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Formal total synthesis of the trinorguaiane sesquiterpenes (+/−)-clavukerin A and (+/−)-isoclavukerin

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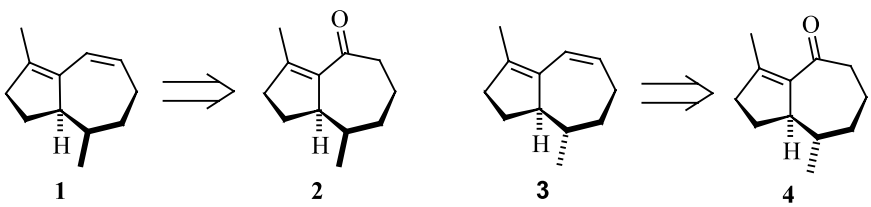
Abstract—A formal total synthesis of racemic (+/−)-clavukerin A and (+/−)-isoclavukerin from 4-methylcyclohept-2-en-1-one is presented. The key step involved a *Danheiser* (trimethylsilyl)cyclopentene annulation. © 2002 Published by Elsevier Science Ltd.

The trinorguaiane sesquiterpenes clavukerin A[1] **1** and isoclavukerin[2] **3** are marine natural products that have been isolated from the Okinawan soft coral *Clavularia koellikeri* during a search for biologically active compounds from marine sources. So far three total syntheses of isoclavukerin[3,4] and five total syntheses of clavukerin A have been described,[4,5] including three enantiocontrolled routes and two for the racemate.

Honda et al.,[5c] Asaoka et al.[4a] and Pak et al.[5a] utilized the skeleton **2** (Scheme 1) as a key fragment in their syntheses of clavukerin A and converted it to the natural product in a two-step procedure. In addition **4** has been converted into isoclavukerin by Asaoka et al. previously.[4a] Therefore, any synthesis of **2** or **4** constitutes a formal synthesis of the natural products clavukerin A **1** and isoclavukerin **3**. Herein we wish to report an efficient and very direct two-step synthesis of racemic fragments **2** and **4** based upon a *Danheiser* (trimethylsilyl)cyclopentene annulation, employing methyl cycloheptenone as a starting material.

4-Methylcyclohept-2-en-1-one (**8**) was prepared in a three-step synthesis. Epoxidation of cycloheptadiene **5** with peracetic acid gave the corresponding epoxide **6**,[6] which in turn was converted to methylcycloheptenol **7** by conjugate addition of methyl cuprate generated in situ from methyl lithium and CuCN.[7] Oxidation of **7** with Jones reagent gave 4-methylcyclohept-2-en-1-one (**8**)[8] (Scheme 1). The *Danheiser* (trimethylsilyl)cyclopentene annulation[9] involving the (trimethylsilyl)allene **9** and methylcycloheptenone **8** was carried out with the use of 1.7 equivalents of titanium tetrachloride in dichloromethane at −78°C.[10] The annulation proceeded smoothly to afford a 1:1 mixture of the *cis* fused diastereoisomers **10** and **11** (Scheme 2). Compounds **10** and **11** could easily be separated by HPLC and the relative configuration of **11** was determined by NOE relationships.

As shown in Scheme 3, treatment of **10** or **11** with K_2CO_3 in methanol followed by addition of tetrabutyl ammonium fluoride generated *rac*-**2** or *rac*-**4**. Characterization of **2** and **4** by ^1H and ^{13}C NMR spectroscopy showed them to be identical to those reported.[4a] The elaboration of **2** to (+/−)-clavukerin A and **4** to (+/−)-isoclavukerin has been reported earlier and thus a formal synthesis of **1** and **3** has been achieved. The



1 **2** **3** **4**

Scheme 1.

