

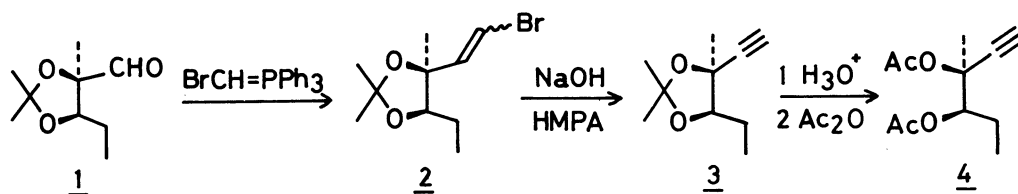
TOTAL SYNTHESIS OF METHYNOLIDE: SYNTHESIS OF TWO INTERMEDIATES,
3,4-DIACETOXY-3-METHYL-1-HEXYNE AND PRELOG-DJERASSI LACTONIC ACID

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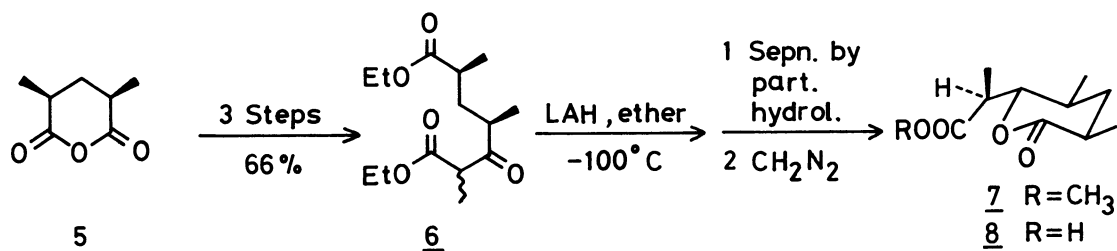
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(+)-3,4-Diacetoxy-3-methyl-1-hexyne and (+)-Prelog-Djerassi
lactonic acid were synthesized as the starting materials for the
total synthesis of methynolide.

(+)-erythro-2,3-Dihydroxy-2-methylvaleric acid¹⁾ was converted into the
isopropylidenedioxy aldehyde (1), bp 90-95°C(60 mmHg), $[\alpha]_D^{25} -9.8^\circ$ (c 0.82, EtOH),
in four steps²⁾ in 66% overall yield. Condensation of 1 with bromomethylene-
triphenylphosphorane³⁾ in ether gave a mixture of the vinyl bromides (2, 88%),
bp 88-94°C(9 mmHg), trans : cis = 53 : 47, which was dehydrobrominated to the
acetylene (3, 88%)⁴⁾, bp 88-89°C(55 mmHg), by heating at 60°C in a mixture of
aqueous sodium hydroxide and HMPA. Acid hydrolysis gave the diol, mp 51-51.5°C,
 $[\alpha]_D^{25} +41.5^\circ$ (c 2.50, EtOH), which was acetylated with acetic anhydride and 4-
dimethylaminopyridine to desired (+)-3,4-diacetoxy-3-methyl-1-hexyne (4, 96%),
bp 105-108°C(8 mmHg), $[\alpha]_D^{25} +75.7^\circ$ (c 1.85, EtOH).



The Prelog-Djerassi lactonic acid (8)⁵⁾ was conveniently prepared by LAH
reduction⁶⁾ of diethyl 2,4,6-trimethyl-3-oxoheptanedioate (6)⁷⁾ derived from
meso-2,4-dimethylglutaric anhydride (5).⁸⁾ The reduction product was a mixture
of the four isomers of 7 (R=Et), which were separated by prep. GLPC.⁹⁾ However,
as it was found that the lactone ring of 7 was most rapidly saponified among
the four isomers, 7 could be easily separated from the mixture by partial
hydrolysis.¹⁰⁾ The overall yield from 5 was ca. 11.5%. Thus, the method has
enabled the facile and rapid preparation of 8 in quantity.



