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STEREO-SELECTIVE SYNTHESIS OF *Erythro*-3-METHYL-1-HEXYN-3,4-DIOL

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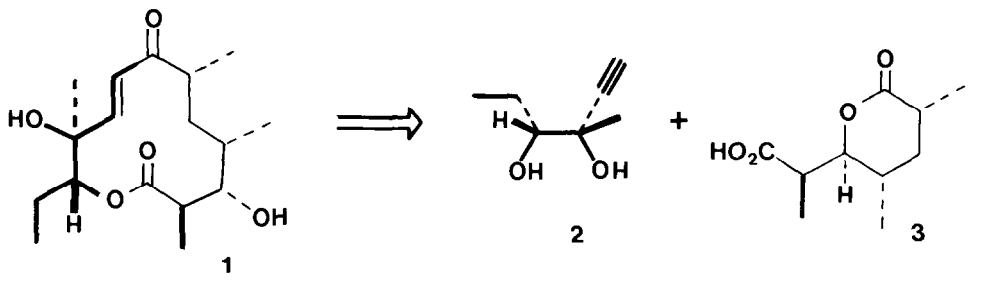
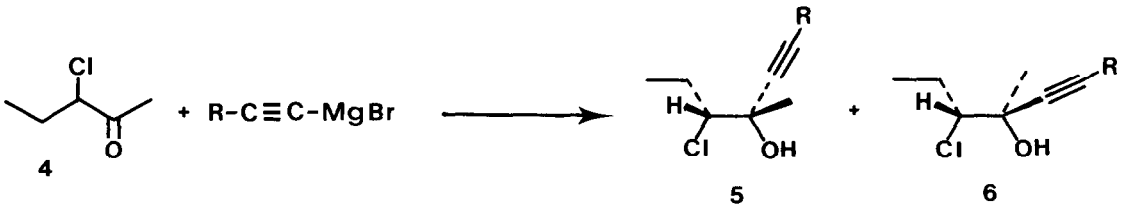
Summary *A very short stereo-selective preparation of the title compound, an intermediate of methynolide synthesis, is described*

Methynolide 1 is the aglycon of a twelve-membered ring macrolide, methymycine (1). Since the first synthesis of (±)-1 by Masamune (2), two additional synthesis have appeared (3). For most of the cases, reports of attempts at convergent synthesis are based on the obtention of the acetylenic derivative 2 and the Prelog-Djerassi lactone 3 (4) :



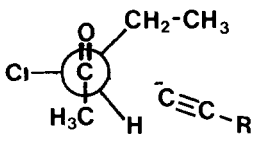
In this communication, we describe a very short stereo-selective synthesis of 2 (3a)(5).

The key step is the addition of acetylenic Grignard reagent (6) to α-chloro ketone 4 (7) (50 % yield, THF, -20 °C, 16 h). The *erythro-threo* ratio is increased using trimethylsilylethynyl Grignard reagent (8) :



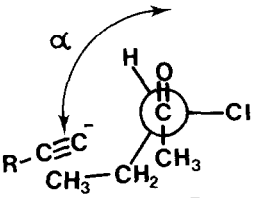
R = H	80	20
R = $Si(CH_3)_3$	94	6

According to the Felkin's model for 1,2 asymmetric induction (9), refining by the Nguyen's calculations (10), the steric hindrance encountered by the acetylenic carbanion is much more serious in B than in A. In B, as R becomes bigger, the acetylenic is pushed toxard the carbonyl, reducing the angle of attack α, and increasing the stereo-selectivity :



