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APPLICATION OF THE INTRAMOLECULAR MAGNESIUM-ENE REACTION TO THE STEREOCONTROLLED TOTAL SYNTHESES OF (±)-12-ACETOXYSINULARENE AND (±)-5-EPI-12-ACETOXYSINULARENE[1]

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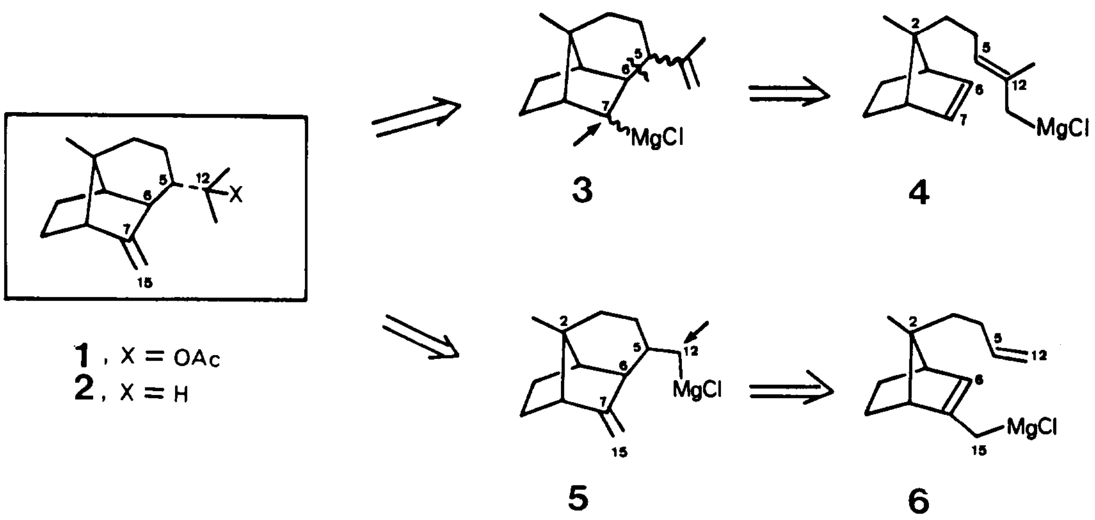
Abstract: The sesquiterpene (±)-12-acetoxysinularene (1) and its C(5)-epimer 13 were each synthesized stereoselectively from the norbornyl-iodoacetal 7 in 5% and 7% overall yields. The critical step 10 → 11 involves the regio- and stereoselective "magnesium-ene" reaction 6 → 5.

The sesquiterpene 12-acetoxysinularene, isolated from *Clavularia inflata*, has been assigned structure 1 by means of chemical correlation and X-ray diffraction analysis[2].

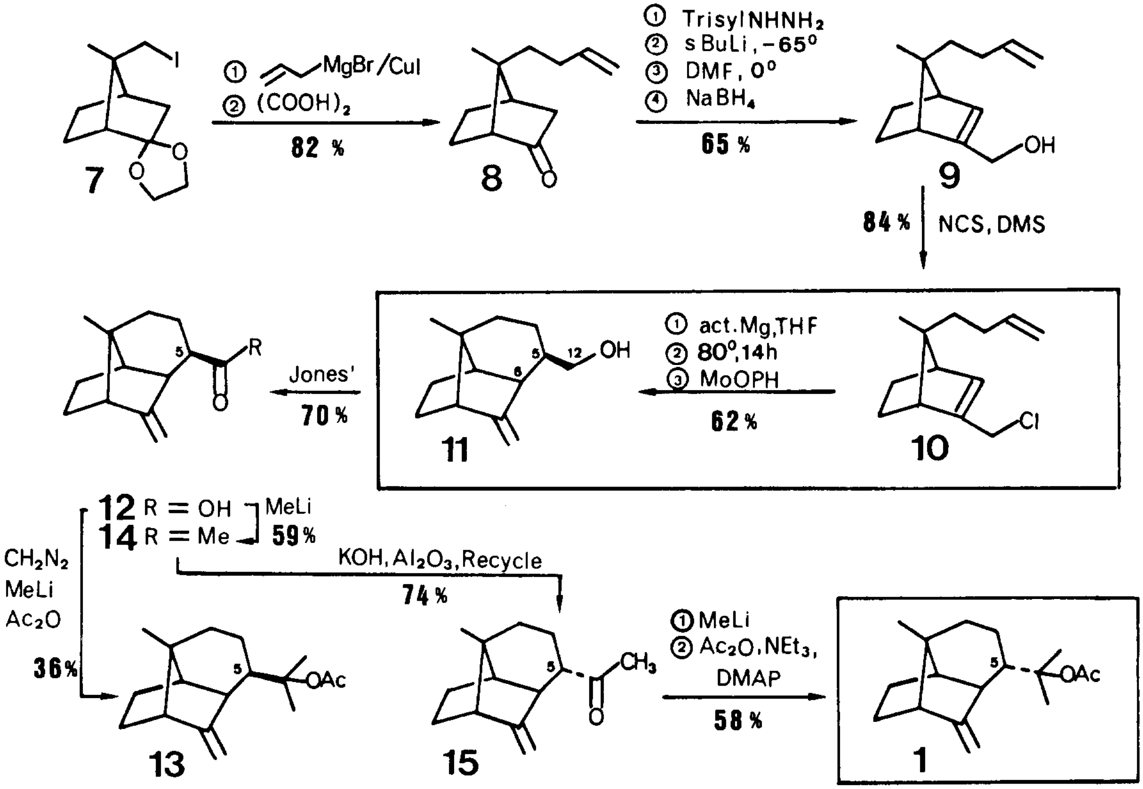
We report here the first synthesis of (±)-1. Our strategy centers on the intramolecular magnesium-ene reaction[3] which has served recently as the key method to construct selectively and efficiently the terpenoids capnellene[4], khusimone[5] and sinularene (2)[6].

