_2Et$, anhyd. benzene, reflux, 2 h, 90%; (c) LAH/$AlCl_3$, THF, 0°C, 1/2 h, 86%; (d) $Ti(OPr^i)_4$, (−)DET, $PhC(CH_3)_2O_2H$, dry DCM, −20°C, 3 h, 85%; (e) Ph_3P, pyridine, I_2, Et_2O:CH_3CN (5:3), 0°C, H_2O, reflux, 6 h, 95%; (f) $CH_2{=}CHCOCl$, Et_3N, DMAP, 5 h, 75%; (g) $(Pcy_3)_2Cl_2Ru{=}CHPh$ (12 mol%), $Ti(OPr^i)_4$, CH_2Cl_2, 40°C, 36 h, 79%; (h) CuI, MeLi, vinylmagnesium bromide −78°C, 81%; (i) NaHMDS, MeI, −78°C, THF, 76%; and (j) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O, 80%.

86% yield. Sharpless asymmetric epoxidation[11] of **5** with D-(−)-DET produced 2,3-epoxy alcohol **6** in 85% yield. Accordingly, a one-pot transformation[12] of 2,3-epoxy alcohol (**6**) into allyl alcohol (**7**) was achieved by the in situ formation of the epoxy iodide and its subsequent reduction with phosphine hydroxyiodide in 95% yield. Reaction of **7** with acryloyl chloride[13] and Et_3N in the presence of a catalytic amount of dimethylaminopyridine (DMAP) in CH_2Cl_2 provided the acrylate ester **8** in 75% yield. Compound **8** was subjected to RCM under reflux conditions for 24 h in CH_2Cl_2 in the presence of Grubb's first-generation (I) catalyst (12 mol%) (Fig. 2) following standard RCM procedure.[14a,b] The expected (5*R*)-5-undecyl-2,5-dihydro-2-furanone **9** was obtained in 30% yield; however, the yield of the RCM[14c] product was improved by working with same mol% catalyst but in more dilutions of **8** as well as catalyst, which indeed minimized the formation of dimeric alkene products arising from undesired cross-metathesis. Thus, compound **9** was obtained in 79% yield. The conjugate addition of a vinyl group on **9** was first carried out by utilizing vinyllithium to generate the cuprate reagent.

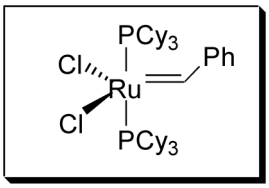


Figure 2. Grubbs first-generation catalyst.

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Because the yields obtained by utilizing vinyl lithium were not satisfactory, a further experiment was carried out by utilizing a mixed cuprate method.[15] In this case, vinyl cuprate reagent was generated from the reaction of vinylmagnesium bromide[16] and methyl copper (generated in situ from methyl lithium and purified cuprous iodide). The vast majority of cyclic enones reacted with organocopper reagents to form conjugate adducts in which the newly introduced vinyl group is axial[17] in position. This is typical of kinetically controlled 1,4-additions, which are subject to the stereoelectronic requirement that the reagent approach the α,β-unsaturated substrate in a plane perpendicular to the α,β-double bond[18] and maintain the orbital overlap throughout the transition state. Thus 1,4-addition product **10** was obtained in 81% as a single diastereomer. The lactone **10** was α-methylated[19] with methyl iodide in excess and $NaN(SiMe_3)_2$ as the base, furnishing **11** in 76% yield. As anticipated, the alkylation is diastereoselective (dr 91: 9), and the Me group in **11** is *trans* to the β substituent. The ratios between diastereoisomers were determined by GC-MS analysis of crude reaction mixture. The final step was achieved by the oxidation of double bond by treatment with RuO_4, as reported in the literature.[20] The physical and spectral data of **1** are identical to those reported in the literature.[7] The synthesized (+)-nephrosteranic acid **1** was evaluated in vitro for antibacterial and antifungal activity using agar well diffusion antimicrobial assay. The antibacterial activity was evaluated against Gram-positive bacterial strains *Staphylococcus aureus* (MTCC 737), *Staphylococcus epidermidis* (MTCC 435), and Gram-negative strains *Escherichia coli* (MTCC 1687) and *Pseudomonas aeruginosa* (MTCC 1688). The antifungal activity was evaluated against pathogenic strains *Sacharomyces sereviseae* (MTCC 36), *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 1344), and *Rhizopus oryzae* (MTCC 262). The MIC (minimum inhibitory concentration) values for antibacterial activity were determined using standard Broth microdilution technique described by NCCLS.[21] Nitrofurantoin was used as a reference antimicrobial drug. Clotrimazole was used as a reference antifungal drug, and streptomycin was used as a reference antibacterial drug. All the biological data are depicted in Tables 1 and 2 as zone of inhibition of growth (ZI), MIC, and inhibitory concentration (IC_{50}) values. From the activity results, compound **1** has show potent antifungal and antibacterial activity against all the tested fungal and bacterial strains. The analysis of ZI and MIC values for antibacterial activity revealed compound **1** has more than 60% antibacterial activity against *Pseudomonas aeruginosa* and moderate activity against other tested bacterial strains in comparison with the tested reference drug's antibacterial activity. Zone of inhibition results for antifungal activity revealed compound **1** has more than 80% activity against *Aspergillus niger* and more than 60% activity against other fungal strains in comparison with tested reference drug's antifungal activity. Cytotoxic activity was evaluated against THP-1 and U-937 human cancer cell lines (human acute monocytic leukemia cell line and human leukemic monocyte lymphoma cell line). Cytotoxicity was measured using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrasolium bromide] assay, according to the method of Mosmann.[22] Etoposide was used as reference cytotoxic drug. IC_{50} values of the test compound (1) were calculated and presented in Table 2. It is evident from the results that the test compound has shown significant decreases in cell viability in the test cell line in a concentration-dependant manner.

