A Bioinspired Approach to Tri-*nor*-guaianes. Synthesis of (−)-Clavukerin A

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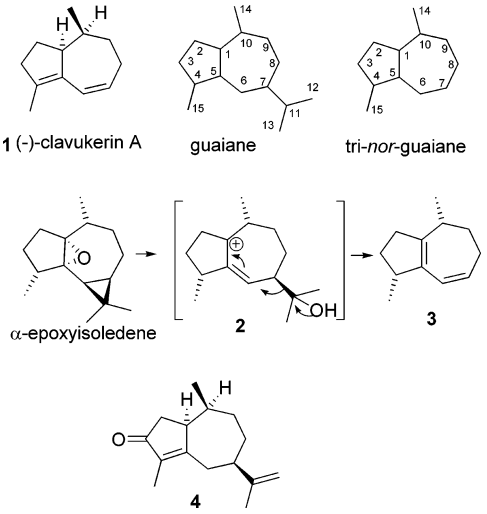
A bioinspired approach to tri-*nor*-guaianes by degradation of the C-7 side chain of related guaia-11-enes is described. In this approach (−)-clavukerin A (**1**) is obtained by selective ozonolysis−Criegge rearrangement of (+)-1α*H*,7α*H*,10α*H*-guaia-4,11-dien-3-one (**4**) to afford 7*β*-hydroxy and 7*β*-acetoxy tri-*nor*-guaiane derivatives **6** and **7**, respectively, which after elimination and deoxygenation give the title compound. The starting guaiadienone is readily obtained from commercially available santonin or (+)-dihydrocarvone.

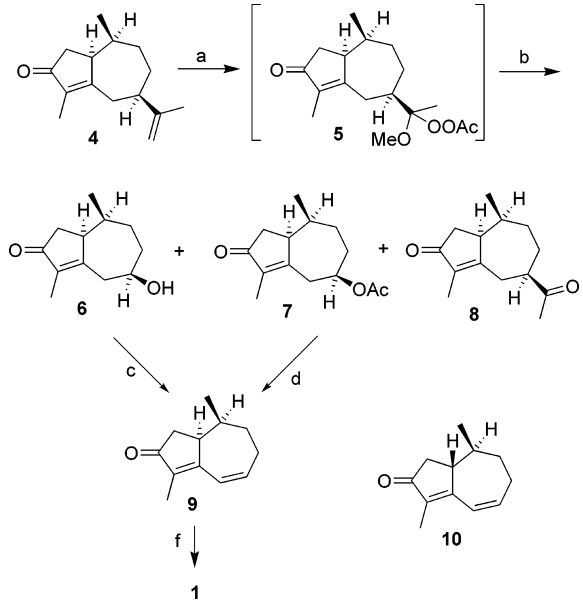
Natural tri-*nor*-guaianes are rare metabolites that have been isolated from terrestrial as well as marine sources.[1] One of their most representative members is (−)-clavukerin A (**1**), an unstable diene isolated from the Okinawan soft coral *Clavularia koellikeri* (stolonifer) by Kitagawa and co-workers.[2] Its structure was assigned as shown on the basis of spectral, chemical, and X-ray crystallographic analysis of its diepoxide, and its absolute configuration was also proposed following a CD study.[2] Bowden and co-workers reported the isolation of a terpenoid from an Australian soft coral *Cespitularia* sp.,[3a] which was later identified as **1**.[3b] The terpenoid origin of tri-*nor*-guaianes has been confirmed by Takeda and Katoh on the biosynthesis of 3,10-dihydro-1,4-dimethylazulene in cultured cells of *Calypogeia granulate* (liverwort)[4a] and by Dai and co-workers in the biosynthesis of **1** in a *Heteroxenia* sp.[4b] Their formation is presumably closely related to guaiane biosynthesis with loss of the isopropyl side chain at an unknown stage of the biosynthetic pathway.[2b,4] The syntheses of **1**[3b,5,6] and other tri-*nor*-guaianes[7] have been challenging due to the difficulties of construction of the perhydroazulene framework with appropriate functionalization and configuration. Several total syntheses of clavukerin A (**1**), in racemic[5] as well as in enantiomeric pure form,[3b,6] have been reported. Two general strategies have been used for the synthesis of its carbon framework: either starting from a suitable cycloheptane derivative and further construction of the five-membered ring[3b,5a,8] or starting from a cyclopentane derivative followed by construction of the seven-membered ring.[5b,6] However, no biomimetic syntheses of tri-*nor*-guaianes via degradation of the isopropenyl side chain of guaianes have been reported. De Groot's group[9] has reported the formation of tri-*nor*-guaiadiene **3** in 20% yield when α-epoxyisoledene was treated with $TsOH{\cdot}H_2O$ in acetone at room temperature. Its formation was explained by acetone elimination from allylic carbocation **2**. Herein we report a bioinspired approach to the synthesis of (−)-clavukerin A (**1**) from guaiadienone **4** via degradation of the isopropenyl side chain. Compound **4** has been reported in *Baccharis boliviensis*[10a] and *Wikstroemia lanceolada*[10b] and is readily available from santonin[11b] or (+)-dihydrocarvone.[11a]

