A Synthesis of the (+)-Prelog–Djerassi Lactone

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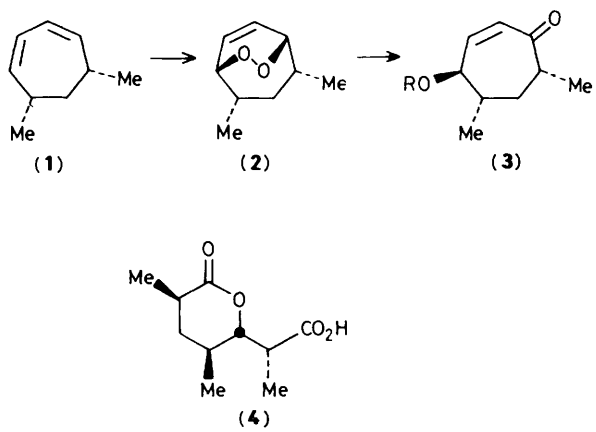
cis-5,7-Dimethylcyclohepta-1,3-diene, which is readily available using organoiron chemistry, was converted to all *cis*-3,7-diacetoxy-4,6-dimethylcycloheptene (**5**), which was subjected to asymmetric enzymatic hydrolysis to give hydroxy acetate (**6**), and this compound was converted in four steps to the (+)-Prelog–Djerassi lactone having high optical purity.

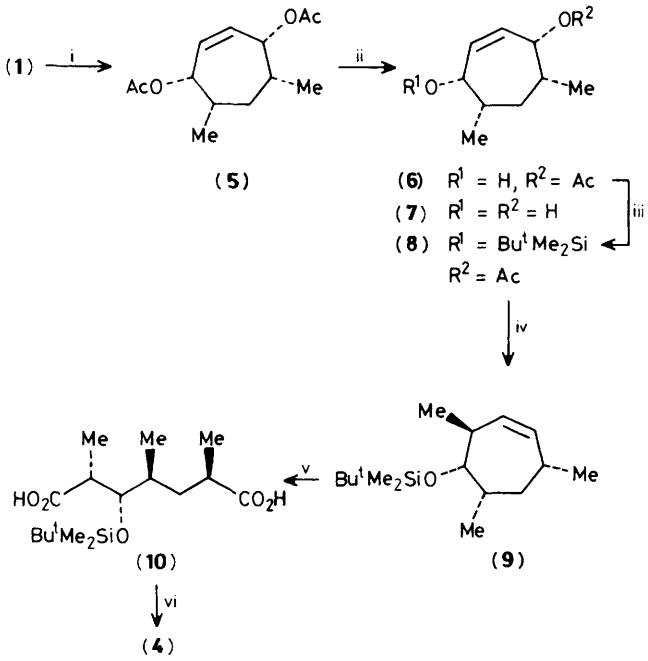
Earlier we described a stereocontrolled synthesis of *cis*-5,7-dimethylcyclohepta-1,3-diene (**1**) using organoiron chemistry,[1] and its conversion *via* the endoperoxide (**2**) to cycloheptenone derivatives (**3**).[2] Compound (**3**) has the correct relative stereochemistry of the methyl substituents for conversion to the Prelog–Djerassi lactone (**4**), a popular contemporary synthetic target,[3] but the 4-hydroxy-derived substituent requires stereochemical inversion. We therefore sought a more direct approach to (**4**), and this communication describes a simple route from (**1**) to the (+)-Prelog–Djerassi lactone having high optical purity.

Diacetoxylation of (**1**) (Scheme 1) using a modification of Bäckvall's procedure[4] led to a single product (**5**) in 63% yield,† stereochemical assignment of which is based on comparison of n.m.r. spectral data with that of the stereoisomeric diacetate[2b] derived from (**2**). Hydrolysis of (**5**) using lipase enzyme[2b,5] gave the hydroxy acetate (**6**), $[\alpha]_D$ +78.7° (*c* 6, CH_2Cl_2), in 48% yield, accompanied by recovered (**5**) (35%) and the corresponding diol (**7**) (15%), both of which could be recycled. The optical purity of (**6**) was judged to be at least 98% enantiomeric excess (e.e.) by ^1H n.m.r. of the derived (*R*)-MTPA ester,‡ and the absolute stereochemistry as shown was assigned by Mosher's method.[6] This stereochemistry is as expected by comparison with lipase-catalysed hydrolysis of 3,5-diacetoxycyclopentene[5c] and the isomeric cycloheptene derivatives reported by us earlier.[2b]



† All new compounds were characterized by 200 MHz ^1H n.m.r. and i.r. spectroscopy, and mass spectrometry and/or combustion analyses.

‡ MTPA = α-Methoxy-α-(trifluoromethyl)phenyl acetic acid.



Scheme 1. *Reagents and conditions*: i, $Pd(OAc)_2$ (11 mol %), $LiOAc{\cdot}2H_2O$ (7 equiv.), 1,4-benzoquinone (2 equiv.), AcOH, room temp., 48 h; ii, lipase, aqueous phosphate buffer, pH 7.5, room temp., 30 h; iii, Bu^tMe_2SiCl, Pr^i_2NEt, dimethylformamide; iv, Me_2CuLi (2 equiv.), Et_2O, 0 °C, 2 h; v, RuO_2 (34 mol %), $NaIO_4$ (2.0 equiv. in 3 portions), 1:1 acetone–H_2O, room temp., 10 h; vi, aq. HCl, tetrahydrofuran, 50 °C.

The intermediate (**6**) was protected as its t-butyldimethylsilyl ether (**8**), $[\alpha]_D$ +2.7° (*c* 3, CH_2Cl_2), which was treated with dimethylcopper lithium to give (**9**), $[\alpha]_D$ +32.8° (*c* 1, CH_2Cl_2) in 77% yield. Oxidative ring cleavage of (**9**) (RuO_2, $NaIO_4$) afforded the diacid (**10**) in 73% yield, which was contaminated by small amounts of the lactone (**4**). This crude material was treated with acid to generate the (+)-Prelog–Djerassi lactone in 91% yield, m.p. 125—127 °C, $[\alpha]_D$ +32° (*c* 1, $CHCl_3$) {lit.: m.p. 124—125 °C, $[\alpha]_D$ +33° (*c* 0.797, $CHCl_3$);[7] m.p. 125—127 °C, $[\alpha]_D$ +38° (solution conditions not given)[8]}. This compound showed spectroscopic data consistent with that reported in the literature.[9]

In conclusion, the use of organoiron chemistry to produce stereospecifically substituted cycloheptadienes, coupled with further diene functionalization, offers attractive methodology for the asymmetric synthesis of key subunits of important macrolide antibiotics.

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