

Chiral Synthesis of a Useful Intermediate for (+)-Isocarbacyclin

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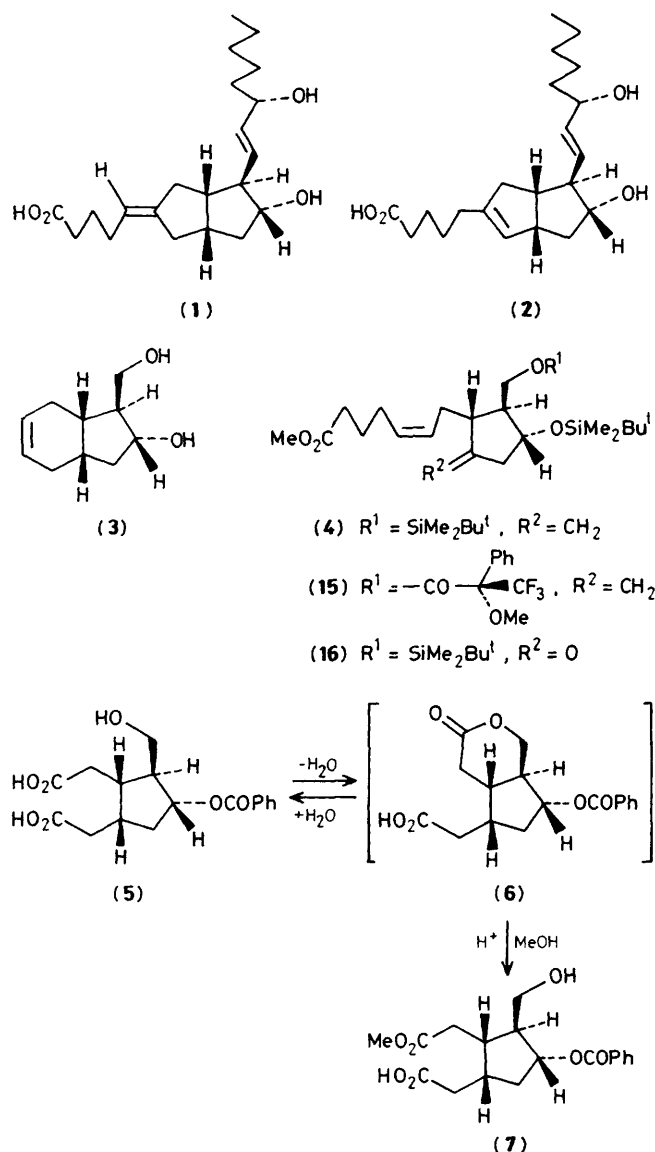
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A useful intermediate (–)-(4) for (+)-isocarbacyclin (2) has been efficiently synthesised *via* extremely regio-controlled mono-esterification of the dicarboxylic compound (5) starting from optically active diol (3).

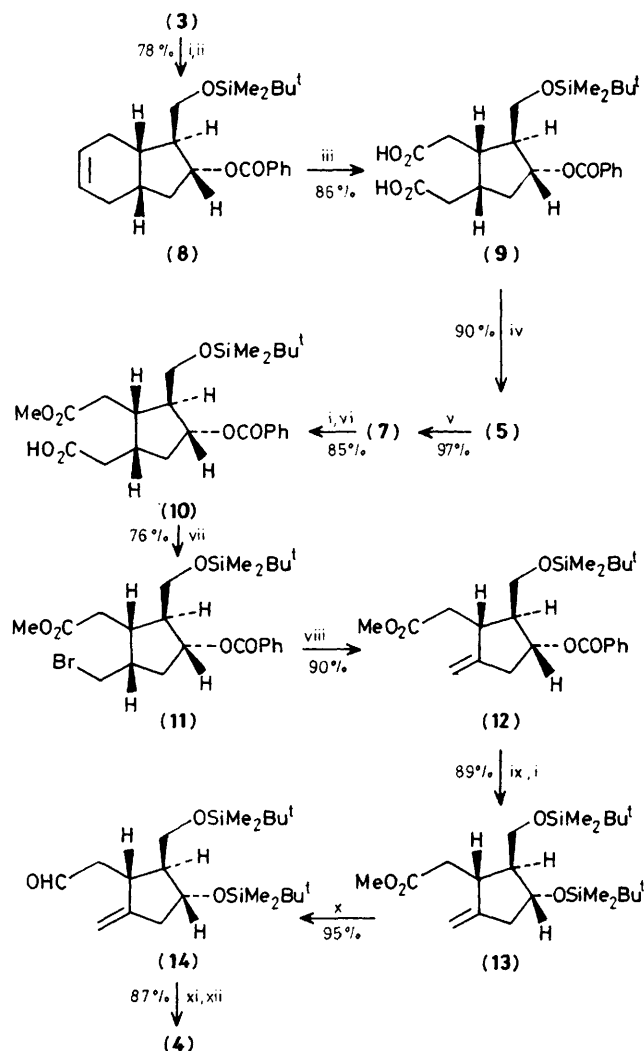
In the preceding communication, we described a chiral synthesis of (+)-carbacyclin (1) utilising our new chiral induction method,¹ in which the optically active diol (3) {m.p. 60.5–62 °C, $[\alpha]_D^{22} -0.5^\circ$ (*c* 1.48, CHCl₃), >98% enantiomeric excess (e.e.)} derived from a prochiral α -symmetric compound, *cis*-cyclohex-4-ene-1,2-bis(acetic acid), was employed.¹ Recently, Shibasaki and Ogawa reported a total synthesis of (+)-isocarbacyclin (2) *via* an intermediate (4) starting from an optically active Corey lactone.²