Removal of the isopropenyl side chain of **4** was carried out by Schreiber and Liew's method.[12] Guaiadienone **4** (Scheme 1) was treated with O_3 in CH_2Cl_2−MeOH to give a monomethoxy hydroperoxide, which was acetylated in situ to obtain compound **5**. Criegge rearrangement[12,13] afforded tri-*nor*-guaiane derivatives **6** (48%) and **7** (28%) and methyl ketone **8** (17%). A *β*-disposition for the oxygenated function at C-7 of **6** and **7** was established by the positive NOE between H-7 and H-1 in **7**. Dehydration of compound **6** was carried out by treatment of **6** with MsCl−Et_3N followed by elimination (Li_2CO_3, DMF, 100 °C) to give dienone **9**



in 92% yield for the two steps. The elimination of acetate **7** was achieved with *p*-TsOH−SiO_2 in benzene[14] at 60 °C (bath temperature) for 6 h. From the ^{1}H NMR spectrum starting material **7** and

Scheme 1. Synthesis of (−)-Clavukerin A (**1**)[a]



[a] Reagents and conditions: (a) (i) O_3, CH_2Cl_2−MeOH, −78 °C, (ii) Ac_2O, Et_3N, DMAP, rt; (b) CH_2Cl_2−MeOH, 60 °C, 48% **6** + 28% **7** + 17% **8**; (c) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C → rt 100%; (ii) Li_2CO_3, DMF, 100 °C, 92%; (d) *p*-TsOH−SiO_2, benzene, 60 °C, 70% **9** + 12% **7**; (f) $LiAlH_4$−$AlCl_3$, Et_2O, −20 °C, 45%.

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tri-*nor*-guaiadienone **9** and its diastereomer **10** were detected in a 7.5:1 ratio.[15] Column chromatography separated compounds **7** (12%) and **9** (70%). Compound **9** was thus obtained in 63% yield from compound **4**. One-step deoxygenation of tri-*nor*-guaiadienone **9** with $LiAlH_4-AlCl_3$[16] at −20 °C afforded compound **1** in 45% yield, as a colorless unstable oil and having the same physical and spectroscopic features as (−)-clavukerin A from *C. koellikeri*.[2]

In summary, we have developed a bioinspired approach to tri-*nor*-guaianes through degradation of the isopropenyl side chain of guai-11-enes by tandem selective ozonolysis−Criegge rearrangement, which introduces oxygenation at C-7. Elimination of that oxygenated function and deoxygenation of the C-3 carbonyl group afforded (−)-clavukerin A (**1**) from guaiadienone **4** in three steps and 29% yield.

