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

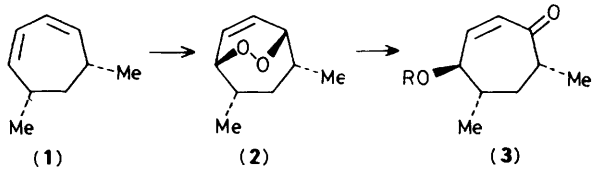
Anthony J. Pearson* and Yen-Shi Lai

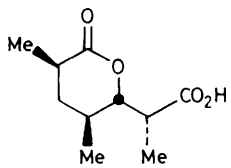
Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106, U.S.A.

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.

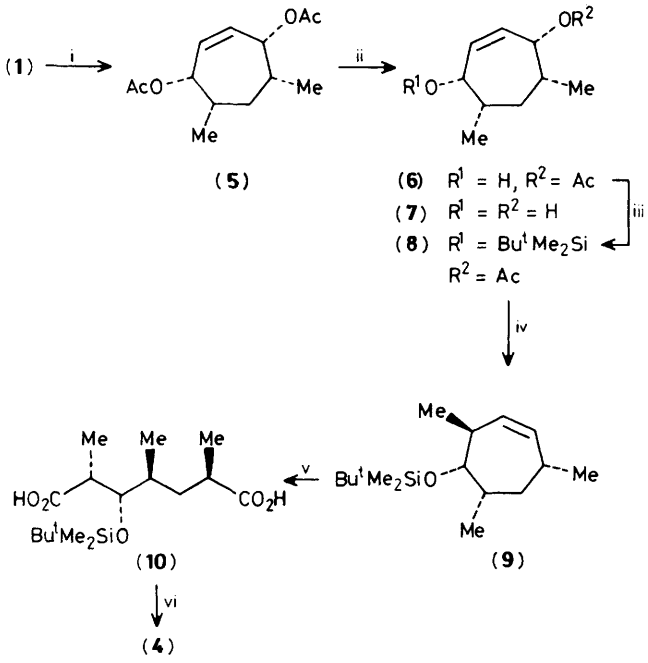
Diacetoxylation of (**1**) (Scheme 1) using a modification of Bäckvall's procedure[4] led to a single product (**5**) in 63% yield,† stereochemical assignment of which is based on comparison of n.m.r. spectral data with that of the stereoisomeric diacetate[2b] derived from (**2**). Hydrolysis of (**5**) 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.

We are grateful to the United States Public Health Service, National Institutes of Health for financial support of this program.

Received, 24th November 1987; Com. 1714

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