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Total Synthesis of Clavukerin A and Its Epimer

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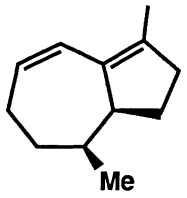
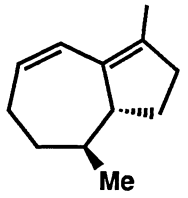
Enantioselective synthesis of clavukerin A and its epimer was carried out. By the comparison of the spectral data and specific rotations of synthesized and natural ones, two trisnorsesquiterpens isolated from *Clavulia* and *Cespitularia* species are confirmed to be identical.

Clavukerin A (**1**) was isolated from an Okinawan soft coral *Clavularia koellikeri* in 1983 and the absolute stereostructure was assigned as shown in the following figure on the basis of the chemical and physicochemical evidence and the X-ray crystallographic analysis.[1] In the same year, Bowden and his co-workers reported the isolation of a terpenoid from an Australian soft coral *Cespitularia*, sp. and the structure was proposed as **2**.[2] However, Kitagawa and his co-workers suggested that the latter terpenoid is the same compound as **1** from the close proximity of their spectra and specific rotation and the revision of the structure from **2** to **1** seems to be necessary.[3]



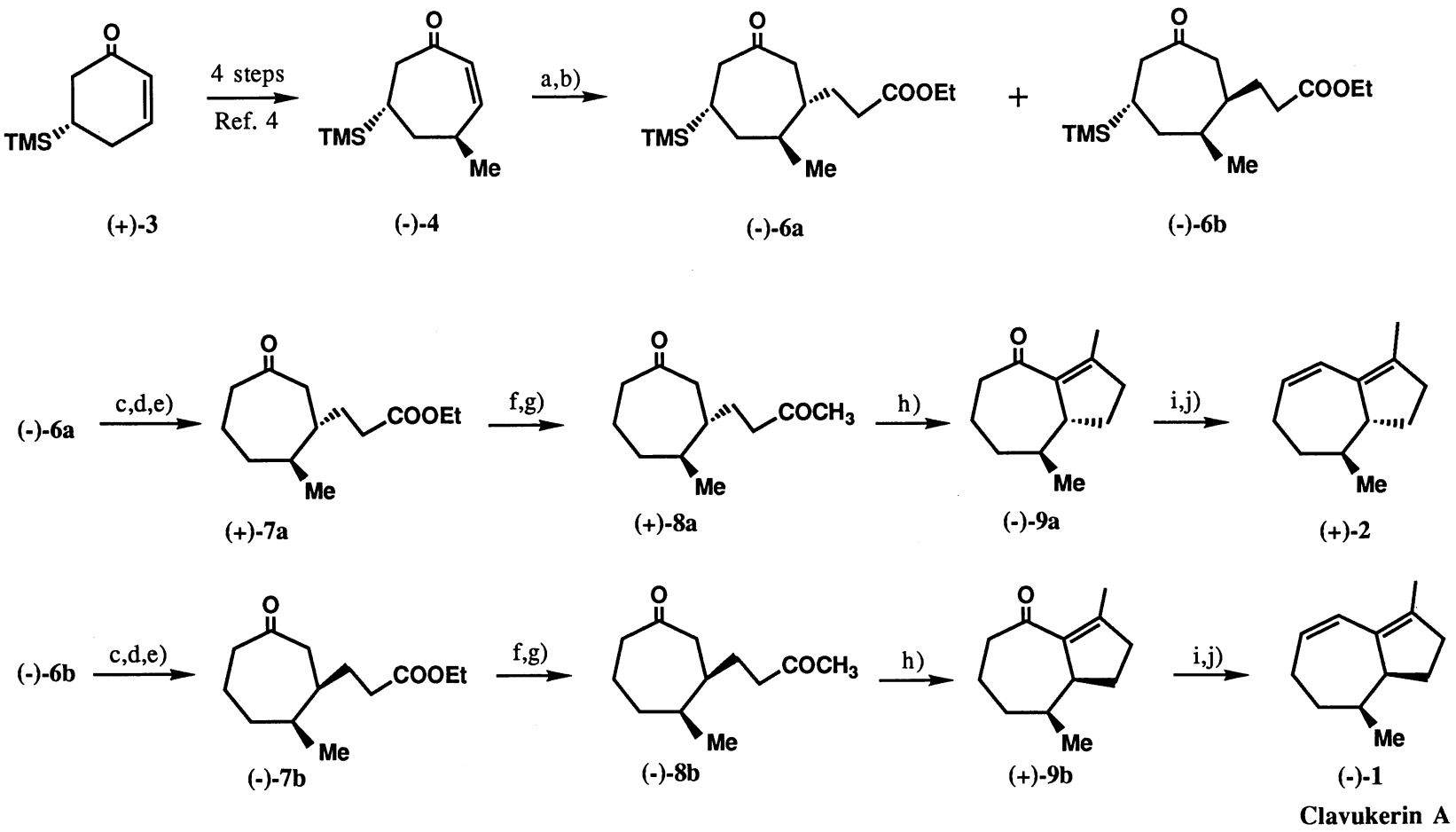
1
Clavukerin A



2

In connection with projected enantioselective synthesis of hydroazulene derivatives, we planned to synthesize optically active **1** and **2**, since the relationship of the above structures will be clarified by the synthesis, and the results would contribute to the elucidation of the biogenetic pathway of them and the related compounds.

As outlined in Scheme 1, we started our work with optically pure (-)-**4**, which is available from cyclohexenone (+)-**3** according to the reported method[4] in 58% overall yield. 1,4-Addition of the zinc homoenolate **5** generated from ethyl



Scheme 1. a) **5**: $Cu(CN)ZnICH_2CH_2CO_2Et$, 2LiCl, TMSCl; b) KF; c) Br_2; d) Zn, EtOH; e) H_2, Pd-C; f) LiOH; g) PivCl, Et_3N, MeMgI; h) 6 M HCl; i) p-$TsNHNH_2$; j) BuLi.

3-iodopropionate[5] to (-)-**4** in the presence of CuCN·2LiCl and chlorotrimethylsilane gave easily separable diastereoisomers (-)-**6a** and (-)-**6b** in the ratio of 3:1 in 86% combined yield.