Experimental Section

General Experimental Procedures. Compound **4** was obtained following the procedure described by us.[11a] All reactions involving air- or moisture-sensitive materials were carried out under argon atmosphere. Commercial reagents and solvents were analytical grade or were purified by standard procedures prior to use. Melting points were recorded on a Büchi B-545 digital melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 243 apparatus in $CHCl_3$ using sodium light (D line, 589 nm). IR spectra were recorded as liquid films in NaCl for oils and as KBr disks for solids. NMR spectra were run in $CDCl_3$, and for compound **1** the solvent was filtered through basic alumina prior to use. The spectra were recorded at 300 or 400 MHz for ^1H and at 75 or 100 MHz for ^{13}C and referenced to the solvent as internal standard. Carbon types were assigned by DEPT experiments. $^1H-^1H$ decoupling and NOE experiments were used in selected cases to aid assignment. Low- and high-resolution mass spectra were recorded on an Autospec GC 8000 apparatus. Reactions were monitored by TLC analysis using Merck silica gel 60 F-254 thin-layer plates. Flash column chromatography was performed on Merk silica gel 60, 0.040−0.063 mm.

Ozonolysis−Criegge Rearrangement of Guaiadienone 4. Through a solution of compound **4** (100 mg, 0.459 mmol) in CH_2Cl_2−MeOH (5:1, 8.4 mL) was bubbled O_3 at −78 °C until disappearance of the starting material (54 min). The solution was purged with argon, and Ac_2O (2.28 mL, 24.16 mmol), Et_3N (2.28 mL, 16.36 mmol), and DMAP (17 mg, 0.140 mmol) were added via syringe. The resulting solution was stirred at room temperature for 19 h, diluted with EtOAc, and washed with 2 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine, and the organic layer was dried over anhydrous $MgSO_4$. Removal of the solvent afforded an oil, which was diluted with CH_2Cl_2−MeOH (5:1, 10 mL) and stirred at reflux for 2 h 30 min and then concentrated in vacuo. Flash column chromatography (hexanes−EtOAc, 9:1 to 5:5) of the crude residue separated 17 mg (17%) of methyl ketone **8**, 30 mg (28%) of acetate **7**, and 43 mg (48%) of alcohol **6**.

(+)-7*β*-Hydroxy-1α*H*,10α*H*-tri-*nor*-guai-4-en-3-one (6): colorless oil; $[\alpha]_D^{24}$ +98.3 (*c* 1.75, $CHCl_3$); IR (NaCl) ν_{max} 3500−3250, 1694, 1622, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.08−3.94 (1H, m, H-7), 2.94 (1H, br d, J = 19.2 Hz, H-6), 2.91 (1H, br s, H-1), 2.60 (1H, br dd, J = 10.5, 18.6 Hz, H-6′), 2.54 (1H, dd, J = 7.2, 18.3 Hz, H-2), 2.12−2.05 (1H, m, H-10), 2.02 (1H, br d, J = 18.4 Hz, H-2′), 1.45−1.86 (1H, m, H-8), 1.86−1.75 (1H, m, H-8′), 1.75−1.68 (2H, m, 2 H-9), 1.66 (3H, br s, 3 H-15), 0.70 (3H, d, J = 6.9 Hz, 3 H-14); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 171.2, 138.5 (C), 70.0, 46.4 (CH), 40.7, 40.5, 35.7 (CH_2), 34.7 (CH), 32.2 (CH_2), 12.9, 8.0 (CH_3); EIMS *m*/*z* 194 ($M^{+\bullet}$, 44), 176 (8), 166 (18), 137 (100), 110 (61); HRMS (EI) calcd for $C_{12}H_{18}O_2$ [$M^{+\bullet}$] 194.1307, found 194.1306.