Table 1. *In vitro* antimicrobial activity of synthesized (+)-nephrosteranic acid **1**

	Zone of inhibition (mm)		MIC[a] (μg/mL)	
Microorganism	Compd. **1**	Streptomycin	Compd. **1**	Nitrofurantoin
Bacterial strains[b]				
SA	14	26	100	50
SE	14	27	125	50
EC	15	31	100	25
PA	15	23	120	100
Fungal strains[c]		Clotrimazole		
SS	16	23		
CA	14	22		
AN	16	18		
RA	15	21		

[a]MIC (minimum inhibitory concentration in μg/mL) was determined as 90% inhibition of growth with respect to positive growth control. Negative control: DMSO, no inhibition.
[b]SA, *Staphylococcus aureus*; SE, *Staphylococcus epidermis*; EC, *Escherichia coli*; PA, *Psudomonas aeruginosa*.
[c]SS, *Saccharomyces serviseae*; CA, *Candida albicans*; AN, *Aspergillus niger*; RA, *Rhizopus orizae*.

Table 2. Cytotoxicity of (+)-nephrosteranic acid **1**

	IC_{50}[a] (μg/mL)	
Cell line	Compd. **1**	Control (etoposide)
THP-1[b]	27.66 ± 5.92	1.4
U-937[c]	24.45 ± 4.32	1.2

[a]IC_{50}: Inhibitory concentration.
[b]THP-1: Human acute monocytic leukemia cell line.
[c]Human leukemic monocyte lymphoma cell line.

In conclusion, a simple, flexible, and highly efficient route to (+)-nephrosteranic acid has been developed employing Sharpless asymmetric epoxidation, RCM, and Gilman addition of vinyl group as key steps. The merits of this synthesis are high enantio- and diastereoselectivity with high-yielding reaction steps. This strategy provides rapid access to a range of analogs of the chiral trisubstituted γ-butyrolactones. The synthesized (+)-nephrosteranic acid **1** is tested for antimicrobial activity, and it was found that compound **1** exhibited potent antifungal, significant antibacterial, and significant cytotoxic activities.

EXPERIMENTAL

NMR spectra were measured on a Gemini 200-MHz Varian instrument and Avance 300-MHz Bruker UX NMR instrument in $CDCl_3$ as reference solvent, and chemical shifts were expressed as δ. Coupling constants J are given in hertz. Tetramethylsilane (TMS) was used as an internal standard for ^1H NMR. Mass spectra were recorded on VG Micromass 7070 H (EI and ESI) and Finnigan Mat 1020

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Mass (GC-MS) instruments. High-resolution (HR) mass spectra were recorded using a VG Autospec magnetic sector mass spectrometer (Waters, Manchester, UK). Infrared (IR) spectra were recorded on Perkin-Elmer model 283B and Nicolet-740 Fourier transform (FT)–IR instruments, and band positions were reported in wave numbers (cm^{-1}). Column chromatography was performed using silica gel H (60–120 μm).