Resolution of 8 with the aid of (-)-D-threo-2-amino-1-(4-methylthiophenyl)-1,3-propanediol¹¹⁾ gave the (+)-lactonic acid, mp 123-125°C, $[\alpha]_D^{25} +43.3^\circ$ (c 2.40, CHCl₃) [lit.⁵⁾ mp 124-125°C, $[\alpha]_D^{25} +33^\circ$ (c 0.797, CHCl₃)]. The (+)-methyl ester (9), mp 94-95°C, $[\alpha]_D^{25} +41.8^\circ$ (c 1.82, MeOH) [lit.⁵⁾ mp 75.5-76.5°C, $[\alpha]_D^{25} +42^\circ$ (c 3.29, MeOH)].

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References and Notes

- 1) L. D. Bergel'son, E. V. Dyatlovitskaya, M. Tichy, and V. V. Voronkova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1612 (1962).
- 2) J. Inanaga, A. Takeda, N. Okukado, and M. Yamaguchi, *Mem. Fac. Sci., Kyushu Univ., Ser. C, Chem.*, 9, 293 (1975).
- 3) G. Kobrich, H. Trapp, K. Flory, and W. Drischel, *Chem. Ber.*, 99, 689 (1966).
- 4) The DL-form of the compound has been prepared by a different route. L. D. Bergel'son, S. G. Batrakov, and A. N. Grigoryan, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1617 (1962).
- 5) C. Djerassi and J. A. Zderic, *J. Am. Chem. Soc.*, 78, 2907, 6390 (1956); R. Anliker, D. Dvornik, K. Gubler, H. Heusser, and V. Prelog, *Helv. Chim. Acta*, 39, 1785 (1956). Three different Syntheses of 8 have so far been reported. [S. Masamune, C. U. Kim, K. E. Wilson, G. O. Spessard, P. E. Georgiou, and G. S. Bates, *J. Am. Chem. Soc.*, 97, 3512 (1975); J. D. White and Y. Fukuyama, *ibid.*, 101, 226 (1979); G. Stork and V. Nair, *ibid.*, 101, 1315 (1979)]. They are stereocontrolled but require fairly long synthetic sequences.
- 6) Reduction of 6 was previously studied by Bergel'son et al. (ref. 7), but they did not give enough evidence on the isolation of 8.
- 7) L. D. Bergel'son and S. G. Batrakov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1259 (1963).
- 8) The meso-anhydride was prepared by the known method [P. F. Wiley, K. Gerzon, H. E. Flynn, M. V. Sigal, Jr., O. Weaver, U. C. Quarck, R. R. Chanvette, and R. Monahan, *J. Am. Chem. Soc.*, 79, 6062 (1957)]. The dl-fraction obtained in a considerable amount in the preparation was reconverted into an equilibrium mixture (meso : dl = 3 : 1) by heating at 160°C for one hour.
- 9) On the isolation and the relative configurations of all the eight lactones of 3-hydroxy-2,4,6-trimethylheptanedioic acid, derived from meso- and dl-2,4-dimethylglutaric anhydrides: A. Nakano, K. Inoue, M. Aiga, N. Okukado, and M. Yamaguchi, in preparation.
- 10) The experimental procedure is summarized as follows. Ethereal LAH (1%, 33 ml) was added to a stirred solution of 6 (5 g) in ether (100 ml) at -100°C in 2-3 min, and after 5 min the reaction mixture was quenched with ethanol (3 ml) and worked up in a usual manner. The product was then stirred with aqueous ethanolic NaOH [303 mg, 1 equiv. to the estimated amount (GLPC) of 7 (R=Et)]. The partially hydrolysed fraction was separated, totally hydrolysed with excess NaOH, lactonized with acid, and methylated by diazomethane to give a mixture of 7 (ca. 66%) and its 2-epimer, from which 7 crystallized out. Mp 73-74°C (hexane-benzene), 0.629 g, 16% from 6.
- 11) R. A. Cutler, R. J. Stenger, and C. M. Suter, *J. Am. Chem. Soc.*, 74, 5475 (1952).

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