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Total synthesis of (–)-clavukerin A*

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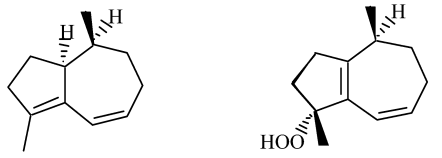
Abstract: (–)-Clavukerin A has been synthesized via *intramolecular* Julia coupling and *intramolecular* sulfone ester cyclization starting from (+)-limonene oxide.

INTRODUCTION

(–)-Clavukerin A (**1**), a trinor-guaiane sesquiterpene, was isolated from the Okinawan soft coral *Clavularia koellikeri* (stolonifer) together with clavukerin C (**2**) by Kitagawa and coworkers [1]. The absolute stereochemistry was assigned as shown on the basis of chemical, physicochemical, and X-ray crystallographic analysis (Fig. 1).

Several syntheses of clavukerin A, including enantiocontrolled routes, have been reported recently [2].



1 **(-)-Clavukerin A** **2** **(-)-Clavukerin C**

Fig. 1 Structures of clavukerin A and clavukerin C.

RESULTS

In this communication, we describe the total synthesis of (–)-**1** using our previously disclosed methodology for medium-size ring construction via *intramolecular* sulfone ester as well as sulfone aldehyde cyclization (*intramolecular* Julia coupling) [3].

Starting with readily available **3** [4], reduction of the aldehyde ($NaBH_4$, MeOH, 0 °C) and conversion of the alcohol to sulfone **4** [5] [PBr_3, Et_2O, 0 °C, then $PhSO_2Na$, dimethylformamide (DMF), 25 °C, 15 h] proceeded in excellent overall yield (85 %). Hydroboration of **4**—disiamylborane [6], tetrahydrofuran (THF), 25 °C, 2.5 h—followed by oxidative work-up gave a single alcohol, which, on treatment with methanesulfonyl chloride (MsCl, NEt_3, 0 °C, 1 h) and sodium iodide in acetone (65 °C, 16 h), furnished crystalline **5** [7] (92 % overall yield). The crucial relative stereochemistry of the newly created chiral center in **5** was proved by detailed nuclear Overhauser effect (NOE) studies on the more rigid bicyclic derivative **6**, obtained upon treatment of **5** with 1.1 equiv of LiHMDS in THF (Fig. 2) [8].

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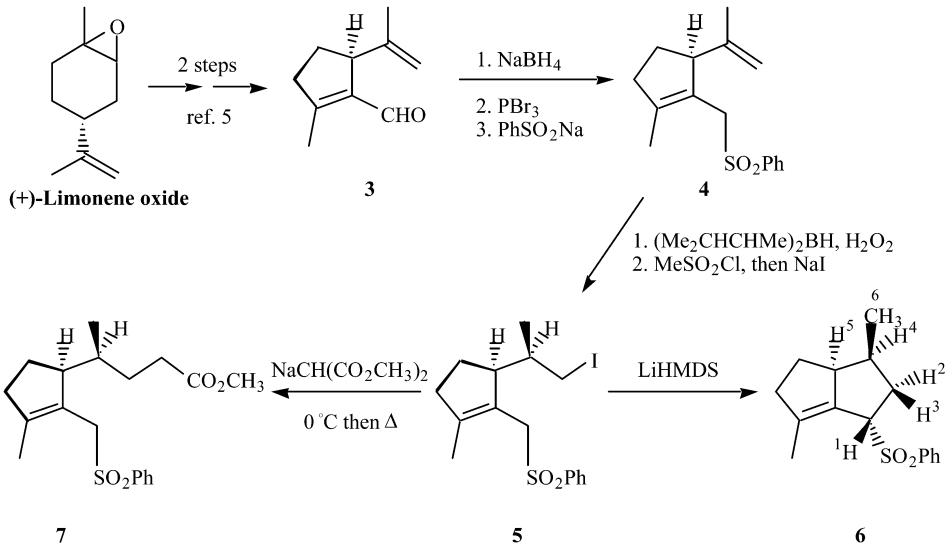

Fig. 2 Synthesis of cyclization precursor **7**.