(+)-7*β*-Acetoxy-1α*H*,10α*H*-tri-*nor*-guai-4-en-3-one (7): colorless oil; $[\alpha]_D^{24}$ +151.5 (*c* 1.30, $CHCl_3$); IR (NaCl) ν_{max} 1740, 1700, 1641, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.08−4.94 (1H, m, H-7), 3.02−2.94 (1H, m, H-1), 2.90 (1H, br d, J = 18.4 Hz, H-6), 2.66 (1H, br dd, J = 11.0, 18.2 Hz, H-6′), 2.54 (1H, dd, J = 6.6, 18.6 Hz, H-2), 2.16−1.90 (2H, m, H-2′, H-10), 2.04 (3H, s, C*H*$_3$CO), 1.92−1.74 (2H, m, 2 H-8), 1.74−1.66 (2H, m, 2 H-9), 1.64 (3H, br s, 3 H-15), 0.69 (3H, d, J = 7.2 Hz, 3 H-14); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 170.1, 169.4, 138.9 (C), 72.2, 46.2 (CH), 40.6, 36.9 (CH_2), 34.6 (CH), 32.1, 31.9 (CH_2), 21.3, 13.1, 8.0 (CH_3); EIMS *m*/*z* 236 ($M^{+\bullet}$, 8), 176 (100), 161 (17), 137 (30); HRMS (EI) calcd for $C_{14}H_{20}O_3$ [$M^{+\bullet}$] 236.1412, found 236.1409.

(+)-7*β*-Acetyl-1α*H*,10α*H*-tri-*nor*-guai-4-en-3-one (8): colorless oil; $[\alpha]_D^{24}$ +128.8 (*c* 0.74, $CHCl_3$); IR (NaCl) ν_{max} 1684, 1623 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.06−3.00 (1H, m, H-1), 2.88 (1H, br d, J = 19.4 Hz, H-6), 2.72 (1H, br t, J = 11.7 Hz, H-7), 2.60−2.44 (2H, m, H-2, H-6′), 2.20 (3H, s, C*H*$_3$CO), 2.16−2.08 (1H, m, H-10), 2.06−1.82 (3H, m, H-2′, H-8, H-9), 1.74 (tt, J = 3.4, 17.3 Hz, H-9′), 1.64 (3H, d, J = 1.5 Hz, 3 H-15), 1.60−1.40 (1H, m, H-8′), 0.62 (3H, d, J = 7.1 Hz, 3 H-14); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.5, 207.8, 172.8, 138.4 (C), 50.3, 45.9 (CH), 41.1, 36.4 (CH_2), 35.1 (CH), 33.5 (CH_2), 28.2 (CH_3), 27.7 (CH_2), 11.9, 7.9 (CH_3); EIMS *m*/*z* 220 ($M^{+\bullet}$, 100), 205 (13), 177 (44), 163 (17), 110 (17), 107 (19); HRMS (EI) *m*/*z* calcd for $C_{14}H_{20}O_2$ [$M^{+\bullet}$] 220.1463, found 220.1474.

(−)-1α*H*,10α*H*-Tri-*nor*-guaia-4,6-dien-3-one (9). From Alcohol 6. To a solution of compound **6** (31 mg, 0.160 mmol) in CH_2Cl_2 (1 mL) at 0 °C under argon were added 134 μL (0.954 mmol) of Et_3N and 57 μL (0.699 mmol) of MsCl. The resulting mixture was stirred at 0 °C for 40 min and then was allowed to warm to room temperature for 45 min. Then, the solution was acidified to pH 1 with 10% aqueous HCl, diluted with EtOAc, washed with aqueous saturated $NaHCO_3$ and brine, and dried ($MgSO_4$) Evaporation of solvents in vacuo afforded a colorless oil (43 mg, 100%).

