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ENANTIOSELECTIVE SYNTHESES OF (+)-α-SKYTANTHINE, (+)-δ-SKYTANTHINE AND (+)-IRIDOMYRMECIN BY AN INTRAMOLECULAR MAGNESIUM-ENE REACTION.[1]

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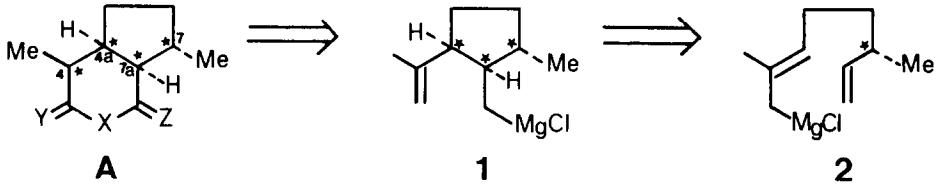
Abstract: Starting from (S)-3-methyl-1-penten-5-ol 3a enantiomerically pure (+)-α-skytanthine 9, (+)-δ-skytanthine 11 and (+)-iridomyrmecin 12 were synthesized *via* the magnesium-ene reaction 2 → 1.

In extension of previous work on intramolecular Mg-ene reactions [2] we considered the prospect of synthesizing monoterpene alkaloids and iridoids A *via* the key step 2 → 1 (Scheme 1). It was hoped that the preexisting chiral center in 2 would induce the desired configuration at the newly formed centers.

Scheme 1

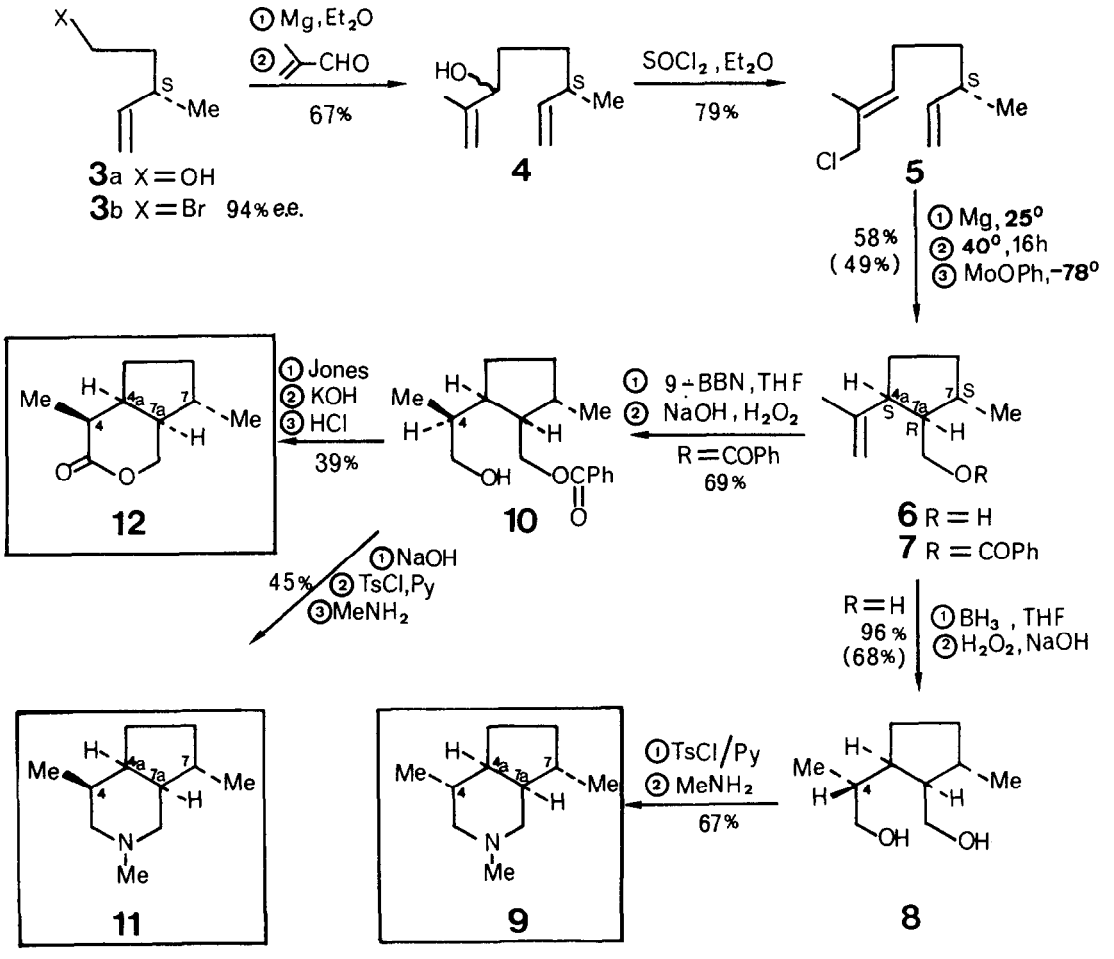


We report here the application of this concept to the total syntheses of enantiomerically pure (+)-α-skytanthine 9, [3] (+)-δ-skytanthine 11 [3] and (+)-iridomyrmecin 12 [4] (Scheme 2).