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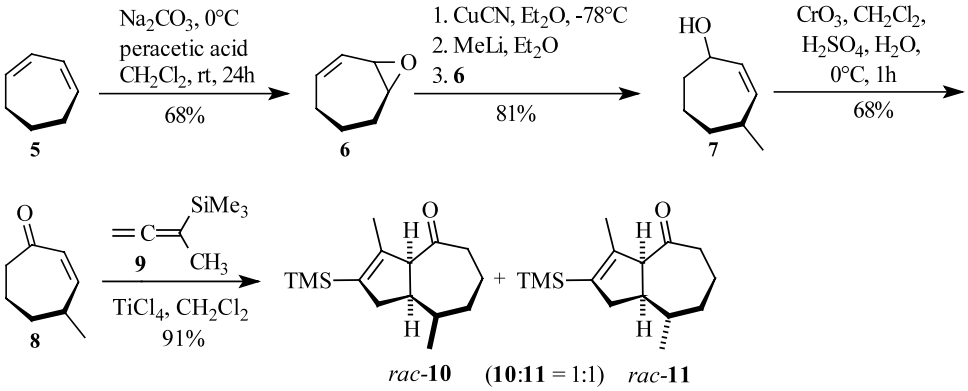
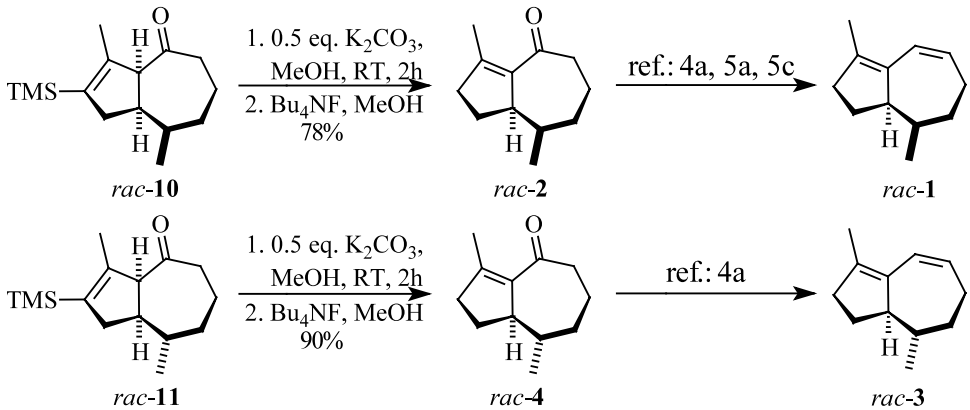


Scheme 2.



Scheme 3.

synthesis of **2** and **4**, respectively, required five steps from commercially available cycloheptadiene **5** and proceeded in 15 and 13% overall yield, respectively.

In conclusion, we have described the formal total synthesis of (+/−)-clavukerin A and (+/−)-isoclavukerin employing a new potent route. The key fragments *rac*-**2** and *rac*-**4** could be obtained in two steps from enone **8**.

Acknowledgements

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10. To a solution of 4-methycyclohept-2-en-1-one (**8**) (500 mg, 4.03 mmol) and 1-methyl-1-(trimethylsilyl)-allene (**9**) (768 mg, 6.98 mmol) in CH_2Cl_2 (20 ml) at −78°C was added dropwise $TiCl_4$ (0.69 ml, 6.98 mmol). The resulting dark red solution was stirred at −78°C for 1 h and then transferred into a mixture of water (100 ml) and diethyl ether (100 ml). The aqueous phase was extracted with diethyl ether (3×100 ml), the combined organic layers were washed with brine (2×20 ml), dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (petroleum ether:diethyl ether=

3:2) to give a 1:1 mixture of **10** and **11** as a colorless oil (914 mg, 3.66 mmol, 91%). **10** and **11** could be separated by HPLC (petroleum ether:diethyl ether = 9:1, Nucleosil 100-7).

