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A STEREOSELECTIVE SYNTHESIS OF (±)-ELEMOL VIA AN INTRAMOLECULAR S_N2' ESTER ENOLATE ALKYLATION

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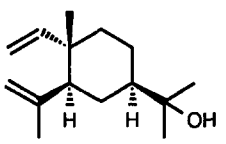
Summary: The monocyclic sesquiterpene, (±)-elemol (**1**) has been synthesized in a highly stereoselective manner by an intramolecular S_N2' ester enolate alkylation route.

Elemol (**1**), a monocyclic sesquiterpene alcohol isolated from Manila elemi oil and Java *Citronella* oil,[1] has been an attractive target as a test ground for new synthetic methodologies such as internal π-allyl nickel cyclization,[2a] macrocyclic contraction[2b,2c] and [2 + 2] photoannelation.[2d] Moreover, structurally related fuscoside B (**2**), recently isolated from *E. fusca*, was shown to selectively inhibit the synthesis of leucotriene and to possibly be an important lead compound for new anti-inflammatory agents.[3] We report here a stereoselective approach to (±)-elemol (**1**) based on our 'folding strain-controlled[4]' intramolecular S_N2' alkylation methodology as a prelude to synthesis of structurally related biologically active natural products such as fuscoside.[5]



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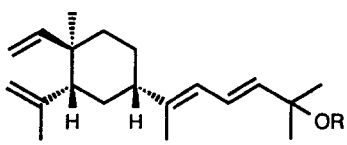
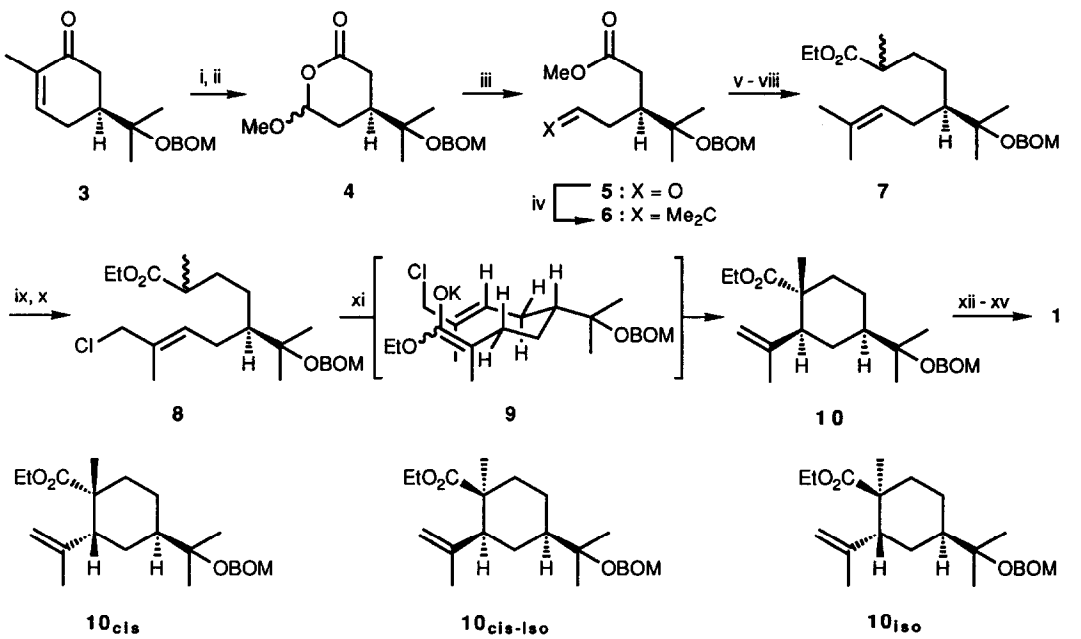