Alcohol 3a, easily accessible in high enantiomeric purity *via* an asymmetric vinylcopper/enoate 1,4-addition [5], was converted into the bromide 3b by successive treatment with mesyl chloride and LiBr [6]. Metalation of 3b with Mg turnings in ether and addition of the resulting Grignard reagent to methacrolein afforded dienol 4 [7] (67%, 1:1-diastereomer mixture). Heating 4 with thionyl chloride in boiling Et_2O gave rearranged allyl chloride 5 [7] (79%).

We then proceeded to the crucial metalation/cyclization/trapping sequence. Slow addition (over 2h) of chloride 5 to a stirred suspension of magnesium powder (*Merck*, 0.1-0.3 mm) in ether at r.t., heating of the resulting solution of 2 at reflux for 14h followed by oxidative trapping of 1 with MoOPh [8] at -78° yielded cyclized alcohols (88.4/5.9/3.0/1.4 isomer mixture, 58%). The major isomer [7], isolated by flash chromatography (49% from 5) was assigned structure 6 based on its conversion into the natural products 9, 11 and 12.

Scheme 2

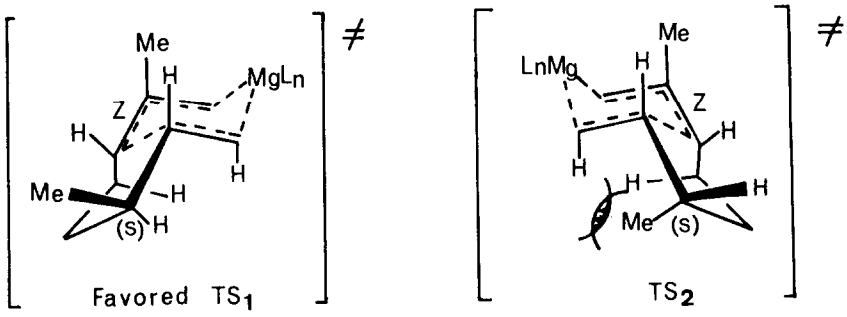


Hydroboration/oxidation [1)BH_3 (4eq), THF, 0°;2) H_2O_2/NaOH, 50°] of 6 gave a 4.2:1-C(4)-epimer mixture [9] from which (+)-α-iridodiol 8 [7,10] (m.p. 81-81°) was separated by flash chromatography. Following the procedure described by *Casinovi* [3b], successive treatment of 8 with tosyl chloride/pyridine and methylamine furnished pure (+)-α skytanthine 9 in 67% yield.

Aiming at the stereoconvergent synthesis of δ-skytanthine 11 it was interesting to note that, after benzoylation of 6, hydroboration of 7 [7] with 9-BBN (5eq 0° to r.t.) proceeded with reversed topicity to give 10 (6:1-C(4)-epimer mixture) [11]. Saponification of crude 10 and flash chromatography yielded pure δ-iridodiol (oil) which was converted into enantiomerically pure (+)-δ-skytanthine 11 as described earlier [3b].

For the synthesis of (+)-iridomyrmecin 12, the non-protected primary alcohol group in 10 was oxidized with *Jones'* reagent to give the corresponding carboxylic acid. Saponification of the benzoate group and spontaneous lactonization of the non-isolated hydroxy acid furnished crude 12 (5:1-C(4)-epimer mixture) from which enantiomerically pure (+)-iridomyrmecin 12 (39% from 10) was obtained by crystallization. Synthetic skytanthines 9 and 11 and (+)-iridomyrmecin 12 were identified by comparison ([α], IR, ^{1}H-NMR, MS) with naturally occurring compounds.

Scheme 3



To rationalize the observed diastereoselectivity in the Mg-ene process 2 → 1 we assume : 1) that 2,3-substituted 2-alkenylmagnesium halides react in their Z-form [2a], and 2) that 2,6-dienylmagnesium halides cyclize under kinetic control preferentially to give five-membered rings with *cis*-disposed Mg - donor and - acceptor sites [12]. Accounting for these premises, comparison of transition states TS_1 and TS_2 shows less steric crowding in transition state TS_1 which leads to the desired topicity of 1 (Scheme 3).

In summary, we believe that the above described stereoselective syntheses exemplify the potential of the Mg-ene process in combination with asymmetric 1,4-additions [13].

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