Novel Synthesis of (−)-Malyngolide using Reactions of Alkylidene Carbenes

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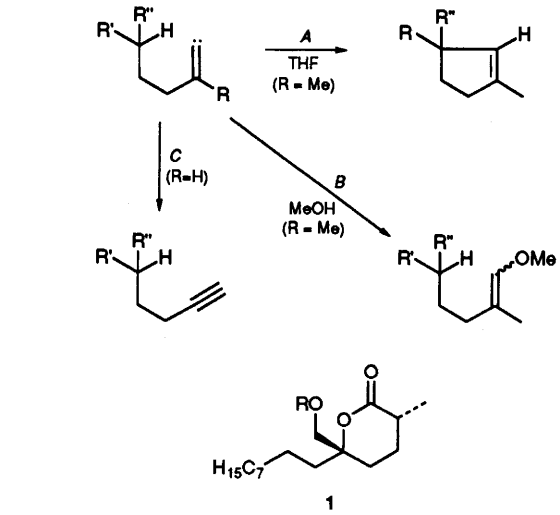
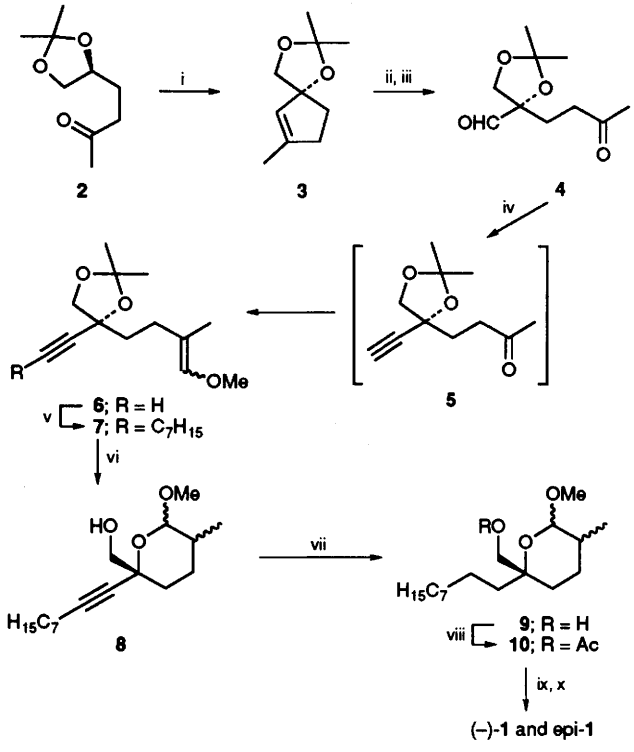
(−)-Malyngolide has been synthesized using three different reactions of alkylidene carbenes, generated by alkenation of carbonyl compounds with dimethyl diazomethylphosphonate.

The interest in carbenoids as useful intermediates for organic synthesis has recently grown a great deal.[1,2] In contrast to many kinds of 'carbenoids', free alkylidene 'carbenes' have not been as widely accepted as valuable species for the synthesis of natural products, although their generation by various methods and attractive reactions have been reported.[3,4] Typical reactions of alkylidene carbenes are: intramolecular C–H insertion that leads to cyclopentene formation (reaction *A* in Scheme 1); intermolecular O–H insertion with an alcohol that gives an enol ether (reaction *B*); and Fritsh–Buttenberg–Wiechell rearrangement that produces a terminal alkyne (reaction *C*). Reported here is a chiral synthesis of (−)-malyngolide **1**,[5] an antibiotic from a blue–green alga,[6] using all three of these reactions.

The cyclopentene **3** was prepared through intermolecular C–H insertion of the alkylidene carbene, which was generated



Scheme 1



Scheme 2 *Reagents and conditions*: i, $(MeO)_2P(O)CHN_2$, Bu^{t}OK, THF, −78 °C, 15 h (68%), or Me_3SiCHN_2, BuLi, THF, −78–0 °C, 1.5 h (72%); ii, cat. OsO_4, *N*-methylmorpholine *N*-oxide, THF, H_2O, room temp. (68%); iii, $NaIO_4$, SiO_2, CH_2Cl_2, room temp., 3 h (93%); iv, $(MeO)_2P(O)CHN_2$ (5 equiv.), K_2CO_3 (5 equiv.), MeOH, room temp., 20 h (46%); v, BuLi, $C_7H_{15}Br$, hexamethylphosphoramide, THF, room temp., 3 h (88%); vi, $HClO_4$, MeOH, room temp., 0.5 h (78%); vii, H_2, PtO_2, EtOH (92%); viii, Ac_2O, pyridine, dimethylaminopyridine, CH_2Cl_2 (84%); ix, Jones oxidation (73%); x, KOH, dioxane, then 6 mol dm^{-3} HCl (73%)

in tetrahydrofuran (THF) with dimethyl diazomethylphosphonate (DAMP),[7] *tert*-butoxide and the ketone **2** that was derived from D-mannitol.[8] For the large-scale preparation of **3**, lithiotrimethylsilyldiazomethane was found to be a more convenient reagent.[9] After cleavage of the double bond,[10] the resulting keto-aldehyde **4** was treated with DAMP and potassium carbonate in methanol. Reaction of the reagents and the aldehyde proceeded rapidly, providing the alkyne **5** *via* rearrangement of the terminal alkylidene carbene. In the same vessel, the keto-group of **5** slowly reacted with the reagents at room temperature, and the carbene intermediate underwent the O–H insertion with the solvent. The result was that enol ether **6** was obtained as a diastereoisomeric mixture in 46% yield from keto-aldehyde **4**, accompanied by 15% yield of the ketone **5**. Alkylation of the alkyne **6** with 1-bromoheptane gave the compound **7** that includes all carbons of the target molecule. Methanolysis of the acetonide and enol ether with catalytic amount of perchloric acid furnished the cyclic acetal **8** as a mixture of stereoisomers. The triple bond in this compound was easily hydrogenated over platinum oxide. Oxidation of the saturated compound **9** with ceric ammonium nitrate and sodium bromate in wet acetonitrile[11] gave the final compounds (**1** and its epimer), however, the yield (less than 10%) was not satisfactory. Therefore, another route to **1** was explored.

After protection of the primary alcohol as an acetate **10**, Jones oxidation gave the lactone acetate, which was hydrolysed with (aq.) sodium hydroxide. Acidification with 6 mol dm^{-3} hydrochloric acid induced relactonization giving a 1 : 1 ratio of (−)-malyngolide **1**, $[\alpha]_D^{22}$ −12.5 (*c* 1.08, $CHCl_3$), lit.,[6] $[\alpha]_D$ −13 and its epimer, $[\alpha]_D^{22}$ + 19.4 (*c* 1.42, $CHCl_3$), lit.,[12] $[\alpha]_D$ + 19.1. The epimer is known to be convertible to **1**.[12] Spectral and physical properties of the synthetic malyngolide were identical with those reported in the literature.[5,6]

Received, 25th May 1993; Com. 3/02986G

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