2 : R = arabinose

Osmylation of enone **3** and subsequent oxidative cleavage of the resulting diol with $Pb(OAc)_4$ in methanol produced acylal **4** in 91% overall yield. Wittig methylenation of aldehyde ester **5**, generated by base treatment of **4**, furnished olefinic ester **6** in 62% yield from **4**. Ester **6** was converted to homologated ester **7** in four straightforward steps [DIBALH, CH_2Cl_2; PDC, CH_2Cl_2; $Ph_3P{=}C(Me)CO_2Et$, CH_2Cl_2; Mg, MeOH[6], then NaOEt, EtOH] in 69% overall yield. Intramolecular S_N2' substrate **8** was prepared from olefin **7** in two steps by SeO_2 allylic oxidation under Sharpless conditions[7] and Hooz chlorination protocol[8] (50% yield). Upon treatment with KHMDS in THF at -18 °C for 4 h, followed by stirring at room temperature for 30 min, compound **8** underwent smooth cyclization to furnish the desired product **10** along with $\mathbf{10_{cis}}$ [cis-elemol skeleton], $\mathbf{10_{cis\text{-}iso}}$ [cis-isoelemol skeleton], and $\mathbf{10_{iso}}$ [isoelemol skeleton] in an 89 : 5 : 5 : 1 ratio in 57% total yield.[9,10] The observed high stereoselectivity can best be rationalized by considering that the reaction proceeds via chair-like *'double H-eclipsed'* transition state geometry **9** where both the nucleophilic ester enolate moiety and electrophilic allylic chloride assume *'H-eclipsed'* conformations with the BOM-protected tertiary carbinol group in an equatorial position.[5] Transformation of the carbethoxy function of **10** to the vinyl group by DIBALH reduction, PCC oxidation and Wittig methylenation led to the desired (±)-elemol (**1**) after removal of the BOM protecting group with Na in ammonia (67% overall yield for four steps). The synthetic elemol had ^1H and ^{13}C NMR data identical to those reported in the literature.[2d,11]

In summary, we have synthesized (±)-elemol (**1**) with high stereoselectivity using an intramolecular S_N2' alkylation route. Efforts are being made to apply this strategy to asymmetric syntheses of a number of biologically active natural products.



Reagents: i) OsO_4 (cat), NMO, acetone : H_2O (4 : 1), rt (97%); ii) $Pb(OAc)_4$ (2.2 eq), MeOH, 0 °C to rt , 30 min (94%); iii) K_2CO_3 (0.15 eq), MeOH, rt, 3h (71%); iv) $Ph_3P{=}C(Me)_2$, THF, -20 °C to rt, 1h (88%); v) DIBALH (2 eq), CH_2Cl_2, -78 °C to rt, 30 min; vi) PDC (3 eq), CH_2Cl_2, reflux, 6h; vii) $Ph_3P{=}C(Me)CO_2Et$, CH_2Cl_2, 35 °C, 15h (76% for 3 steps); viii) Mg (4 eq), MeOH, rt, overnight; 0.15M NaOEt in EtOH, rt, 20h (91%); ix) SeO_2, t-BuOOH, CH_2Cl_2, rt, 5h, then $NaBH_4$, EtOH, -20 °C to rt, 30 min (52%, 69% based on recovered sm); x) *n*-Bu_3P (3 eq), CCl_4, ether, rt, 30 min (97%); xi) KHMDS, THF (0.004M), -18 °C, 4h, then rt, 30 min (57%); xii) DIBALH (2.5 eq), toluene, -78 °C to rt, 1h; xiii) PCC (2.8 eq), NaOAc (3 eq), CH_2Cl_2, rt, 2h; xiv) $Ph_3P{=}CH_2$, THF, -78 °C to rt, 30 min (67% for 3 steps); xv) Na, NH_3, THF, -78 °C, 1h (100%).

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9. All new compounds exhibited satisfactory spectroscopic data and the ratio of stereoisomers was determined by capillary g. c. analysis and/or rigorous analysis of 400 MHz ^1H NMR spectra.
10. Stereochemistry of isomers of **10** was confirmed by conversion into the corresponding stereoisomers of elemol. For ^1H NMR spectral data of cis-elemol, cis-isoelemol and isoelemol, see ref 2c, ref 2b and ref 2c, respectively.
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