Introduction of the remaining two-carbon unit was easily accomplished by reacting **5** with the sodium salt of methyl malonate, initially at 0 °C for 1 h, followed by heating at 140 °C for 16 h to effect decarbalkoxylation. This one-pot sequence allowed the preparation of **7** [9] in 51 % yield without isolation of the malonate intermediate. Ring closure [10] was achieved by slow addition of 2.2 equiv LiHMDS (1.0 M in THF) to a solution of **7** in THF at 0 °C to give **8** [11] in 89 % isolated yield (Fig. 3). Reduction of **8** with sodium borohydride gave **9** [12] as a single diastereomer (93 % yield). Alternatively, **9** can be prepared as a single stereoisomer via intramolecular Julia condensation [13] of aldehyde **10** [14] with 1.7 equiv LiHMDS (1.0 M in THF, 0 °C, 39 % yield). The stereocontrolled outcome of the cyclization suggests a highly organized transition state **11** with kinetic sulfone deprotonation as we had observed previously in the total synthesis of heliannuol A [3]. Finally, β-hydroxy sul-

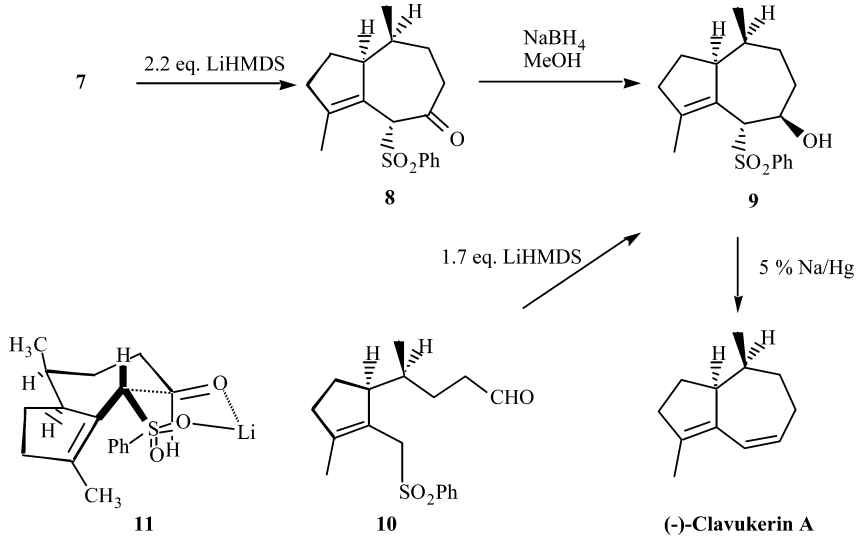

Fig. 3 Synthesis of (–)-clavukerin A.

fone **9** underwent Julia elimination by treatment with sodium-amalgam (MeOH, 0 °C, 3 h, 89 % yield) to give synthetic (–)-clavukerin A.

In summary, an *intramolecular* Julia condensation, as well as a sulfone ester cyclization, provides efficient methods for the stereocontrolled construction of the clavukerin nucleus.

