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SYNTHESIS OF (±)-6-PROTOILLUDENE AND (±)-3-EPI-6-PROTOILLUDENE BY INTRAMOLECULAR MAGNESIUM-ENE- AND KETENE/ALKENE ADDITION REACTIONS [1)]

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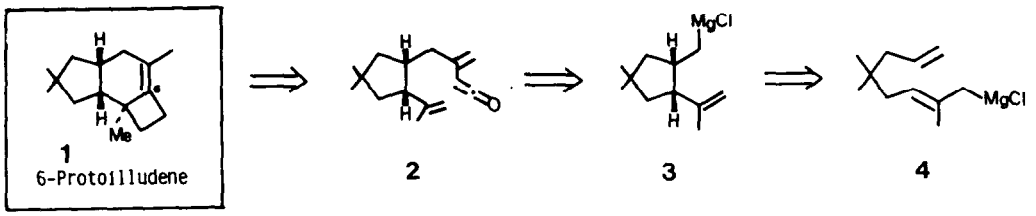
Summary: The sesquiterpene (±)-6-protoilludene (1) and its C(3)-epimer 11 were synthesized from aldehyde 5. The key steps are a regio- and stereo-selective type-I-magnesium-ene reaction 4 → 3 and an intramolecular vinylketene/alkene addition 2 → 9a + 9b.

6-Protoilludene, isolated from Basidiomycetes [2)] and, more recently, from the ascomyte *Ceratocystis Piceae* [3)] has been assigned structure 1. The hydrocarbon 1 and/or the corresponding tertiary cation appear to serve as pivotal intermediates in the biosyntheses of various fungal sesquiterpenes such as illudanes, marasmanes, lactarames and fommanosin [2b,4)]. Despite the elaboration of Diels-Alder- [5a)] and photo-cycloaddition- [5b)] routes to the protoilludane skeleton only one synthesis of (±) 1 has been reported [6)].

Scheme 1

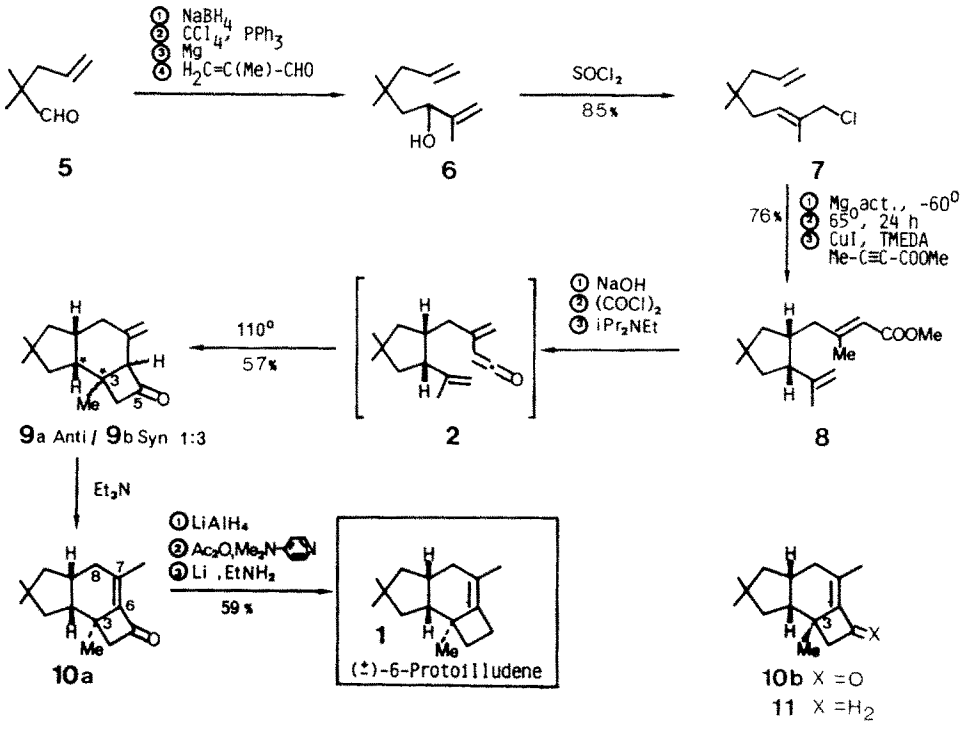


1 6-Protoilludene 2 3 4

We describe here a more direct synthesis of (±)-6-protoilludene and its C(3)-epimer. Our strategy (Scheme 1) features an intramolecular ketene/olefin addition [7)] of 2 which in turn should derive from the intramolecular type-I-magnesium ene process [8)] 4 → 3.