[(2*S*, 3*R*)-3-Undecyloxiran-2-yl] Methanol (6)

To a cooled (−30°C) suspension of activated, powdered 4 Å MS (1 g) in CH_2Cl_2 (25 mL), (−)-DET (0.04 mL, 0.24 mmol), $Ti(OPr^i)_4$ (0.06 mL, 0.21 mmol), and cumene hydroperoxide (0.3 mL, 1.01 mmol) were added. After 20 min, a solution of allylic alcohol **5** (0.5 g, 2.35 mmol) in CH_2Cl_2 (10 mL) was added at −30°C over 20 min. The resulting mixture was stirred at that temperature for 3 h, quenched with a cooled solution of ferrous sulfate and tartaric acid (stoichiometric amount) in deionized water, stirred vigorously for 30 min, and extracted with ether (50 mL × 3). The combined organic layers were treated with a precooled (0°C) solution of 5 mL of 30% NaOH (w/v) in brine and stirred for 1 h at rt. The two layers were separated, and the aqueous layer was extracted with ether (40 mL × 3). The combined ether layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed (SiO_2, ethylacetate/hexane = 1.5:8.5) to give **6** (0.46 g, 85%) as a white solid.

$[\alpha]_D^{27} = +14.9$ ($c = 1.0$, $CHCl_3$); IR (KBR), ν (cm^{-1}): 3445, 2619, 2849, 1598, 1384, 1262, 725; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.80$ Hz, 3H, CH_2CH_3), 1.26 (s, 18H, $9 \times CH_2$), 1.41–1.60 (m, 2H, CH_2), 2.80–2.88 (m, 1H, CH), 2.89–2.96 (m, 1H, CH), 3.52–3.62 (m, 1H, CH_2OH), 3.80–3.90 (m, 1H, CH_2OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.6, 25.9, 29.3, 29.5, 31.5, 31.8, 56.0, 58.5, 61.7; ESI-MS: $m/z = 251$ $[M + Na]^+$.

(3*R*)-1-Tetradecen-3-ol (7)

To a stirred solution of epoxy alcohol **6** (2.25 g, 9.8 mmol) in dry Et_2O-CH_3CN (5:3), 15 mL were added sequentially of PPh_3 (7.46 g, 28.6 mmol), pyridine (3.1 mL, 38.1 mmol), and I_2 (4.82 g, 19.06 mmol) at 0°C. After stirring for 2 h at 0°C, H_2O (0.35 mL, 19.06 mmol) was added into the system. The reaction mixture was refluxed for 6 h at 40°C, then 20% $Na_2S_2O_3$ (aq.) (15 mL) and saturated $NaHCO_3$ (aq.) (15 mL) were added to quench the reaction, and the organic layer was extracted with ether (3 × 50 mL). The combined ether extracts were washed with 5% HCl (4 × 10 mL), H_2O, and brine and then dried. Evaporation of the solvent gave the residue, which was flash-chromatographed [eluting with hexane–ethylacetate (9:1)] to give **7** (2.0 g, 95%) as colorless oil.

$[\alpha]_D^{27} = -6.5$ ($c = 1.0$, $CHCl_3$); IR (neat), ν (cm^{-1}): 3350, 2925, 2854, 1640, 1462, 990, 920, 721; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.80$ Hz, 3H, CH_2CH_3), 1.25 (s, 18H, $9 \times CH_2$), 1.49–1.59 (m, 2H, CH_2), 4.02–4.08 (m, 1H, CHOH), 5.05–5.22 (dd, $J = 15.8$, 12.0 Hz, 2H, $CHCH_2$), 5.78–5.90 (dq, $J = 16.6$, 10.5, 6.0 Hz, 1H, $CHCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.6, 25.4, 29.2, 29.6, 32.0, 37.0, 73.2, 114.4, 141.4; EI-MS: m/z (%) = 212 (M^+, 6), 195 (6), 129 (10), 45 (100).

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1*R*-1-Undecyl-2-propenyl Acrylate (8)

To a cooled solution of **7** (2.15 g, 10.14 mmol) in dry DCM (20 mL), DMAP (cat. amt.) and triethyl amine (7.1 mL, 50.7 mmol) were added under an N_2 atmosphere. After 15 min, acryloyl chloride (0.9 mL, 12.16 mmol) was added, and resulting solution was stirred at rt for 4 h. It was washed with 5% HCl (1×5 mL), saturated $NaHCO_3$, H_2O (1×5 mL), and brine (1×5 mL). After the combined organic extracts were dried over sodium sulfate, the solvent was evaporated and the residue was purified by column chromatography (silica gel, 60–120 mesh, ethylacetate–hexane 0.5:9.5) to give **8** (2.04 g, 75%) as a colorless syrup.