A

Transition state leading to the *erythro* isomer



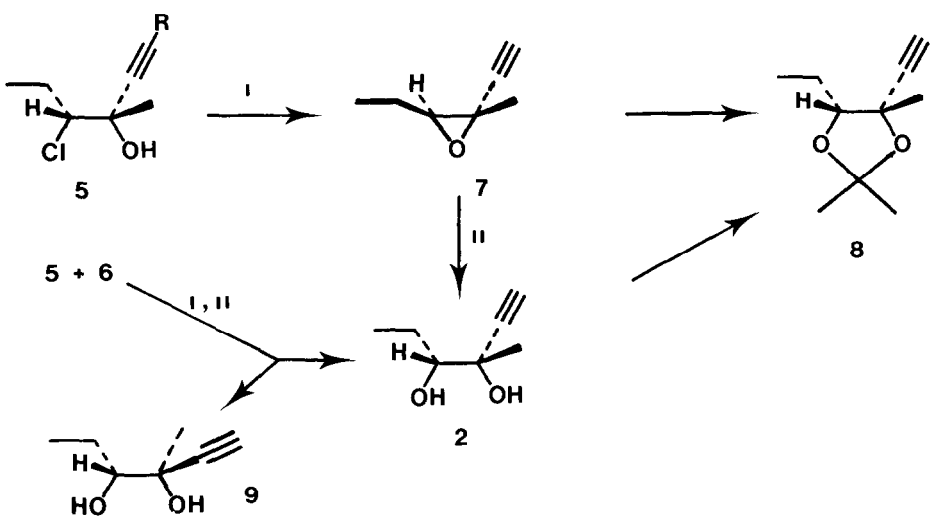
B

Transition state leading to the *threo* isomer.

Although acetylenic Grignard reagents (but not lithium acetylide) show higher selectivity than the others Grignard reagents (11), just few data are reported concerning condensation with halogeno-aldehydes (12) and alkoxy-aldehydes (13). Addition of acetylenic Grignard reagent to 3-pentanol-2-one occurs contrary to Cram's rule (5a).

After separation of chlorhydrine mixture (14), cyclisation of pure 5 in epoxyde *threo* 7 (85 %, K_2CO_3-methanol, r.t., 0.5 h, with possibly protolysis of trimethylsilyl group)(15), and hydrolysis (95 %, DMSO-H_2O (5/3), 100 °C, 16 h)(16), *erythro* diol 2 is isolated (m p. 71 °C, pentane-CCl_4)(17). The same procedure can be carried out on the product mixture 5 + 6 (R = H or $Si(CH_3)_3$) leading to 2 and 9, from which pure 2 is obtained by crystallisation (18).

Treatment of diol 2 by dimethoxypropane-acetone (with TsOH) gives acetonide 8 (92 %)(19). 8 can be obtained in quantitative yield directly from 7 (acetone, CH_2Cl_2, BF_3-2 Et_2O, r.t., 10 mn)(20) :



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8 Satisfactory analyses ans spectral data were obtained for all new compounds.

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14 Column chromatography (silice, pentane-diethylether 95-5) led to the isolation of 5 and 6.
NMR ^1H ($CDCl_3$, 250 MHz, δ ppm) : 5 R = $Si(CH_3)_3$: methine 3.77 (d.d. J = 11 and 2 Hz).
6 R = $Si(CH_3)_3$: methine 3.86 (d.d. J = 11 and 2 Hz).

15 NMR ^{1}H ($CDCl_3$, 200 MHz, δ ppm), 7 : methyl 1.50 (s.), methine 3.12 (t. J = 6.3 Hz).

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17 litt. (+)-2 m.p.: 51-51.5 °C (3b).

18 NMR ^{1}H ($CDCl_3$, 200 MHz, δ ppm) 2 : methine 3.32 (d.d. J = 10.2 and 2.5 Hz), ethynyl 2 47 (s.); methylene 1.72 (q.d.d. J = 7.5, 14.0 and 2.5 Hz, 1H); 1.52 (q.d.d. J = 7.5, 14.0 and 10.2 Hz, 1H); methyle 1.46 (s.) and 1.07 (t. J = 7.5 Hz).
9 : methine 3.52 (d.d. J = 10.2 and 2.2 Hz); ethynyl 2.49 (s.); methylene 1.79 (q.d.d. J = 7.5, 14.0 and 2.2 Hz, 1H) and 1.40 (q.d.d. J = 7.5, 14.0 and 10.2 Hz, 1H); methyle 1.44 (s.) and 1.06 (t. J = 7.5 Hz).

19 NMR ^{1}H ($CDCl_3$, 250 MHz, δ ppm) 8 : methine 3.56 (d.d. J = 8.0 and 5.0 Hz); ethynyl 2.49 (s.); methylene 1.67 (q.d.d. J = 7.5, 14.0 and 5.0 Hz, 1H), and 1.86 (q.d.d. J = 7.5, 14.0 and 8.0 Hz, 1H); methyle 1.54 (s.), 1.51 (s.), 1.36 (s.), 1.05 (t J = 7.5 Hz).

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