To implement this plan (Scheme 2) aldehyde 5 [9)] was reduced with $NaBH_4$ (2.4 eq, MeOH, 0°, 95%). Treatment of the resulting alcohol with PPh_3 (1.3 eq) in CCl_4 [10)] (reflux, 1.5h, 69%) furnished a chloride which was metalated with anthracene-activated magnesium [8b,11)]; addition of this Grignard reagent to methacrolein afforded dienol 6 [12)] (46%). Rearrangement of 6 with $SOCl_2$ [13)] (excess, Et_2O, reflux, 20h) gave the desired allyl chloride 7 [12)] in 85% yield.

Scheme 2



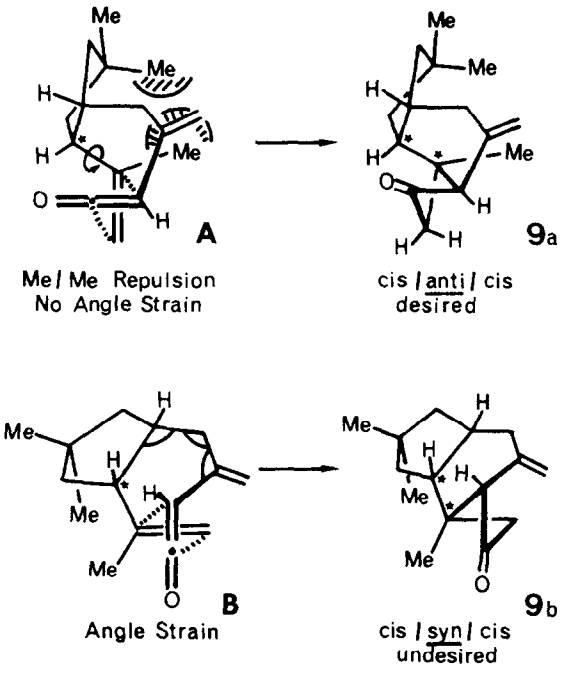
The crucial Mg-ene/conjugate trapping operation 7 → 8 was carried out as follows. Slow addition of chloride 7 to anthracene-activated magnesium (5eq) in THF [8b] at -65°, warming of the mixture to r.t. over 1 h and heating the resulting solution (0.2 N) of dienylmagnesium chloride at 65° gave the non-isolated cyclized Grignard compound 3. Addition of this solution to CuI (1.1eq), TMEDA (3eq) in THF at -65°, stirring of the mixture at -60° to -40° for 1.5h followed by addition of methyl-2-butynoate (0.95 eq) to the such obtained organocopper reagent [14] at -78° furnished conjugated ester 8 [12] in 76% yield. In line with the usual, kinetically controllled topology of 2,7-octadienylmagnesium chloride cyclizations [8] we assigned the *cis*-substitution to product 8 which was confirmed by its following conversion into 6-protoilludene.

Saponification of ester 8 with 0.7 N NaOH ($MeOH/H_2O$ 5:1, 65°, 3h) gave in 100% yield a 4:1-mixture of α,β- and *exo*-β,γ-unsaturated acids [12] which on treatment with oxalyl chloride (5eq, toluene, r.t. 3h) followed by heating of the crude acid chloride with ethyldiisopropylamine (18eq, toluene, 0.003N solution, under reflux) afforded a 1:3-mixture of 9a [12] + 9b [12] in 57% yield. The olefinic bond was efficiently shifted into the carbonyl-conjugated 6-position [15] under mildly basic conditions (excess of NEt_3, MeOH, r.t., 18h, 85% yield). After flash chromatography the minor isomer 10a was reduced with $LiAlH_4$ (excess, Et_2O, 0°, 5 min, 99%). Acetylation of the resulting allylic alcohol (Ac_2O(excess), DMAP cat., CH_2Cl_2, r.t., 3h) and C,O-hydrogenolysis [16] (excess of Li, $EtNH_2$, r.t., 10 min) gave (±)-6-protoilludene (59% yield from 10a), identified by comparison (IR, ^{1}H-NMR, ^{13}C-NMR, capillary GC) with (-)-1 of natural origin.

Analogous reduction of the major enone isomer 10b gave 3-epi-6-protoilludene (11) in 61% overall yield.

The observed diastereoselectivity of the crucial [2 + 2]-cycloaddition step 2 → 9 can be rationalized by comparison of transition states A and B (Scheme 3) assuming a concerted *supra/antara-facial* alkene/methyleneketene addition [17].

Scheme 3



Inspection of Dreiding models reveals that transition state A which leads to the desired *cis/anti/cis*-configuration of 9a, suffers from non-bonding interactions between the olefinic methyl and one of the geminal methyl groups. Methyl/methyl-repulsion is much less severe in transition state B which, however, encounters angle compressions at the bridge carbons. Based on the observed predominance of product 9b we conclude that the steric hindrance overrides the angle strain thus favoring B over A.

In summary, this synthesis exemplifies once more the general potential of the Mg-ene reaction in combination with electrophilic trapping and alkene-cyclizations thereby providing insight into the stereochemistry of intramolecular ketene additions.

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