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

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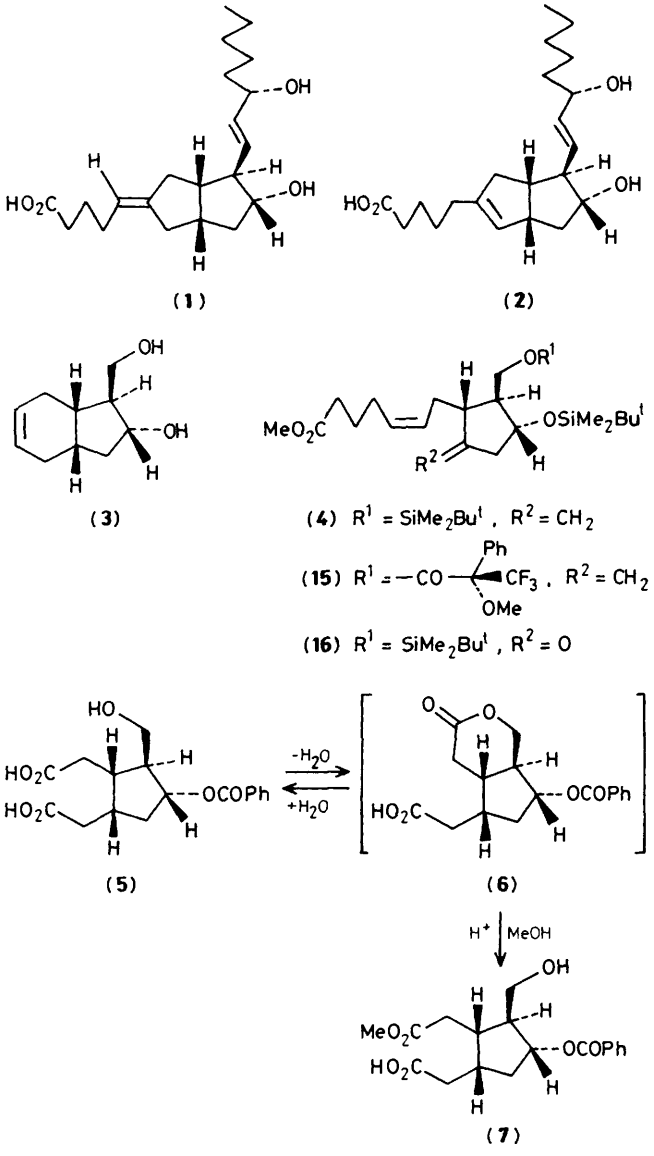
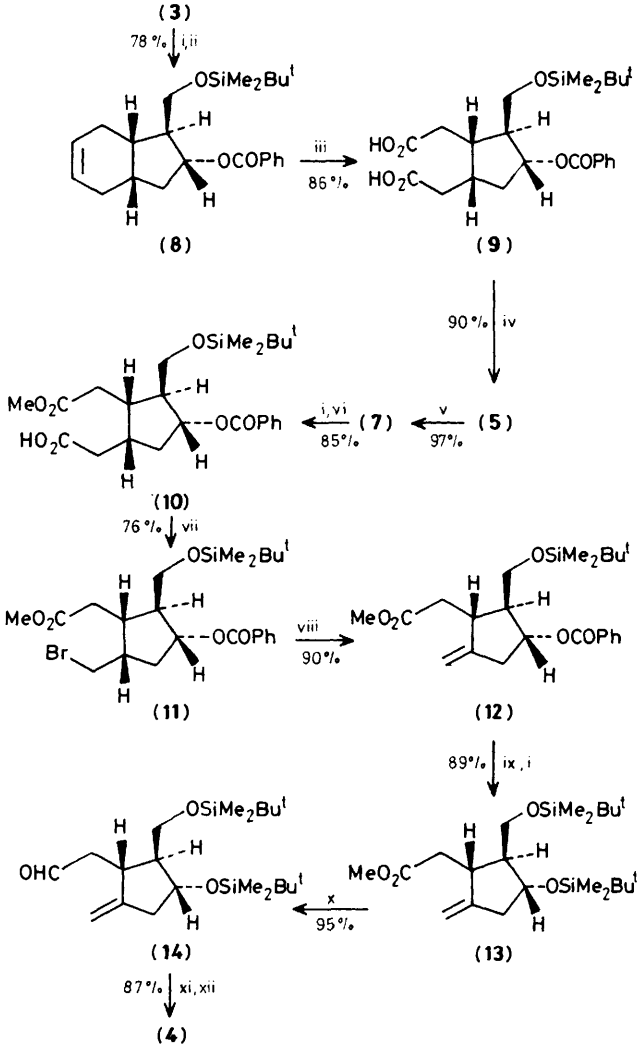
A useful intermediate (−)-(**4**) for (+)-isocarbacyclin (**2**) has been efficiently synthesised *via* extremely regio-controlled mono-esterification of the dicarboxylic compound (**5**) starting from optically active diol (**3**).

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° (*c* 1.48, $CHCl_3$), >98% enantiomeric excess (e.e.)} derived from a prochiral σ-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^tMe_2SiCl, imidazole, dimethylformamide (DMF); ii, PhCOCl, pyridine; iii, $NaIO_4$, $KMnO_4$, Na_2CO_3, dioxane–water (2.3 : 1); iv, AcOH–water (3 : 1); v, TsOH, MeOH, CH_2Cl_2; vi, Na_2CO_3, MeOH–THF–water (3 : 1.5 : 1); vii, HgO, Br_2, CCl_4, 88 °C; viii, DBU, toluene, 50 °C; ix, MeONa, MeOH; x, DIBAH, toluene, −70 → −65 °C; xi, $HO_2C[CH_2]_4PPh_3Br$, Bu^tOK, THF; xii, CH_2N_2, Et_2O.

† In fact, lactone (**6**) (28% yield) was obtained by treating the dicarboxylic compound (**5**) with a catalytic amount of TsOH in CH_2Cl_2 at room temperature. Treatment of compound (**6**) with a small excess of MeOH in the presence of a catalytic amount of TsOH in CH_2Cl_2 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 Bu^tMe_2SiCl 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**), $[\alpha]_D^{20}$ −40.3° (*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_2N_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.

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References

1 Y. Nagao, T. Nakamura, M. Ochiai, K. Fuji, and E. Fujita, *J. Chem. Soc., Chem. Commun.*, 1986, preceding communication.
2 Y. Ogawa and M. Shibasaki, *Tetrahedron Lett.*, 1984, **25**, 1067.
3 R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, 1955, **33**, 1701.
4 (a) N. J. Bunce, *J. Org. Chem.*, 1972, **37**, 664; (b) J. Cason and D. M. Walba, *ibid.*, 1972, **37**, 669.