We have designed a new chiral synthesis of the intermediate (–)-(4) based on an extremely regioselective mono-esterification of the two carboxy groups of (5), which should be readily

available from (3). We anticipated that compound (5) could be lactonised *in situ* between one of the carboxy groups and the primary hydroxy group, under acidic conditions giving the fairly strained lactone (6).† The lactone carbonyl of (6) should



Scheme 1



Scheme 2. Reagents and conditions: i, Bu^tMe₂SiCl, imidazole, dimethylformamide (DMF); ii, PhCOCl, pyridine; iii, NaIO₄, KMnO₄, Na₂CO₃, dioxane–water (2.3:1); iv, AcOH–water (3:1); v, TsOH, MeOH, CH₂Cl₂; vi, Na₂CO₃, MeOH–THF–water (3:1.5:1); vii, HgO, Br₂, CCl₄, 88 °C; viii, DBU, toluene, 50 °C; ix, MeONa, MeOH; x, DIBALH, toluene, –70 → –65 °C; xi, HO₂C[CH₂]₄PPh₃Br, Bu^tOK, THF; xii, CH₂N₂, Et₂O.

† In fact, lactone (6) (28% yield) was obtained by treating the dicarboxylic compound (5) with a catalytic amount of TsOH in CH₂Cl₂ at room temperature. Treatment of compound (6) with a small excess of MeOH in the presence of a catalytic amount of TsOH in CH₂Cl₂ gave the desired monomethyl ester (7) (92% yield).

be readily attacked by methanol to give the monomethyl ester (7) (Scheme 1).†

The dicarboxylic acid (5) was prepared as follows. Diol (3) was subjected to silylation (82% yield) followed by benzoylation (95% yield) to give the selectively protected compound (8). Lemieux–Rudloff oxidation [NaIO_4 (5.3 equiv.), KMnO_4 (0.2 equiv.), and Na_2CO_3 (0.5 equiv.)]³ of (8) gave dicarboxylic acid (9) (86% yield) which was treated with aqueous acetic acid to afford (5) in 90% yield (Scheme 2).

Compound (5) was stirred at room temperature in the presence of a catalytic amount of toluene-*p*-sulphonic acid (TsOH) (0.05 equiv.) and MeOH (3 equiv.) in CH_2Cl_2 to afford exclusively the monomethyl ester (7) in 97% yield as expected. Compound (7), after protection with $\text{Bu}^t\text{Me}_2\text{SiCl}$ to give (10) (85% yield), was treated with yellow mercury(II) oxide (0.6 equiv.) in CCl_4 under azeotropic conditions (bath temp. 88°C) followed by bromination with a CCl_4 solution of Br_2 (1.1 equiv.) to afford bromide (11) (76% yield).⁴ Dehydrobromination of (11) with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) (10 equiv.) in toluene at 50°C gave the unsaturated compound (12) (90% yield) which was methanolysed and then silylated to yield the disilylated compound (13) (89% yield). Compound (13), after reduction with di-isobutylaluminium hydride (DIBAH) (1.1 equiv.) in

toluene to aldehyde (14) (95% yield), was converted into the desired bis-alkene (4) {87% yield from (14), $[\alpha]_{\text{D}}^{20} -40.3^\circ$ (*c* 1.12, CH_3OH)} via Wittig reaction with (4-carboxybutyl)-triphenylphosphonium bromide (5.6 equiv.) in the presence of Bu^tOK (10.5 equiv.) followed by methylation with CH_3N_2 . All physical data of compound (4) proved to be identical with those of an authentic sample.² The enantiomeric purity of (4) was shown to be $>98\%$ by ^1H n.m.r. (400 MHz) analysis of its methoxy(trifluoromethyl)phenylacetyl (MTPA) derivative (15). Compounds (4) and (13) should be useful in the synthesis of the precursor (16) for various prostaglandins.

We thank Dr. Shibasaki (Sagami Chemical Research Center) for providing physical data for compound (4).

Received, 28th August 1986; Com. 1237

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