Scheme 1



The strategy described in Scheme 1 differs from our previous approach to sinularene[6] (4 → 3 → 2) in so far as the crucial sequence (6 → 5 → 1) features the magnesium ene unit as part of the norbornene skeleton which carries the enophilic chain at C(2). Thus, by reversing the position of the reaction partners the C(5),C(6)-bond would close with concomitant formation of both the C(7),C(15)-methylene group and the C(12)-Mg functionality.

Scheme 2



Coupling[7,8] of the iodo-acetal 7[8] with allylmagnesium bromide (3 eq.)/CuI (0.25 eq., Et_2O, 3 hr reflux) followed by deacetalization[8] (aq. $(COOH)_2$, CH_2Cl_2, SiO_2, 14 hr, 25°) gave the ketone 8[9] (82%). The crystalline trisylhydrazone of 8 (2,4,6-triisopropylbenzenesulfonyl hydrazide (1.1 eq.), HCl, CH_3CN, 25°, 10 hr 76%, m.p. 172-175°) was treated with *sec*-butyllithium (2.2 eq., TMEDA/hexane (1:1), -65°, 2 hr, then 0°, 30 min.) followed by trapping of the norbornenyllithium intermediate with DMF[10] (1.5 eq., 0°, 30 min., aq. work-up). Reduction of the resulting conjugated aldehyde with $NaBH_4$ (1.2 eq., MeOH, 0°) gave the allylic alcohol 9[9] (65% overall yield from 8). After conversion[11] of 9 to the chloride 10[9] (NCS (1.5 eq.), DMS (1.8 eq.), 0°, 2 hr, 84%) we proceeded to the crucial magnesium-ene reaction.

Metalation of 10 using precondensed magnesium in THF[12], heating of the 0.059 N 2-alkenylmagnesium chloride solution at 80° for 14 hr and oxidation of the cyclized Grignard product with molybdenumpentoxide/pyridine/HMPA complex[13] (1.1 eq., -78°, 1 hr) afforded the tricyclic alcohol 11[9] in one synthetic operation (62% from 10) as a single stereoisomer. The depicted C(5)-configuration was expected from previous experience[4,6] and confirmed by the following transformations. Oxidation of 11 with Jones' reagent[14] (15 min, 0°) furnished the carboxylic acid 12[9] (m.p. 108-110°, 70%) which on successive esterification (CH_2N_2), addition of methyllithium (excess, ether, 25°, 18 hr) and acetylation[15], ether, 0°, 24 hr) gave (±)-5-epi-12-acetoxysinularene (13[9,16], 36% from 12).

Consequently conversion of acid 12 to the sesquiterpene 1 required epimerization at C(5). To this end 12 was transformed into the methyl ketone 14[9] (i) MeLi (5 eq.); THF, 0°, 3 hr; ii) TMSCl; iii) 1M HCl, 59%)[17] which was adsorbed onto a layer of basic aluminium oxide (10% KOH) placed on top of a column of SiO_2. After 30 min. elution (hexane/ether 95:5) gave pure 15[9] and the more polar 14 (1:1.3 ratio). Recycling 14 using the same procedure conveniently afforded the desired epimer 15[9] in 74% overall yield. Addition of MeLi (5 eq., ether, reflux, 30 min., 85%) followed by acetylation[15] (acetic anhydride (10 eq.), Et_3N (10 eq.), DMAP (0.1 eq.)) of the carbinol furnished (±)-12-acetoxysinularene (1,[9] 58% from 15) identified by comparison (IR, ^1H-NMR, mass spectra) with the naturally occurring sesquiterpene (-)-1.

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