ACKNOWLEDGMENT

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5. ({[(5*S*)-5-isopropenyl-2-methylcyclopent-1-en-1-yl]methyl}sulfonyl)benzene (**4**): colorless solid, melting point (mp) 95.5–98 °C; $[\alpha]_D$ + 152.0° (c 1.14, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.86 (d, 2H), 7.75 (t, 1H), 7.65 (t, 2H), 4.74 (s, 1H), 4.61 (s, 1H), 4.06 (d, 1H, J = 14.0 Hz), 3.56 (d, 1H, J = 14.0 Hz), 3.45–3.35 (m, 1H), 2.35–2.15 (m, 2H), 2.02–1.92 (m, 1H), 1.68–1.58 (m, 1H), 1.53 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 147.80, 145.25, 140.41, 134.42, 130.00, 129.25, 125.32, 112.28, 56.17, 54.83, 38.00, 28.10, 19.00, 14.18; IR (KBr) υ 3000–2820, 1665, 1640, 1580, 1445, 1400, 1370, 1305, 1290, 1145, 1125, 1080 cm^{-1}; MS (Cl, CH_4) mass-to-charge ratio (*m/z*) 277 $(M + H)^+$; anal. calculated for $C_{16}H_{20}O_2S$: C, 69.53; H, 7.29; S, 11.60; found: C, 69.55; H, 7.33; S, 11.34.
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7. [({(5*S*)-5-[(1*R*)-2-iodo-1-methylethyl]-2-methylcyclopent-1-en-1-yl}methyl)sulfonyl]benzene (**5**): colorless solid, mp 84.5–85.5 °C, $[\alpha]_D$ + 66.7° (c 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.87 (d, 2H), 7.74 (t, 1H), 7.65 (t, 2H), 4.16 (d, 1H, J = 14.3 Hz), 3.79 (d, 1H, J = 14.3 Hz), 3.11 (dd, 1H, J = 9.7, 3.1 Hz), 2.93 (dd, 1H, J = 10.7, 9.8 Hz), 2.95 (m, 1H), 2.30–2.08 (m, 3H), 1.88–1.73 (m, 1H), 1.62–1.52 (m, 1H), 1.27 (s, 3H), 1.06 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 145.92, 140.18, 134.49, 130.02, 129.22, 125.10, 55.00, 53.25, 38.65, 37.82, 23.00, 19.59, 14.25, 11.35; IR (KBr) υ 2950–2850, 1660, 1580, 1450, 1445, 1400, 1370, 1310, 1300, 1230, 1180, 1140, 1130, 1080 cm^{-1}; MS (Cl, CH_4) *m/z* 405 $(M + H)^+$; anal. calculated for $C_{16}H_{21}I0_2S$: C, 47.53; H, 5.24; S, 7.93; found: C, 48.07; H, 5.23; S, 8.18.
8. Key NOEs were observed between 1H and 3H, 1H and $6CH_3$, 2H and 4H, 4H and 5H.
9. Methyl(4*S*)-4-{(1*S*)-3-methyl-2-[(phenylsulfonyl)methyl]cyclopent-2-en-1-yl}pentanoate (**7**): oil, $[\alpha]_D$ + 37° (c 0.68, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.87 (d, 2H), 7.74 (t, 1H), 7.64 (t, 2H), 4.08 (d, 1H, J = 14.4 Hz), 3.92 (d, 1H, J = 14.4 Hz), 3.61 (s, 3H), 2.91–2.88, (m, 1H), 2.45–2.22 (m, 2H), 2.20–2.08 (m, 2H), 1.92–1.70 (m, 2H), 1.58–1.35 (m, 2H), 1.25 (s, 3H), 1.20–1.08 (m, 1H), 0.87 (d, 3H), J = 6.8 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 174.04, 144.27, 139.97, 133.93, 129.50, 128.76, 125.55, 54.21, 53.07, 51.08, 37.26, 32.47, 31.72, 25.33, 22.42, 17.65, 13.58; IR (neat) υ 2950, 1730, 1585, 1445, 1375, 1310, 1240, 1145, 1080 cm^{-1}; MS (Cl,

CH_4) *m/z* 351 $(M + H)^+$; anal. calculated for $C_{16}H_{21}I0_2S$: C, 65.11; H, 7.48; S, 9.15; found: C, 65.37; H, 7.33; S, 8.76.