$[\alpha]_D^{27} = -10.5$ ($c = 1.0$, $CHCl_3$); IR (neat), ν (cm^{-1}): 2925, 2854, 1727, 1637, 1404, 1191, 984; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.80$ Hz, 3H, CH_2CH_3), 1.25 (s, 18H, $9 \times CH_2$), 1.54–1.60 (m, 2H, CH_2), 5.15–5.20 (m, 1H, $CHCH_2$), 5.25–5.28 (m, 1H, $CHCH_2$), 5.68–5.85 (m, 1H, $CHCH_2$), 5.76–5.82 (dd, $J = 2.1$, 10.2 Hz, 1H, $COCHCH_2$), 6.0–6.16 (dd, $J = 17.4$, 10.1 Hz, 1H, $COCHCH_2$), 6.34–6.43 (dd, $J = 17.4$, 2.1 Hz, 1H, $COCHCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.6, 25.0, 29.3, 29.5, 31.8, 34.2, 74.9, 116.5, 128.8, 130.4, 136.5, 165.4; ESI-MS: $m/z = 289$ $[M + Na]^+$. ESI-HRMS calcd. for $C_{17}H_{30}O_2Na$ $[M + Na]$: 289.2157; found: 289.2143.

(5*R*)-5-Undecyl-2,5-dihydro-2-furanone (9)

$Ti(OPr^i)_4$ (3.2 mL, 10.82 mmol) was added to a stirred solution of **8** (0.96 g, 3.6 mmol) in CH_2C1_2 (30 mL) under a nitrogen atmosphere at 23°C. The resulting solution was refluxed at 40°C for 1 h, and then Grubb's catalyst (0.355 g, 0.43 mmol) in CH_2C1_2 (36 mL) was added. The reaction mixture was stirred at reflux for an additional 35 h. The mixture was cooled to 23°C and filtered through a pad of silica gel. Evaporation of the solvent gave a residue, which was flash chromatographed over silica gel to provide the lactone **9** (0.68 g, 79.3%) as a colorless syrup.

$[\alpha]_D^{27} = -66.2$ ($c = 1.0$, $CHCl_3$); IR (neat), ν (cm^{-1}): 2920, 2852, 1741, 1657, 1467, 1442, 1160, 1013; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.80$ Hz, 3H), 1.25 (s, 18H, $9 \times CH_2$), 1.60–1.76 (m, 2H), 4.96–5.02 (m, 1H, *H*CO), 6.07–6.10 (dd, $J = 6.0$, 2.2 Hz, 1H, CHC*H*CO), 7.38–7.41 (dd, $J = 6.0$, 1.5 Hz, 1H, C*H*CHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.6, 24.9, 29.2, 29.5, 31.8, 33.1, 83.3, 121.4, 156.2, 173.0; ESI-MS: $m/z = 261$ $[M + Na]^+$. ESI-HRMS calcd. for $C_{15}H_{26}O_2Na$ $[M + Na]$: 261.1840; found: 261.1830.

(4*R*, 5*R*)-5-Undecyl-4-vinyltetrahydro-2-furanone (10)

Recrystallized CuI (1.42 g, 7.5 mmol) was taken in 20 mL THF (under dry and nitrogen purged conditions) and was cooled to −78°C, and methyl lithium (7.5 mL, 7.5 mmol of 1 M) in ether was added. The suspension warmed to rt and stirred for 15 min. The resultant bright-orange suspension of methyl copper was cooled to −78°C, and vinyl magnesium bromide (7.5 mL, 7.5 mmol of 1 M in THF) was added. The mixture was stirred for 15 min at −78°C, and then **9** (0.18 g, 0.75 mmol) was added.

The pale yellow solution was allowed to warm at rt, whereupon the solution became black. The mixture was stirred at rt for 2 h and then rapidly poured into 100 mL of vigorously stirred, saturated NH_4Cl solution. The pH of solution was adjusted to 8–10 by addition of conc. NH_4OH. The hydrolysis mixture was stirred at rt until all the copper salts had dissolved (1.5 h). The bright-blue solution was extracted with ether, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, ethylacetate–hexane, 0.1:9.9) to give **10** (161 mg, 80.7%) as colorless syrup.

$[\alpha]_D^{27} = +36.4$ ($c = 1.0$, $CHCl_3$); IR (neat), ν (cm^{-1}): 3081, 2925, 2854, 1782, 1643, 1462, 1423, 1208, 922, 760; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.80$ Hz, 3H, CH_2CH_3), 1.25 (s, 18H, $9 \times CH_2$), 1.60–1.72 (m, 2H), 2.35–2.68 (dq, 2H, CH_2CO), 2.71–2.81 (m, 1H, $CHCHCH_2$), 4.02–4.12 (m, 1H, *H*CO), 5.13–5.21 (m, 2H, $CHCH_2$), 5.65–5.72 (ddd, $J = 17.3$ Hz, 10.5, 7.5 1H, $CHCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.6, 25.6, 29.2, 29.5, 31.8, 33.6, 35.4, 46.2, 84.7, 117.9, 135.7, 175.6; ESI-MS: $m/z = 289$ $[M + Na]^+$. ESI-HRMS calcd. for $C_{17}H_{30}O_2Na$ [M + Na]: 289.2143; found: 289.2155.

