Synthesis of (+)-Carbacyclin based on a New Chiral Induction Procedure

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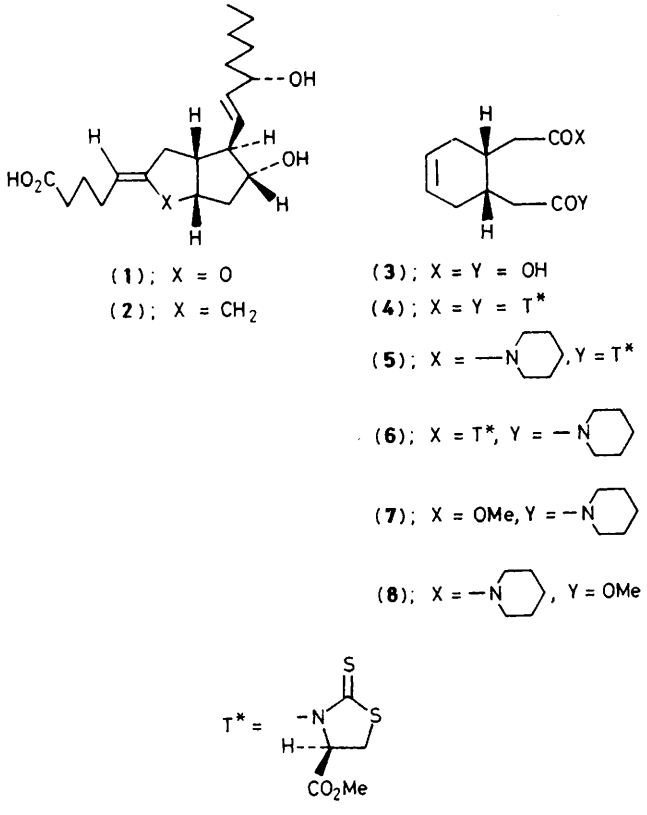
The chiral bicyclic β-keto ester (**14**), which is synthesised by our methods involving stereoselective differentiation between two identical groups in the diamide (**4**) of (*R*)-4-methoxycarbonyl-1,3-thiazolidine-2-thione and regiocontrolled Dieckmann-type cyclisation of half-thiol diester (**11**), has been successfully converted into (+)-carbacyclin (**2**).

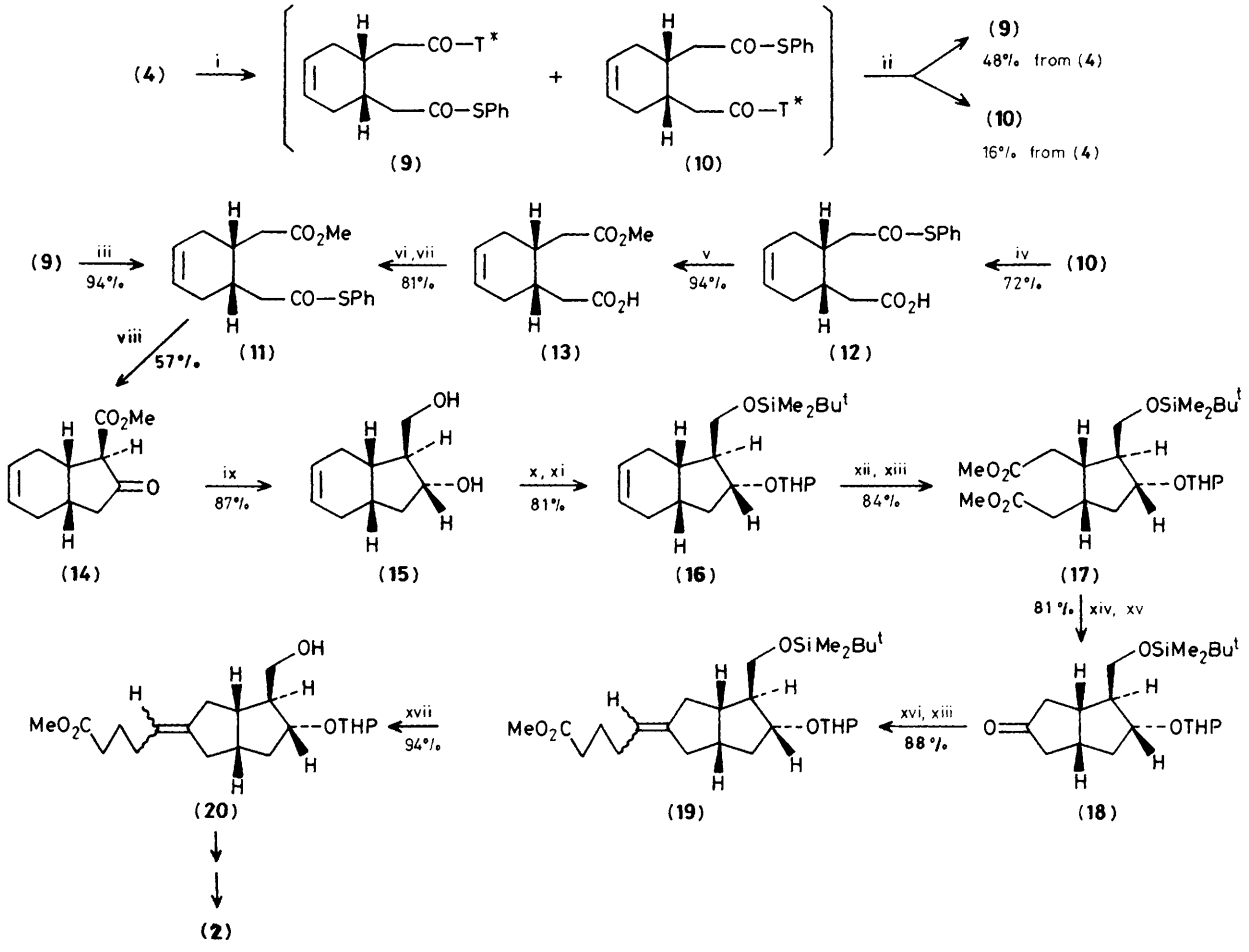
It is well known that naturally occurring prostacyclin (PGI_2) (**1**) exhibits powerful inhibition of platelet aggregation but is chemically labile.[1] (+)-Carbacyclin (carba-PGI_2) (**2**) is a stable analogue having a physiological activity similar to that of (**1**) and thus is a potential therapeutic agent.[2] Since its discovery, a number of synthetic methods for (**2**) have been reported,[2] and the optically active Corey lactone and its analogues have been used. Here we describe a new chiral synthesis of (+)-carbacyclin (**2**) utilising our chiral induction procedure shown in Scheme 1.