10. For other recent examples of *intramolecular* condensations between esters and α-sulfonylcarbanions, see: J. C. Carretero and R. G. Arrayás. *J. Org. Chem*. **60**, 6000–6001 (1995); P. Magnus, J. Booth, N. Magnus, J. Tarrant, S. Thom, F. Ujjainwalla. *Tetrahedron Lett*. **36**, 5331–5334 (1995); H. K. Jacobs and A. S. Gopalan. *J. Org. Chem*. **59**, 2014–2019 (1994).
11. (4*R*,8*S*,8a*S*)-3,8-dimethyl-4-(phenylsulfonyl)-2,4,6,7,8,8a-hexahydroazulen-5(1*H*)-one (**8**): colorless solid, mp 114–115 °C; $[\alpha]_D$ + 34.0° (c 0.99 $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.93 (d, 2H), 7.72 (t, 1H), 7.63 (t, 2H), 5.17 (s, 1H), 3.18–3.08 (m, 1H), 2.70–2.60 (m, 1H), 2.40–2.10 (m, 4H), 2.02–1.80 (m, 2H), 1.70–1.55 (m, 2H), 1.46 (s, 3H), 0.84 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 206.78, 152.97, 145.08, 138.52, 133.58 (2x), 128.55, 80.15, 56.03, 44.10, 41.96, 38.83, 34.02, 31.35, 20.20, 18.79; IR (KBr) υ 2960, 2820, 1730, 1585, 1445, 1375, 1320, 1310, 1150, 1080 cm^{-1}; MS (Cl, CH_4) *m/z* 319 $(M + H)^+$; anal. calculated for $C_{18}H_{22}O_3S$: C, 67.89; H, 6.96; S, 10.07; found: C, 67.64; H, 6.92; S, 10.07.
12. (4*R*,5*R*,8*S*,8a*S*)-3,8-dimethyl-4-(phenylsulfonyl)-1,2,4,5,6,7,8,8a-octahydroazulen-5-ol (**9**): colorless solid, mp 133–134 °C; $[\alpha]_D$ + 50.5° (c 1.0 $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.86 (d, 2H), 7.66 (t, 1H), 7.55 (t, 2H), 4.45 (d, 1H, *J* = 4.5 Hz), 4.30 (m, 1H), 4.08 (d, 1H, *J* = 5.8 Hz), 2.75 (m, 1H), 2.30–2.15 (m, 1H), 2.15–1.82 (m, 4H), 1.70–1.55 (m, 2H), 1.58 (s, 3H), 1.40–1.25 (m, 1H), 1.22–1.10 (m, 1H), 0.77 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (125 MHz acetone-d_6) δ 145.25, 142.10, 133.90, 130.13, 129.24, 128.48, 71.57, 70.69, 51.17, 38.12, 37.81, 31.02, 28.80, 28.69, 16.07, 15.39; IR (KBr) υ 3510, 2940, 2920, 1645, 1585, 1475, 1445, 1430, 1395, 1370, 1295, 1255, 1235, 1205, 1130, 1050 cm^{-1}; MS (Cl, CH_4) *m/z* 321 $(M + H)^+$; anal. calculated for $C_{18}H_{24}O_3S$: C, 67.47; H, 7.55; S, 10.00; found: C, 67.26; H, 7.50; S, 9.73.
13. *Intramolecular* Julia condensations have also been reported for macrocyclizations: (a) K. Takeda, A. Nakajiama, E. Yoshii. *Synlett* 249–250 (1995) and earlier papers; (b) D. R. Williams, P. J. Coleman, C. R. Nevill, L. A. Robinson. *Tetrahedron Lett*. **34**, 7895–7898 (1993); (c) D. R. Williams and P. J. Coleman. *Tetrahedron Lett*. **36**, 35–38 (1995).
14. The aldehyde was prepared from **7** via DIBAL-H reduction; (4*S*)-4-{(1*S*)-3-methyl-2-[(phenylsulfonyl)methyl]cyclopent-2-en-1-yl}pentanal (**10**): colorless oil, $[\alpha]_D$ +31° (c 2.0 $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 9.70 (t, 1H, *J* = 1.4 Hz), 7.87 (d, 2H), 7.73 (t, 1H), 7.63 (t, 2H), 4.08 (d, 1H, *J* = 14.3 Hz), 3.92 (d, 1H, *J* = 14.3 Hz), 2.89 (m, 1H), 2.55–2.38 (m, 2H), 2.22–2.04 (m, 2H), 1.91–1.70 (m, 2H), 1.58–1.38 (m, 2H), 1.24 (s, 3H), 1.15–1.05 (m, 1H), 0.86 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 202.99, 144.73, 140.40, 134.33, 129.91, 129.15, 125.92, 54.78, 53.56, 42.51, 37.75, 33.30, 29.40, 22.87, 18.25, 14.03; IR (neat) υ 2950, 1720, 1445, 1315, 1305, 1145, 1130, 1080 cm^{-1}; MS (Cl, CH_4) *m/z* 321 $(M + H)^+$.