(3*S*,4*S*,5*R*)-3-Methyl-5-undecyl-4-vinyltetrahydro-2-furanone (11)

Compound **10** (129 mg, 0.48 mmol) in anhydrous tetrahydrofuran (THF) was added to a solution of NaHMDS (1.06 mL, 1.06 mmol) in 4 mL of anhydrous THF and stirred for 0.5 h at −78°C. CH_3I (0.3 mL, 4.6 mmol) was added and stirred for another 2 h. The reaction mixture was allowed to warm to −20°C, quenched with 8 mL of 2 N HCl, and extracted with ethyl acetate. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (silica gel, 100–200 mesh, ethylacetate–hexane, 0.2:9.8) to afford **11** as colorless syrup (102 mg, 76%, de = 91:9 from GC MS).

$[\alpha]_D^{27} = +28.5$ ($c = 1.0$, $CHCl_3$); IR (neat), ν (cm^{-1}): 2925, 2854, 1776, 1646, 1460, 1218, 1031, 771; ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, $J = 6.80$ Hz, 3H, CH_2CH_3), 1.2 (d, $J = 8.3$ Hz, 3H, $CHCH_3$), 1.28 (s, $9 \times CH_2$, 18H), 1.60–1.72 (m, 2H), 2.21–2.49 (dq, $J = 11.3$, 7.5, 4.5 Hz, 1H, CHCO), 2.70–2.84 (m, 1H, $CHCHCH_2$), 4.1 (m, $J = 8$ Hz, 1H, *H*CO), 5.18–5.24 (m, 2H, $CHCH_2$), 5.60–5.80 (ddd, $J = 17.3$, 9.8, 8.3 Hz, 1H, $CHCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.9, 14.2, 22.7, 25.8, 29.4, 29.4, 29.6, 31.9, 33.5, 33.8, 49.6, 82.4, 118.9, 135.2, 177.4; ESI-MS: $m/z = 303$ $[M + Na]^+$. ESI-HRMS calcd. for $C_{18}H_{32}O_2Na$ [M + Na]: 303.2306; found: 303.2300.

(+)-Nephrosteranic Acid (1)

$NaIO_4$ (98 mg, 0.45 mmol) and $RuCl_3$ (3.0 mg, 0.011 mmol) were added to a stirred solution of **11** (45 mg, 0.11 mmol) in a solvent mixture of CCl_4 (0.2 mL), CH_3CN (0.2 mL), and H_2O (0.3 mL) at rt. After 3 h at rt, CH_2Cl_2 (2 mL) was added, and the aq. phase was separated and extracted with CH_2Cl_2. The combined organic layers were filtered through celite. After evaporation of the volatiles, the residue was diluted with Et_2O (2 mL), and sat. $NaHCO_3$ solution (2 mL) was added. The organic phase was separated, and the aqueous one was acidified with 3 mL of 1 M HCl solution. The product was extracted with CH_2Cl_2 and dried (Na_2SO_4). The solvent

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was evaporated and purified by column chromatography (ethylacetate/hexane 70:30) to afford **1** as white crystals (26 mg, 80%). Mp 105°C; $[\alpha]_D^{27} + 27.6$ (*c* 0.5, $CHCl_3$) [lit.[7] $[\alpha]_D^{27} + 27.2$ (c 1.45, $CHCl_3$]; IR (neat), ν (cm^{-1}): 3448, 2924, 2854, 1748, 1436, 1188, 1116, 721; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, $J = 6.3$ Hz, 3H, CH_2CH_3), 1.26–1.78 (m, 23H), 1.35 (d, $J = 6.8$ Hz, 3H, $CHCH_3$), 2.65–2.85 (m, $J = 11.3$, 9.0 Hz, 1H, CHCO), 2.90–3.10 (m, 1H, $CHCO_2H$) 4.48–4.61 (ddd, $J = 9.0$, 4.0 Hz, 1H, HCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 14.8, 22.5, 25.3, 29.1, 29.3, 29.4, 29.6, 32.0, 36.1, 54.0, 79.1, 175.3, 176.7; EI-MS: *m/z* (%) 298 ($[M]^+$, 4), 283 (49), 253 (10), 143 (6), 129 (21), 45 (100).

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