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A Stereoselective Route to a Cyclopentanoid Natural Product Synthon Via Intramolecular Ester Enolate Alkyaltion

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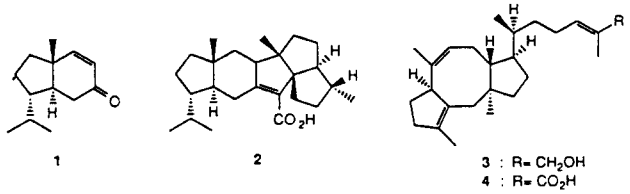
Vicinally substituted cyclopentanecarboxylates represent frequently encountered structural features in the synthesis of natural products. We recently reported a general, stereoselective method for the construction of such systems based on an acyclic intramolecular ester enolate alkylation protocol (Kim *et al.*, 1988; Kim *et al.*, 1994). In this note we wish to describe a stereoselective and efficient route to *trans*-hydrindenone (**1**), a synthetic intermediate for retigeranic acid (**2**) (Wender and Singh, 1990) (Scheme 1). This methodology should also be applicable to the synthesis of biologically active and structurally interesting cyclopentanoid natural products such as ceroplastol II (**3**) and albolic acid (**4**) (Kato *et al.*, 1988).



TMS-Cl accelerated conjugate addition of allylcopper (Lipshutz *et al.*, 1990) to readily available cyclohexenone **5** (Sorenson *et al.*, 1973), followed by hydrolysis of the resulting silyl enol ether, afforded cyclohexanone **6** in 60% yield. Conversion of ketone **6** into cyclization substrate **7** was accomplished according to a well-established, operationally simple, and highly efficient six-step sequence in 63% overall yield. Treatment of ester **7** with KHMDS in THF at −78 to −40 ℃ for 5 hr furnished cyclopentanecarboxylate **9** with a 13 to 1 stereoselectivity in 91% yield probably via the more stable 'eclipsed' transition state geometry **8**. DIBAL reduction of **9**, PCC oxidation, and Wacker reaction (Tsuji, 1984) produced keto aldehyde **10** (59% yield for three steps), which has been previously synthesized and converted to the desired *trans*-hydrindenone (**1**) by Fallis (Attah-Poku *et al.*, 1985) utilizing Stork' s internal Michael-aldol dehydration protocol (Stork *et al.*, 1982).

In summary, we have developed a flexible and stereoselective synthetic scheme to functionalized vicinally substituted cyclopentanecarboxylates, as illustrated by the stereoselective construction of trans-hydrindenone (**1**). Application of this general strategy to the construction of the aforementioned complex cyclopentanoid natural products is currently being pursued.

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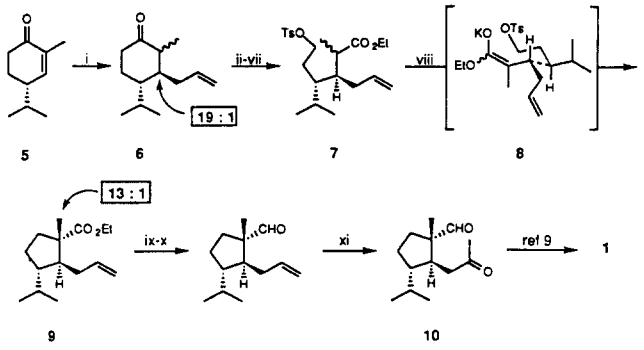

Reagents: i) a) (allyl)Cu·TMS-Cl·MgBrl, THF, −78℃, 3 h; b) (*n*-Bu)4NF, THF, 0℃, 30 min (60%); ii) LDA, TMS-Cl, THF, −78℃, 30 min (100%); iii) *m*-CPBA, CH_2Cl_2, 0℃, 10 min; iv) $(n\text{-Bu})_4NF$, THF, 0℃, 10 min (84% for 2 steps); v) $Pb(OAc)_4$, abs. EtOH, 0℃, 30 min; vi) $NaBH_4$, EtOH, 0℃, 10 min (81% for two steps); vii) TsCl, pyridine, 0℃, 7 h (92%); viii) KHMDS, THF, −78 to −40℃, 5 h (91%); ix) DIBAL, toluene, −20℃, 30 min (100%); x) PCC, CH_2Cl_2, 0℃, 30 min (90%); xi) cat. $PdCl_2$, CuCl, O_2, DMF:H_2O (7:1), rt, 2.5 h (65%).

Scheme 1

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(University of Ottawa) for spectral data of compound (**5**).

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