rac-(3a*S*,8*R*,8a*R*)-3,8-Dimethyl-2-(trimethylsilyl)-3a,5,6,7,8,8a-hexahydroazulene-4(1*H*)-one (*rac*-10): $R_f = 0.45$ (petroleum ether:diethyl ether = 9:1)—FT-IR (Film): $\tilde{\nu}$ (cm^{-1}) = 2955 (s), 2929 (s), 2859 (s), 1699 (s), 1617 (m), 1455 (m), 1380 (w), 1338 (w), 1248 (s), 1197 (w), 1181 (w), 1120 (w), 171 (w), 1008 (w), 975 (w), 942 (w), 837 (s), 753 (s), 624 (s).—^{1}H NMR ($CDCl_3$, 300.1 MHz): δ (ppm) = 0.17 (s, 9H, TMS), 0.81 (d, 3H, $^3J = 7.2$ Hz, 8-CH_3), 1.15–1.38, 1.48–1.57 (2m, 5H, je 2×6-H, 7-H, 1×8-H), 1.71 (ddd, 3H, $^4J_a = 1.0$ Hz, $^4J_b = 1.9$ Hz, $^4J_c = 2.4$ Hz, 3-CH_3), 2.19 (m_c, 2H, 2×1-H), 2.32 (ddd, 1H, $^3J_a = 2.2$ Hz, $^3J_b = 9.3$ Hz, $^3J_c = 18.4$ Hz, 8a-H), 2.39–2.54 (m, 2H, 2×5-H), 3.43 (m_c, 1H, 3a-H).—^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = 0.8 (q, TMS), 15.9 (q, 3-CH_3), 24.1 (q, 8-CH_3), 25.4, 31.9 (2t, C-6, C-7), 34.4 (d, C-8), 36.7 (t, C-1), 40.5 (t, C-5), 44.0 (d, C-8a), 72.5 (d, C-3a), 139.2 (s, C-2), 146.4 (s, C-3), 213.7 (s, C-4).—MS (GC/MS 70 eV): m/z (%) = 250 (15) [M^+], 235 (18) [M^+–CH_3], 225 (1), 207 (12) [M^+–CH_3–CO], 194 (15) [M^+–C_2H_4–CO], 177 (12) [M^+–$(CH_3)_3Si$], 160 (4) [M^+–$HOSi(CH_3)_3$], 145 (18) [M^+–$HOSi(CH_3)_3$–CH_3], 133 (6), 117 (6), 106 (12), 93 (8), 73 (100) [$(CH_3)_3Si^+$], 59 (10), 45 (10), 41 (4) [$C_3H_5^+$].—$C_{15}H_{26}Osi$ (250.46): calcd C, 71.94; H, 10.64; found C, 72.07; H, 10.51%. *rac*-(3a*S*,8*S*,8a*R*)-3,8-Dimethyl-2-(trimethylsilyl)-3a,5,6,7,8,8a-hexahydroazulene-4(1*H*)-one (*rac*-11): $R_f = 0.41$ (petroleum ether:diethyl ether = 9:1).—FT-IR (Film): $\tilde{\nu}$ (cm^{-1}) = 2954 (s, CH), 1705 (s, C=O), 1628 (m, C=C), 1456 (m), 1405 (m, CH-def.), 1377 (m), 1328 (m), 1247 (s), 1202 (w), 1181 (w), 1160 (w), 1130 (w), 1077 (w), 997 (w), 931 (w), 836 (s), 754 (s), 690 (s).—^{1}H NMR ($CDCl_3$, 300.1 MHz): δ (ppm) = 0.22 (s, 9H, TMS), 0.84 (d, 3H, $^3J = 6.4$ Hz, 8-CH_3), 1.12–1.74 (m, 5H, 1×1-H_a, 2×6-H, 7-H), 1.84 (ddd, 3H, $^4J_a = 0.7$ Hz, $^4J_b = 1.4$ Hz, $^4J_c = 2.2$ Hz, 3-CH_3), 2.08 (ddd, $^4J = 1.6$ Hz, $^3J_a = 10.4$ Hz, $^3J_b = 18.6$ Hz, 8a-H), 2.15–2.35 (m, 3-H, 1×1-H_b, 2×5-H), 2.59 (mc, 1H, $^3J_a = 1.6$ Hz, $^3J_b = 8.5$ Hz, 1×8-H), 3.58 (dd, 1H, $^4J = 2.2$ Hz, $^3J = 10.4$ Hz, 3a-H).—^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (ppm) = −0.4 (q, TMS), 16.9, 21.3 (2q, 8-CH_3, 3-CH_3), 22.4, 34.6, 41.6, 43.8 (4t, C-1, C-5, C-6, C-7), 36.1 (d, C-8), 47.3 (d, C-8a), 66.3 (d, C-3a), 137.1 (s, C-2), 147.6 (s, C-3), 209.7 (s, C-4).—MS (GC/MS 70 eV): m/z (%) = 250 (15) [M^+], 235 (18) [M^+–CH_3], 221 (6) [M^+–CO–H], 207 (12) [235-CO], 194 (15), 177 (12) [M^+–$(CH_3)_3Si$], 160 (8), 145 (25) [M^+–$HOSi(CH_3)_3$–CH_3], 133 (14), 117 (6), 105 (12), 97 (8), 73 (100) [$(CH_3)_3Si^+$], 59 (10), 45 (10).