Recently, we reported a novel method of chiral induction into *cis*-cyclohex-4-ene-1,2-bis(acetic acid) (**3**) *via* a highly diastereoselective aminolysis of the diamide (**4**) of (*R*)-4-methoxycarbonyl-1,3-thiazolidine-2-thione [(*R*)-4-MCTT] with piperidine (1 equiv.).[3] Although piperidine amides (**5**) and (**6**) were obtained in a ratio of 94 : 6, we examined similar differentiation reactions between two identical groups in (*R*)-4-MCTT diamide (**4**) by using various nucleophiles [PhSLi, PhSNa, PhSH–1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), PhSH–Et_3N, Bu^{t}SLi, PhOLi, MeOH–Lewis acids] in anticipation of the difficulty of removal of the piperidyl group in (**5**). Thus, diastereoselective differentiation of the two (*R*)-4-MCTT groups in (**4**) was observed over the range of ratios 54 : 46 to 80 : 20. In view of the diastereoselectivity, yield, and chromatographic separation of the two diastereoisomeric products, we adopted the thiolysis of (**4**) with PhSH (1.1 equiv.) in the presence of Et_3N (1.1 equiv.) in CH_2Cl_2 at 0 °C in the synthesis of (**2**). A mixture of the resulting products [(**9**) : (**10**) 76 : 24 (h.p.l.c. analysis[3])] was separated on a silica gel column to give each pure compound (**9**) [> 99% diastereoisomeric excess (d.e.) (h.p.l.c. analysis), 48% yield from (**4**)] and (**10**) [16% yield from (**4**)] respectively. The major product (**9**) was converted into the half-thiol diester (**11**) {94% yield, $[\alpha]_D^{25}$ −3.8° (*c* 1.0, $CHCl_3$)} by selective methanolysis with MeONa. The minor product (**10**) was subjected to the latent enantioconvergent procedure [(**10**) → (**12**) → (**13**) → (**11**)] (yields 72, 94, and 81%, respectively) by utilising the σ-symmetry of the molecule (**3**) which is a precursor of (**10**).[4] The absolute configuration of (**11**) was determined by its chemical conversion into compound (**7**) {$[\alpha]_D^{20}$ −12.8° (*c* 1.0, $CHCl_3$)}, the antipode of the piperidine amide (**8**), {$[\alpha]_D^{20}$ +12.5° (*c* 0.41, $CHCl_3$)} derived from the known compound (**5**).[3] Compound (**11**) was subjected to an elaborate Dieckmann-type cyclisation in the presence of lithium di-isopropylamide (LDA) (2.5 equiv.) and hexamethylphosphoramide (HMPA) (1 equiv.) in tetrahydrofuran (THF) at −55 °C to afford the desired β-keto ester (**14**) {57% yield, m.p. 60.5—61 °C, $[\alpha]_D^{23}$ −160.9° (*c* 0.21, $CHCl_3$), >98% enantiomeric excess (e.e.), 400 MHz ^{1}H n.m.r. analysis in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(hfc)$_3$]} together with the starting compound (**11**) (13% recovery).† Compound (**14**), after reduction with $LiAlH_4$ (1.2 equiv.) to diol (**15**)‡ (87%), was selectively converted into doubly protected diol (**16**) [81% from (**15**)] by treatment with Bu^{t}Me$_2$SiCl and then with dihydropyran. Compound (**16**) was subjected to Lemieux–Rudloff oxidation [$NaIO_4$ (5 equiv.), $KMnO_4$ (0.2 equiv.), and Na_2CO_3 (0.5 equiv.)][5] followed by esterification with CH_2N_2 to give dimethyl diester (**17**) (84%). Diester (**17**) was treated with dimsylsodium [NaH, dimethyl sulphoxide (DMSO)] (2 M) to give a mixture of β-keto ester isomers, which was heated at 175 °C for 7 min in HMPA–water (20 : 1) to afford bicyclic pentanone (**18**) in good (81%) yield. Wittig reaction of (**18**) with (4-carboxybutyl)triphenylphosphonium bromide (2.9 equiv.) in the presence of dimsylsodium gave a mixture of unsaturated



