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TOTAL SYNTHESIS OF (±)CHOKOL-A VIA AN INTRAMOLECULAR TYPE-I-MAGNESIUM ENE REACTION [1].

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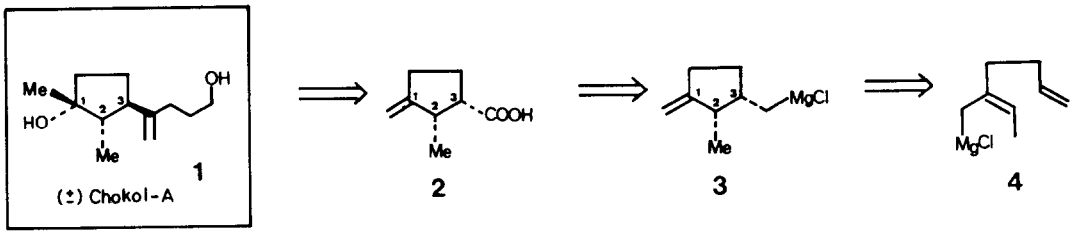
Summary: The sesquiterpene (±)chokol-A (1) was synthesized in a diastereoselective manner starting from 1-hexen-5-one-trisylhydrazone (5). The key step 7 → 8 involves the regio- and stereo-selective magnesium-ene reaction 4 → 3.

The fungitoxic sesquiterpene chokol-A, isolated from stromato of *Epichloe typhina* has been shown by spectral evidence to possess constitution and relative configuration 1 [2].

We describe here the first total synthesis of (±)-1 as part of a program directed toward the study and application of stereoselective Mg-ene processes [3].

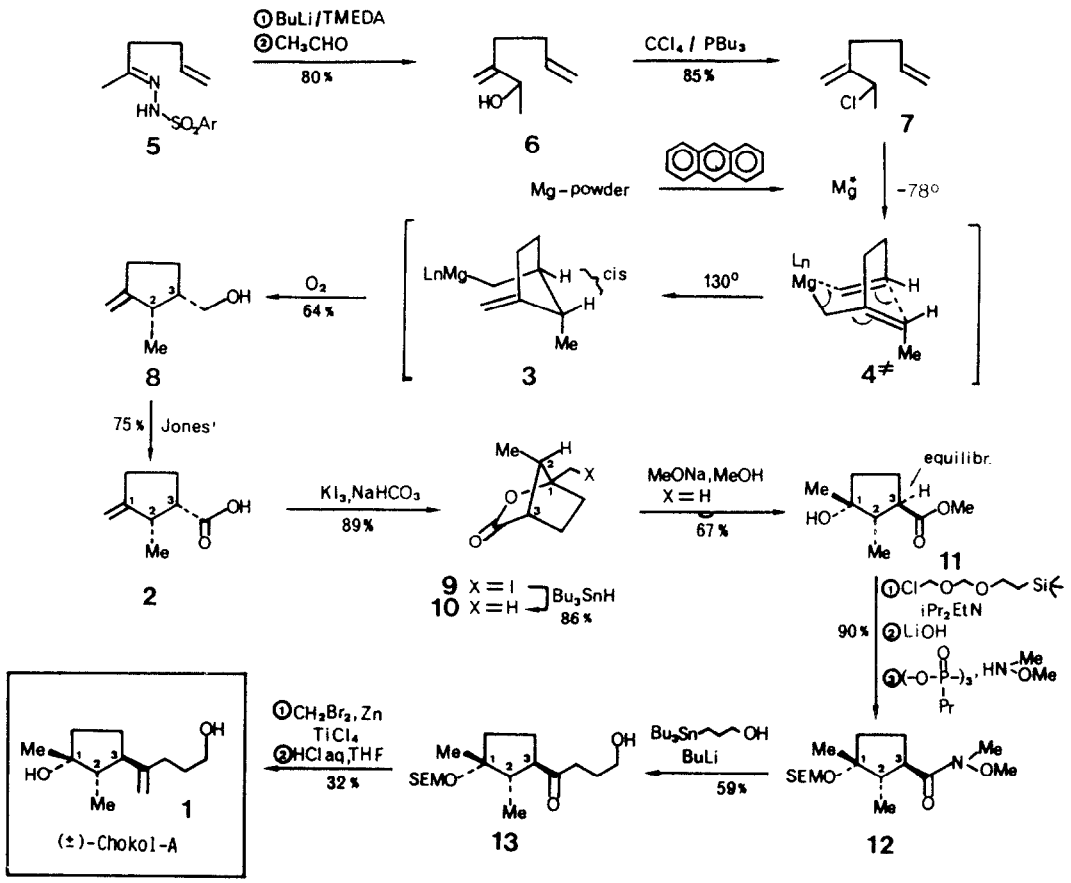
Scheme 1



Thus, on disconnective analysis (Scheme 1) we envisaged a threefold use of the carboxyl group in 2: internal delivery of the tertiary C-(1)-hydroxyl, C(3)-epimerization and serving as a handle for the pentenol side chain. The key intermediate 2 containing the required Me/COOH-*cis*-disposition should be readily accessible *via* the Mg-ene cyclization 4 → 3.

