



8-Endo Cyclization of (Alkoxy carbonyl)methyl Radicals: Stereoselective Synthesis of (-)-Clavukerin A and (-)-11-Hydroxyguaiene

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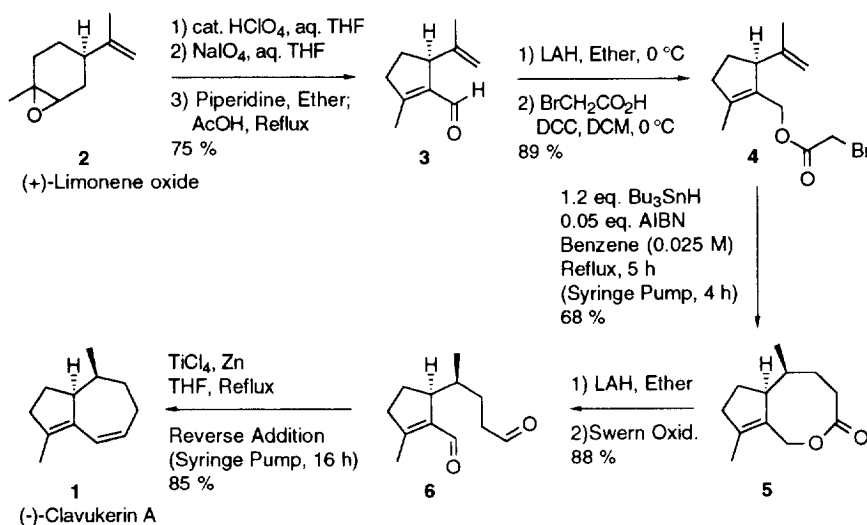
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Abstract: (-)-Clavukerin A was synthesized from (+)-limonene oxide via 8-endo radical cyclization. (-)-11-Hydroxyguaiene was also synthesized, but its spectroscopic data did not match with those reported for the natural product. Copyright © 1996 Elsevier Science Ltd

Clavukerin A (**1**) was isolated from the Okinawan soft coral *Clavularia koellikeri* by Kitagawa and coworkers.¹ Considerable amount of work was directed towards synthesis of this trinorguaiane sesquiterpene,² but the known syntheses of the natural enantiomer are lengthy and inefficient.^{2b,2d}

We reported some time ago that 8-endo cyclization is the preferred mode of reaction for (alkoxy carbonyl)methyl radicals generated from bromoacetates.³ In the present study, this unique reaction was utilized in the synthesis of (-)-clavukerin A.

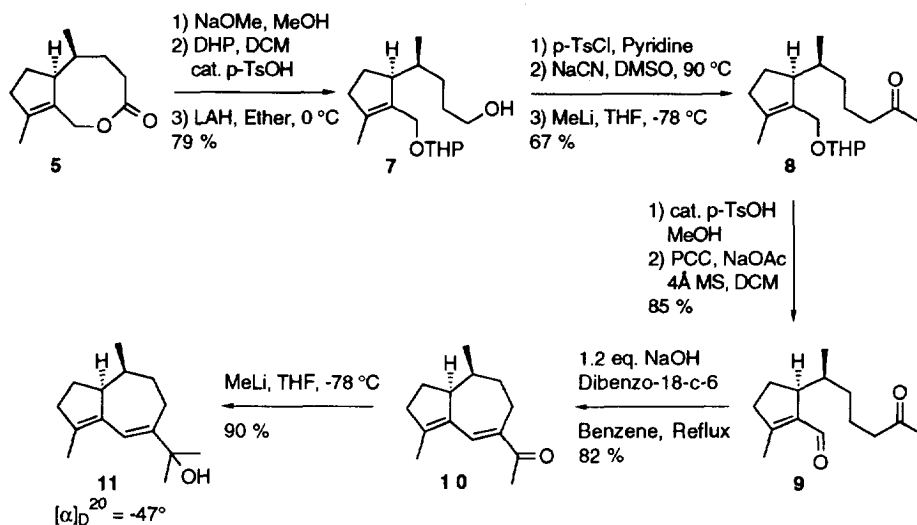
The bromoacetate **4**, prepared from the known aldehyde **3**,⁴ reacted with tributylstannane under the standard high dilution conditions to yield the heptanolactone **5** as the only cyclization product. (Scheme 1)



Scheme 1

The lactone **5** was reduced to a diol via lithium aluminum hydride reduction, and subsequent oxidation led to the isolation of the dialdehyde **6**.^{2c} (-)-Clavukerin A (**1**)⁵ was obtained via intramolecular McMurry-type coupling reaction using titanium chloride and zinc metal.⁶

The heptanolactone **5** was also envisaged as a good intermediate for the synthesis of 11-hydroxyguaiene (**11**) isolated by Bohlmann from the roots of *Parthenium hysterophorus*.⁷ Basic methanolysis of the lactone **5**, THP protection of the resulting primary alcohol, and subsequent lithium aluminum hydride reduction led to the preparation of the mono-protected diol **7**. The ketone **8** was isolated upon tosylation of **7**, cyanide substitution, and addition of methyllithium. (Scheme 2)



Scheme 2

The ketoaldehyde **9** was prepared via deprotection of **8** and PCC oxidation. Intramolecular aldol condensation of **9** provided the dienone **10** in good yield, which gave the desired dienol **11** upon addition of methyllithium. The product **11**, however, was found to possess different spectroscopic characteristics⁸ from those reported by Bohlmann. It appears that the structure of 11-hydroxyguaiene reported by Bohlmann has to be revised.

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- ¹³C NMR (50.3 MHz, CDCl₃) δ 138.6, 135.0, 128.7, 123.8, 54.52, 37.81, 34.47, 34.30, 27.23, 26.73, 14.44, 11.48; $[\alpha]_D^{24} = -50^\circ$ (c 0.55, CHCl₃).
- (-)-Clavukerin A(**1**) was obtained in 9 steps from (+)-limonene oxide (34 % overall yield). This is by far the most efficient synthesis.
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- ¹H NMR (200 MHz, CDCl₃) δ 0.78 (d, 3H, J = 6.6 Hz), 1.36 (s, 6H), 1.74 (s, 3H), 3.15 (1H), 6.39 (s, 1H); ¹³C NMR (20.1 MHz, CDCl₃) δ 147.7, 137.9, 134.2, 117.7, 74.35, 50.94, 37.92, 35.77, 34.83, 29.06, 28.86, 26.88, 25.47, 14.54, 14.41; MS (EI) 220 (M⁺, 30), 205 (76), 202 (100), 187 (33), 177 (20), 159 (62), 145 (70), 131 (54), 119 (30), 105 (36), 91 (31), 77 (16), 55 (23), 43 (68); $[\alpha]_D^{20} = -47^\circ$ (c 0.34, CCl₄). Reported value⁷ for 11-hydroxyguaiene; $[\alpha]_D^{24} = +34^\circ$ (c 2.5, CHCl₃).