† On treatment with dimsylsodium or dimsylpotassium at 15—18 °C, half-thiol ester (**11**) was converted into the antipodal compound (10—24% e.e.) of (−)-(**14**).

‡ Total yields of other diastereoisomeric diols were shown to be less than 5%. Compound (**15**): m.p. 60.5—62 °C (from Et_2O–hexane); ^{1}H n.m.r. ($CDCl_3$, 100 MHz) δ 1.05—2.66 (m, 9H), 2.78 (br s, 2H, 2 × OH), 3.58 (dd, 1H, *J* 7.7 and 10.6 Hz, $-H_aCH_b$–OH), 3.85 (dd, 1H, *J* 4.0 and 10.6 Hz, $-H_aCH_b$–OH), 4.08 (dd, 1H, *J* 6.9 and 12.3 Hz, C*H*–OH), and 5.77 (br s, 2H, olefinic).



Scheme 1. *Reagents and* conditions: i, PhSH, Et_3N, CH_2Cl_2, 0 °C; ii, silica gel column, hexane–THF (3 : 1); iii, MeONa–MeOH, THF, −78 °C; iv, 10% HCl–dioxane (1 : 6), 60 °C; v, MeONa–MeOH, THF, −60 → 10 °C; vi, dicyclohexylcarbodiimide–hydroxybenzotriazole, THF; vii, PhSH, Et_3N; viii, LDA, HMPA–THF, −55 °C; ix, $LiAlH_4$, THF, −78 °C → room temp.; x, Bu^tMe_2SiCl, imidazole, dimethylformamide (DMF); xi, dihydropyran, pyridinium toluene-*p*-sulphonate, CH_2Cl_2; xii, $NaIO_4$, $KMnO_4$, Na_2CO_3, dioxane–water (2.2 : 1); xiii, CH_2N_2, Et_2O; xiv, NaH, DMSO; xv, HMPA–water (20 : 1), 175 °C; xvi, $HO_2C(CH_2)_4PPh_3Br$, NaH, DMSO, 45 °C; xvii, Bu^n_4NF, THF. THP = tetrahydropyran-2-yl.

products (**19**)§ in excellent (88%) yield. Selective deprotection of the Bu^tMe_2Si group of (**19**) furnished alcohol (**20**) (94%), whose conversion into (+)-carbacyclin (**2**) was achieved by the known procedure developed by the Ono research group. All physical data of the synthesised compound (**2**) {m.p. 62.5—64 °C (diethyl ether–hexane), $[\alpha]_D^{21}$ +90.9° (*c* 0.19, MeOH)} were identical with those of the authentic sample.[2d,i]

We thank Dr. Y. Arai (Ono Pharm. Co. Ltd.) for the gift of authentic (+)-carbacyclin.

Received, 28th August 1986; Com. 1235

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§ The ratio between the (*E*)- and (*Z*)-forms of (**19**) was estimated to be *ca.* 58 : 42 based on the isolation yield of each pure geometrical isomer from a mixture of 15-oxo-carbacyclin methyl ester and its (*Z*)-isomer which was derived from (**19**).