A mixture of the crude oil and Li_2CO_3 (100 mg, 1.325 mmol) in DMF (4 mL) under argon was heated at 100 °C (bath temperature) for 22 h. Then, the reaction was quenched with saturated aqueous NH_4Cl, and the mixture was diluted with H_2O and extracted with EtOAc as usual. The combined organic layers were washed with brine and dried ($MgSO_4$), and the solvent was removed in vacuo to give 26 mg (92%) of tri-*nor*-guaiadienone **9**: white crystals, mp 34−36 °C (hexanes−EtOAc); $[\alpha]_D^{24}$ −337 (*c* 1.36, $CHCl_3$); IR (KBr) ν_{max} 3080, 1695, 1634 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.48 (1H, br d, J = 12 Hz, H-6), 6.15 (1H, ddd, J = 4.1, 6.2, 12.1 H, H-7), 3.06−3.02 (1H, m, H-1), 2.55 (1H, dd, J = 6.8, 18.8 Hz, H-2), 2.52−2.42 (1H, m, H-8), 2.41−2.30 (1H, m, H-8′), 2.20 (1H, dd, J = 2.8, 18.8 Hz, H-2′), 2.22−2.12 (1H, m, H-10), 1.96−1.78 (2H, m, 2 H-9), 1.75 (3H, d, J = 1.6 Hz, 3 H-15), 0.71 (3H, d, J = 6.8 Hz, 3 H-14); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0, 166.8 (C), 140.3 (CH), 137.5 (C), 124.7, 46.6 (CH), 39.7, 34.2 (CH_2), 33.2 (CH), 27.0 (CH_2), 11.2, 8.1 (CH_3); EIMS *m*/*z* 176 ($M^{+\bullet}$, 100), 161 (22), 147 (13), 133 (29), 105 (32), 91 (47); HRMS (EI) *m*/*z* calcd for $C_{12}H_{16}O$ [$M^{+\bullet}$] 176.1201, found 176.1193.

From Acetate 7. To a solution of compound **7** (42 mg, 0.178 mmol) in benzene (3.62 mL) was added 268 mg of *p*-TsOH−SiO_2,[14] and the mixture was heated at 60 °C under argon for 6 h. Flash chromatography on silica gel eluting with hexanes−EtOAc (95:5 to 6:4) separated 5 mg (12%) of starting material **7** and 22 mg (70%) of dienone **9** with physical and spectroscopic features identical to the dienone obtained from alcohol **6**.

(−)-1α*H*,10α*H*-Tri-*nor*-guaia-4,6-diene [(−)-clavukerin A] (1). A solution of $AlCl_3$ (758 mg, 5.675 mmol) in Et_2O (1 mL) at 0 °C was added to a suspension of $LiAlH_4$ (48 mg, 1.261 mmol) in Et_2O (3.3 mL) at 0 °C and stirred until bubbling stopped. The mixture was cooled at −20 °C, and a solution of compound **9** (37 mg, 0.210 mmol) in Et_2O (1 mL) was added via syringe. After 9 min the reaction was quenched with ice and extracted with Et_2O, washed with brine, and dried over $MgSO_4$. Removal of the solvent gave an oil, which was chromatographed on silica gel (pentane) to afford 15.4 mg (45%) of an unstable, colorless, volatile oil, which was identified as (−)-clavukerin A (**1**): $[\alpha]_D^{24}$ −43.3 (*c* 0.09, $CHCl_3$) [lit.[2a] $[\alpha]_D^{20}$ −53 (*c* 0.30, $CHCl_3$)]; IR (NaCl) ν_{max} 1660, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.21 (1H, br d, J = 12.0 Hz, H-6), 5.54 (1H, dt, J = 4.9, 12.4 Hz, H-7), 2.84−2.81 (1H, m, H-1), 2.37−2.14 (4H, m, 2 H-3, 2 H-8), 2.00−1.82 (2H, m), 1.73 (3H, s, 3 H-15), 1.82−1.47 (3H, m), 0.75 (3H, d, J = 6.8 Hz, 3 H-14); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 134.9 (C), 128.8, 123.7 (CH), 54.5 (CH), 37.8, 34.4 (CH_2), 34.2 (CH), 27.2, 26.7 (CH_2), 14.5, 11.4 (CH_3); EIMS (EI) *m*/*z* 162 ($M^{+\bullet}$, 100), 147 (76), 133 (31), 119 (37), 105 (76); HRMS (EI) *m*/*z* calcd for $C_{12}H_{18}$ [$M^{+\bullet}$] 162.1408, found 162.1417.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra of compounds **1** and **6**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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