Starting from the known trisylhydrazone 5, Ar = 2,4,6-triisopropylphenyl [4] (Scheme 2) treatment with *n*BuLi (3.1 eq, hexane/TMEDA 1:1, -78° → 0°, 30 min) followed by trapping of the vinyllithium intermediate with acetaldehyde [5] (1.3eq.,0°,1h) furnished allylic alcohol 6 [6] (80% yield). Addition of nBu_3P (3eq) to a solution of 6 in CCl_4 [7] (at 0°, then r.t., 3h) furnished smoothly allylic chloride 7 [6] (85% yield).

Scheme 2



Chloride 7 was metalated at low temperature [8] with anthracene-activated magnesium [9] ;heating of the transient allylmagnesium chloride 4 to 130° and oxidation of the cyclized Grignard reagent 3 with air furnished cyclopentylmethanol 8 [6] in 64% yield from 7 [10].The high regio- and stereo-selectivity of the cyclization process 4 → 3 parallels that of the higher homologue 2-ethylidene-6-heptenylmagnesium chloride [3c] and agrees with a concerted reaction involving a (Z)-ene unit as depicted by transition state 4‡.

Unambiguous evidence for the *cis*-configuration in 8 was provided by its conversion into (±)-chokol-A as follows. Oxidation of alcohol 8 with Jones' reagent (1.4 moleq, acetone, 0°, Vibromix, 5 min) gave carboxylic acid 2 [6] (75%) which on iodolactonization ($NaHCO_3$ (6eq), I_2 (1.1eq), KI (3.4eq), H_2O, 0°, 1h) furnished cleanly iodolactone 9 [6] (86%). Reduction of iodide 9 with Bu_3SnH (1.2eq, AIBN cat., THF, reflux 16 h) yielded crystalline (pentane) lactone 10 [6] (86%, m.p. 49.5-50°). Methanolysis of 9 with NaOMe/MeOH (5 eq, reflux, 6.5h) was accompanied by the desired C(3)-epimerization to provide hydroxyester 11 [6].

For assembling the C(3)-side chain we took advantage of the clean acylation of N-methoxy-N-methylamides with organometallic reagents [11]. Protection of alcohol 11 with 2-(trimethylsilyl)ethoxymethyl chloride [12] (3eq, iPr_2NEt (6eq), THF, reflux, 15 h), ester saponification with LiOH (10eq, aq. THF,0°, 20h), carboxyl-activation/amidation [13] (propylphosphonic anhydride (3eq), N-ethylmorpholine (7eq), N,O-dimethylhydroxylamine-hydrochloride (2.2eq), DMF, r.t., 4h) gave 12 [6] (90% yield from 11). Addition of 12 to a solution of lithium 3-lithiopropoxide (1,3 eq, THF, -78° → r.t.) prepared *in situ* by transmetalation of 3-(tributylstannyl) propanol with *n*BuLi [14] (2 eq, THF, -35°, 2h) gave hydroxyketone 13 [6] in 59% yield. Finally, olefination of 13 with an excess of the methylenebromide/Zn/$TiCl_4$ (1:0.8:3) reagent [15] followed by O-deprotection (0.25 N HCl, THF/H_2O 3:1, r.t., 4 days) afforded (±)-chokol-A (32% from 13), identified by comparison (IR, ^{1}H-NMR, ^{13}C-NMR) with the natural product [2].

In summary, (±)-chokol-A has been synthesized by a non-optimized sequence of 13 steps in 3% overall yield *via* the readily accessible lactone 10. Furthermore, 10 may serve as a platform for the syntheses of other cyclopentanoid sesquiterpenes such as the chokols-B and -C [2], cyclonerodiol [16], and cyclonerotriol [17]. Accordingly, this work describes a practical preparation of allylmagnesium chlorides [10] and illustrates again the utility of intramolecular metallo-ene reactions in organic synthesis.

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10 It was advantageous to modify the published procedures [8c,9] by removing the orange Mg-anthracene complex before metalation. The following experimental procedure is representative for the conversion 7 → 8: Anthracene (250 mg, 1.4 mmol) and anhydrous, oxygen-free THF (2 ml) were added under argon to flame-dried Mg-powder (Ventron-325 mesh, 2.5g, 103 mmol). Ultrasonication of the mixture for 5 min, and after addition of further THF (75ml), for 15h (→ +60°), removal of the supernatant orange solution by means of a syringe and washing of the residue with THF gave the activated magnesium which was suspended in THF (150 ml). Chloride 7 (1.14g, 7.9 mmol) in THF (15ml) was added by means of a syringe drive over a period of 5h to the stirred Mg-suspension at -78°. Warming up to r.t., transfer of the supernatant solution into an argon-filled Carius-tube, heating at 130° for 6h, passing a stream of purified air (aq KOH, conc. H_2SO_4, anhyd. $CaSO_4$) through the solution at r.t. for 30 min, work-up and chromatography gave a 46:3:1-mixture (GC, 706 mg, 71%) of exomethylene alcohol 8 and two minor isomers. After subjecting this mixture to the reaction sequence 8 → 9 → 10 lactone 10 was readily purified by crystallization.

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