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STEREOSELECTIVE TOTAL SYNTHESES OF (±)-SINULARENE AND OF (±)-5-EPI-SINULARENE VIA INTRAMOLECULAR TYPE-I-"MAGNESIUM-ENE" REACTION

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<u>Abstract</u>: (±)-Sinularene (<u>1</u>) as well as (±)-5-epi-sinularene (<u>9</u>) were synthesised in a stereocontrolled manner from the norbornene <u>2</u> in overall yields of 4% and 8%, respectively. The key step $5 \neq 6$ involves a regio- and stereoselective intramolecular "magnesium-ene" reaction.

The sesquiterpene (-)-sinularene, isolated from the soft coral *Sinularia mayi*, has been shown by X-ray-evidence to possess the unusual structure $\underline{1}$.¹ Its racemate was recently synthesised in a non-stereoselective manner.²

We present here a different, stereoselective synthesis of both, (\pm) -sinularene $(\underline{1})$ and (\pm) -5-epi-sinularene $(\underline{9})$. The cornerstone of our strategy is an intramolecular type-I-"Mg-ene" reaction,³ (Scheme 1) recently employed for the

Scheme 1



synthesis of $(\pm) - \Delta^{9}(12)$ -capnellene.⁴,⁵ Thus, starting from the known norbornene $\underline{2}^{6}$ we envisaged to form in the critical step the bonds C(7),C(15) and C(6),C(5) thereby closing a six-membered ring. Founded on previous experience^{3b} and on model examinations we stood a good chance to establish the desired relative configuration of the centers C(5)/C(6) by thermodynamic control.

Scheme 2



SINULARENE

5-EPI-SINULARENE

Treatment of the tosylate 2 with NaI (2 equiv, acetone, reflux,9h) gave the iodide 3⁷ (87%) which was employed to alkylate the dienolate anion prepared from tiglic acid (i) LDA (2.3 equiv), THF, 4° ; ii) HMPA, 3 (0.91 equiv), $-78^\circ \rightarrow 0^\circ$, 4h/r.t., 16h). Remarkably only γ -alkylation took place⁸ to give cleanly the (E)-carboxylic acid $4^{7,8}$ (m.p. 70-71°, 78% yield). Reduction of 4 with LiAlH₄, followed by treatment of the resulting alcohol⁷ with mesyl chloride/pyridine (2.5 equiv, 0°, 3h) and 1N aq. HCl (0°, 10 min) furnished the allylic chloride 57 (55%), purified by rapid filtration through silica gel. Now the stage was set for the critical cyclisation step. Slow addition (over 2h) of 5 to a rotating slurry of precondensed magnesium¹⁰ (2 equiv, THF, $-78^{\circ} \rightarrow$ r.t. over 2 h), heating the resulting 0.05 N solution of 2-alkenylmagnesium chloride at 50° for 16 h, followed by carbonation of the cyclised Grignard product (excess CO_2 -10°, then 80°/2h, sealed tube) furnished after crystallisation (hexane) the carboxylic acid 67,11 (m.p. 149°, 47% yield from 5). The configuration of 6 follows from its smooth iodolactonisation¹² as well as from trapping of the cyclised organomagnesium chloride with 0, followed by Jones' oxidation which furnished the ketone 7 identified by comparison (¹H-NMR, IR) with authentic 7². Accordingly,

 (\pm) -5-epi-sinularene (9) was obtained from 6 as follows. Reduction with LiAlH₄ (THF, reflux, lh) gave the crystalline (pentane, -30°) alcohol $\underline{8}^7$ (m.p. 65-67°, 100%). Hydrogenation of $\underline{8}$ (H₂, Pt, MeOH) afforded a saturated alcohol⁷ (m.p. 38-39°, 99%) which on successive acetylation (AcCl, NEt, (3 equiv), DMAP, CH₂Cl₂, O° , 2h) and acetate pyrolysis (distillation through a quartz tube with an argon stream, 500°, 0.4 Torr) furnished (±)-5-epi-sinularene (9)^{7,13} in 70% yield from 8. Our initial hope to achieve thermodynamic control over C(5) by cyclising the Grignard reagent derived from 5 at higher temperature did not materialise due to destruction. Consequently, we had recourse to a less direct thermodynamic stereoselection. O-Methylation of 8 (i) NaH (1.5 equiv), DMF, r.t.; ii) HMPA (1 equiv), MeI (2 equiv), r.t. 16 h) gave the ether 107 (89%). Ozonolysis of 10 (i) O_3 , MeOH, -78°; ii) Me₂S -78° \rightarrow r.t., 2h) furnished a methylketone⁷ which epimerised smoothly on base treatment (1.5% KOH in EtOH, H₂O 15:1, reflux, 7h, 90% yield) yielding the C(5)-epimeric ketone7 (90% yield); subsequent Wittig reaction¹⁴ (Ph₃P=CH₂ (4 equiv), THF, r.t., 16 h, 69%) afforded the sterically pure ether 11^7 . Having arrived at the desired configuration of C(5) there remained only hydrogenation¹⁵ (99%), ether cleavage (Me₂SiCl, NaI (10 equiv), MeCN, r.t., 2h, 78%),¹⁶ acetylation¹⁵ and ester pyrolysis (76%)¹⁵ to obtain selectively (±)-sinularene. The synthetic (±)-l displays IR, lH-NMR and mass spectra identical to those of the naturally occurring sesquiterpene (-)-1. We believe that this work illustrates once more the value of intramolecular "magnesium-ene" reactions in organic synthesis.

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- 11) The mother liquors of 6 contain 4% of a not yet identified carboxylic acid.
- 12) Treatment of a solution of $\underline{6}$ in 5% aq. NaHCO₃ with KI₃ (2 equiv, 24 h, r.t.) furnished a crystalline iodolactone⁷ (m.p. 76 79°, 59% yield).
- 13) ¹H-NMR of <u>9</u> (CDCl₃, standard TMS, δ(ppm)= 0, s= singlet, d= doublet, J= spin-spin coupling constant (Hz)): 0.81 (d, J= 6.5, 3H); 0.89 (s, 3H); 0.96 (d, J= 6.5, 3H); 1.1 - 2.4 (13H); 4.41 (s, 1H); 4.89 (s, 1H).
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