[6] 1,4-Addition of a similar zinc homoenolate generated from (1-ethoxy)cyclopropyl trimethylsilyl ether[7] to (-)-**4** gave almost the same selectivity and chemical yield. Elimination of the trimethylsilyl group from (-)-**6a** was carried out with 3 molar equivalents of bromine in carbon tetrachloride at rt for 1 h, and then the desilylated bromo derivatives were reduced with zinc in refluxing ethanol for 15 min to give crude enone which was hydrogenated in the presence of 10% Pd-C in ethanol at rt 1 h to give desilylated product (+)-**7a** in 70% overall yield. In a similar manner, (-)-**6b** gave (-)-**7b** in 56% yield. Hydrolysis of the ester group of (+)-**7a** was carried out with lithium hydroxide in methanol (45 °C, 45 min), and resulted carboxylic acid was transformed into methyl ketone (+)-**8a** [79% from (+)-**7a**] via mixed anhydride with pivalic acid.[8] Intramolecular aldol type condensation under acidic conditions (6 M HCl-THF at reflux for 45 min) gave (-)-**9a**[9] in 87% yield. In the same way, (-)-**8b** was obtained in 64% overall yield from (-)-**7b**, and (-)-**8b** was converted to (+)-**9b**[9] in 97% yield

As a method to convert the enone derivatives to the corresponding dienes, reduction of the enones to allylic alcohol followed by dehydration was proved to be useless, since 1,4-elimination is the predominant reaction in this system. Thus the Shapiro reaction was chosen. Reaction of (-)-**9a** with tosylhydrazine in ethanol gave an easily separable mixture of two diastereomers (15:1) in 95% combined yield. For the regioselective Shapiro reaction of hydrazones of unsaturated cyclic ketones, the use of methyllithium as a base in benzene-ether is reported to be the best choice,[10] in this case, however, the use of methyllithium in benzene-ether or hexane solution gave no diene product, and the use of butyllithium in place of methyllithium in benzene or hexane gave the expected product. Treatment of the major hydrazone with excess (ca. 4 equiv.) butyllithium in hexane at -10-0 °C for 15 min gave diene (+)-**2** [$[\alpha]_D^{21}$+110.4°(c 0.66, $CHCl_3$)] in 35% yield. In the same way, enone (+)-**9b** furnished a 7:1 mixture of hydrazone in 87% yield by the reaction with tosylhydrazine, and the treatment of the major isomer with butyllithium as mentioned above gave clavukerin A [$[\alpha]_D^{21}$-52.2°(c 0.60, $CHCl_3$), lit.[1] $[\alpha]_D^{20}$-53°($CHCl_3$)] in 32% yield. From the spectral feature and the specific rotation values of (-)-**1** and (+)-**2**,[11] it is concluded that the compound isolated by Bowden et al.[2] is the same compound as clavukerin A.

