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Radical Cyclization of β-Alkoxyacrylates: A Formal Synthesis of (-)-Kumausallene

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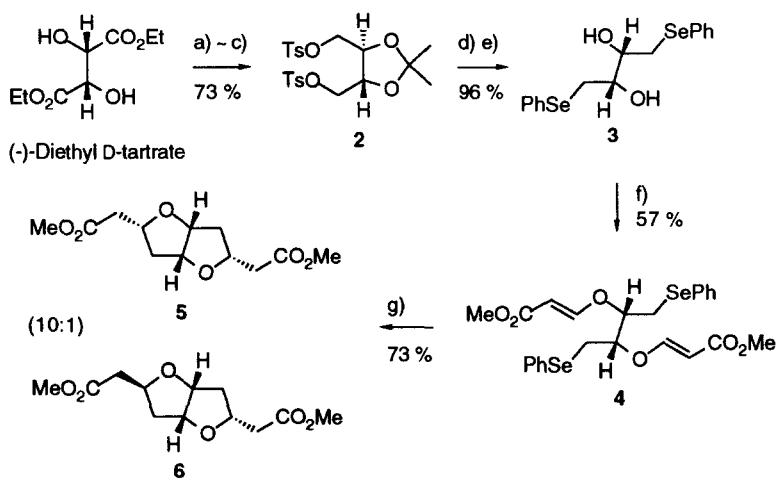
Abstract : Radical cyclization reaction of a bis(β-alkoxyacrylate) intermediate prepared from (-)-diethyl D-tartrate proceeded stereoselectively to give a 2,6-dioxabicyclo[3.3.0]octane product, which was converted into a known intermediate in the synthesis of kumausallene.

(-)-Kumausallene (**1**) was isolated from the red alga *Laurencia nipponica* Yamada by Kurosawa and coworkers.[1] The most characteristic feature of **1** is the 2,6-dioxabicyclo[3.3.0]octane ring system, which was constructed from a *cis*-hydrobenzofuranone intermediate obtained from 1-vinylcyclopentane-1,2-diol and α-(benzyloxy)-acetaldehyde via Prins cyclization-pinacol rearrangement strategy in the total synthesis of (±)-kumausallene by Overman.[2]

Our interest in **1** originated from the possibility of building up the 2,6-dioxabicyclo[3.3.0]octane ring system employing two concomitant radical cyclizations of β-alkoxyacrylates[3], and we now wish to report a formal synthesis of (-)-**1** based on this radical cyclization concept.

(-)-Diethyl D-tartrate was converted into the bis(phenylselenide) **3** via the ditosylate **2**. Reaction of **3** with methyl propiolate produced the bis(β-alkoxyacrylate) **4** in a moderate yield. Radical cyclization of **4** proceeded uneventfully to give a 10:1 mixture of the bicyclic products **5**[4] and **6** in 73 % yield (Scheme 1).



a) $Me_2C(OMe)_2$, p-TsOH, Acetone, r.t.; b) LAH, THF, 0 °C; c) p-TsCl, Pyridine, 0 °C, 12 h
d) THF-H_2O-TFA (5:2:1), Reflux, 5 h; e) $(PhSe)_2$, $NaBH_4$, EtOH, Reflux, 2 h
f) $HCCCO_2Me$, NMM, DCM, r.t. 3 h
g) 2.5 eq. Bu_3SnH, 0.25 eq. AIBN, Benzene (0.02 M), Reflux, 5 h (Syringe Pump, 4 h)

Scheme 1

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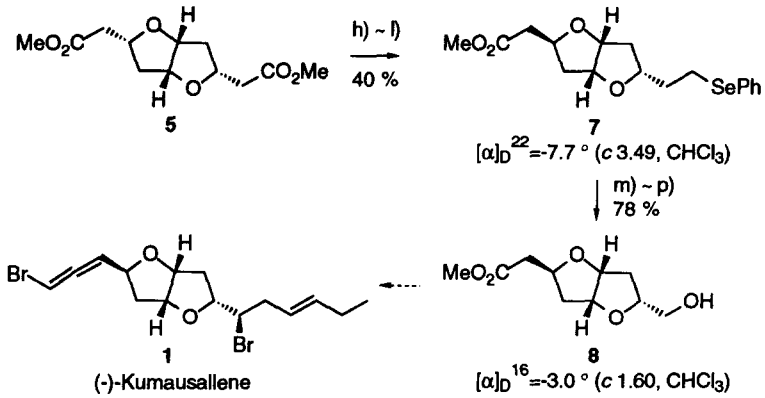
Partial hydrolysis of the diester **5** was best achieved by use of pig liver esterase,[3] and the monocarboxylic acid was converted into the corresponding phenylselenide via reduction with borane, tosylation, and phenylselenide substitution, from which the more stable phenylselenide **7** (4.4:1 favored over the original phenylselenide) was prepared under basic retro Michael-Michael addition conditions.



h) PLE (450 unit/mmol), pH 7.5 Phosphate Buffer-DMSO (3:1) (0.08 M), r.t. 2 h
i) BH_3-THF, THF, 0 °C, 18 h; j) p-TsCl, Pyridine, 0 °C, 12 h
k) $(PhSe)_2$, $NaBH_4$, MeOH, Reflux, 2 h; l) MeONa, MeOH, Reflux, 3 h
m) mCPBA, $NaHCO_3$, DCM, r.t. 30 min / Hexane, Reflux, 5 h
n) cat. OsO_4, NMO, Acetone-H_2O (10:1), r.t. 3 h
o) $Pb(OAc)_4$, Na_2CO_3, DCM, r.t. 30 min; p) $NaBH_4$, MeOH, r.t. 10 min

Scheme 2

Synthesis of the known intermediate **8** was achieved via the oxidation of **7** to the corresponding selenoxide and thermal elimination, dihydoxylation of the vinyl derivative, lead tetraacetate cleavage, and sodium borohydride reduction (Scheme 2). The primary alcohol **8**[6] was converted into **1** in the Overman synthesis, and this constitutes a formal synthesis of (-)-**1**.

In the present synthesis, an enantiomerically pure 2,6-dioxabicyclo[3.3.0]octane intermediate **5** was synthesized in a few steps from (-)-diethyl D-tartrate demonstrating another interesting example of the radical cyclization of β-alkoxyacrylates.

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4. ^1H NMR (500 MHz, $CDCl_3$) δ 1.86 (ddd, 2H, *J* = 13.8, 6.6, 1.3 Hz), 2.34 (ddd, 2H, *J* = 13.8, 7.5, 6.2 Hz), 2.60 (dd, 2H, *J* = 15.5, 5.9 Hz), 2.78 (dd, 2H, *J* = 15.5, 7.6 Hz), 3.70 (s, 6H), 4.38 (m, 2H), 4.50 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.49, 84.92, 77.11, 51.62, 41.00, 38.76; IR (neat, cm^{-1}) 2948.6, 1736.9, 1603.6, 1436.9, 1314.4, 1260.0, 1203.5, 1162.4, 1074.5, 998.2, 841.2; MS (CI) 259 (M+1, 100), 227 (75), 209 (91).
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6. In the Overman synthesis, the corresponding aldehyde was prepared from **8** for the synthesis of (±)-**1**. We prepared **8** from the aldehyde and characterized it as it is more stable. The spectroscopic data for the primary alcohol **8** were found to be identical with those reported by Overman in the reference 2.