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6) The stereochemistry of the adducts (**6a** and **6b**) was not clear at this stage, and the structures were confirmed after the conversion to the enones **9a** and **9b**.[9)]
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9) Synthesis and their utilization of racemic **9a** and **9b** were reported by Posner et al.; G. H. Posner, K. A. Babiak, G. L. Loomis, W. J. Frazee, R. D. Mittal, and I. L. Karle, *J. Am. Chem. Soc.*, **102**, 7498 (1980).
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11) The NMR spectral data of some intermediates, clavukerin A and its epimer (+)-**2** are shown below. (+)-**7a**: $[\alpha]_D^{26}$+19.8°(c 2.7, $CHCl_3$); ^{1}H-NMR($CDCl_3$): δ=1.02(3H, d, J=5 Hz), 1.25(3H, t, J=7 Hz), 1.2-2.0(8H, m), 2.15-2.70(6H, m), 4.05(2H, q, J=7 Hz) ppm; ^{13}C-NMR($CDCl_3$): δ=14.2, 20.5, 29.4, 31.3, 35.0, 38.1, 41.2, 43.7, 45.5, 60.3, 173.4, 213.6 ppm. (-)-**7b**: $[\alpha]_D^{24}$-3.55°(c 4.0, $CHCl_3$); ^{1}H-NMR($CDCl_3$): δ=0.92(3H, d, J=7 Hz), 1.25(3H, t, J=7 Hz), 1.2-3.0(14H, m), 4.05(2H, q, J=7 Hz) ppm; ^{13}C-NMR($CDCl_3$): δ=14.3, 15.1, 21.0, 27.2, 32.2, 35.3, 37.1, 38.4, 43.8, 45.9, 60.2, 173.3, 213.5 ppm. (-)-**9a**: $[\alpha]_D^{15}$-5.32°(c 1.02, $CHCl_3$); ^{1}H-NMR($CDCl_3$): δ=0.97(3H, d, J=4 Hz), 2.05(3H, s), 1.1-2.9(12H, m) ppm; ^{13}C-NMR($CDCl_3$): δ=17.0, 21.4, 24.4, 29.1, 38.1, 39.7, 40.3, 45.2, 52.5, 139.8, 155.5, 203.2 ppm; mp 13.5-14.5 °C (pentane). (+)-**9b**: $[\alpha]_D^{13}$+87.94°(c 1.07, $CHCl_3$); ^{1}H-NMR($CDCl_3$): δ=0.76(3H, d, J=6 Hz), 1.2-2.7(11H, m), 2.03(3H, s), 3.0-3.4(1H, m) ppm; ^{13}C-NMR($CDCl_3$): δ=12.1, 16.7, 19.8, 28.0, 36.6, 37.5, 39.7, 46.0, 50.9, 136.1, 156.3, 202.8 ppm; mp 30-31 °C (pentane). (+)-**2**: ^{1}H-NMR(270 MHz, $CDCl_3$): δ=0.96(3H, d, J=6.4 Hz), 1.3-1.4(3H, m), 1.7-1.8(1H, m), 1.74(3H, s), 2.0-2.2(2H, m), 2.2-2.4(4H, m), 5.65(1H, ddd, J=12.2, 6.8, and 4.3 Hz), 6.24(1H, d, J=12.2 Hz); ^{13}C-NMR(22.4 MHz, $CDCl_3$): δ=14.6, 22.0, 29.3, 30.4, 36.7, 36.7, 39.9, 55.7, 124.4, 129.3, 136.7, 138.6 ppm. Clavukerin A [(-)-**1**]: ^{1}H-NMR(270 MHz, $CDCl_3$): δ=0.75(3H, d, J=6.9 Hz), 1.5-2.0(5H, m), 1.73(3H, s), 2.2-2.3 (4H, br s), 2.8-2.9(1H, br s), 5.54(1H, dt, J=12.5 and 4.7 Hz), 6.21(1H, d, J=12.5 Hz); ^{13}C-NMR(22.4 MHz, $CDCl_3$): δ=11.5, 14.5, 26.8, 27.3, 34.3, 34.5, 37.8, 54.6, 123.9, 128.8, 135.1, 138.8 ppm.

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