Cyclopentenone Derivatives, XIV[1]

Stereoselective Formation of Prostacyclin Intermediates

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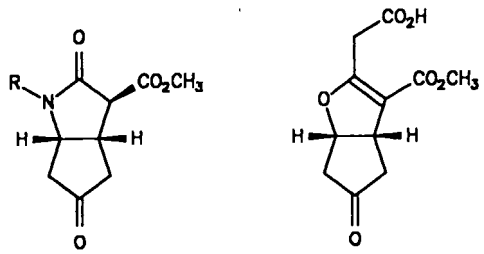
A regioselective and stereoselective route to a prostacyclin intermediate is reported.

Investigating the scope of annulation reactions with 4-acetoxycyclopentenone[2] we recently prepared the heterocyclic compounds **1**[3] and **2**[4].

Scheme 1



1 **2**

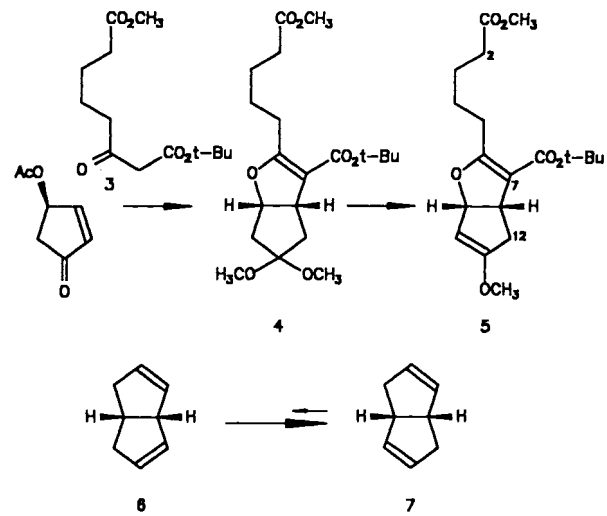
As enol ether **2** represents the framework of prostacyclins, we started a more detailed investigation of these annulations, aiming at prostacyclins with an acceptor substituent in the 7-position (prostaglandin numbering). Furthermore, a synthetically flexible approach could also lead to longer ester sidechains. Both variations have attracted the interest of medicinal chemists, as a higher solvolytic stability of the enol ether moiety has been observed for derivatives of this type[5,6].

First of all we prepared diester **4** using β-ketoester **3** in the annulation sequence.

Our next aim was of course to regioselectively establish substituents in the cyclopentanone part of the molecule, as for a synthesis of prostacyclins one has to stereoselectively introduce the sidechain in the 12-position. A most simple approach would be the regioselective formation of enol ethers starting from **4** by proton-catalyzed elimination of methanol. Dihydrofuran **4** served extremely well for this purpose and very cleanly gave rise to just the one enol ether **5** in a thermodynamically controlled process.

The higher thermodynamic stability of bicyclooctadienes of type **7** compared to that of isomer **6**, which is probably due to *peri* interactions in isomers of type **6** but may also be caused by higher ring strain for these compounds, was recently documented in our laboratory with various other derivatives (see below). This observation opens the road to highly regioselective transformations in this series. Some applications to natural products synthesis are in progress and will be disclosed soon. To be able to use **5** for a synthesis of prostacyclin derivatives, regioselective functionalization at the methyl enol ether was given first priority. This transformation could be achieved using standard reaction conditions, and these results prove **5** to be a valuable intermediate (see Scheme 3). Of particular interest is the thermodynamically controlled electrophilic attack with orthoformate under Lewis acidic conditions which again gave rise to a type **7** product (**10**, Scheme 3).

Scheme 2



3 **4** **5**

6 **7**

As noticed with thioether **8**, which is formed in an irreversible process, acetal **9** was also initially obtained as the product of kinetic control with concomitant shift of the double bond. Further treatment under acidic conditions, however, generated a mixture of **9** and **10** with **10** prevailing in a ratio larger than 3:1.

As the selective hydrolysis of the enol ether moiety could be achieved via acetal **11**, which resulted on acid-catalyzed addition of methanol, the reduction of the unstable ketone **12** was studied next. Contrary to expectations, hydride delivery did not take place from the convex side but yielded β-hydroxy compound **13** with excellent stereoselectivity, which is obviously due to the shielding capacity of the acetal group. The epimeric α-alcohol was secured in a Mitsunobu inversion with subsequent hydrolysis. The sequence provides access to an advanced pure stereoisomer en route to var-

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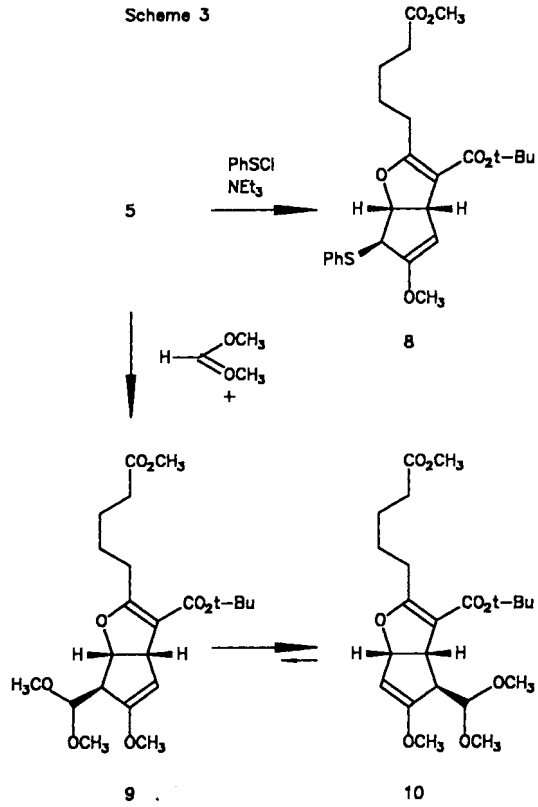
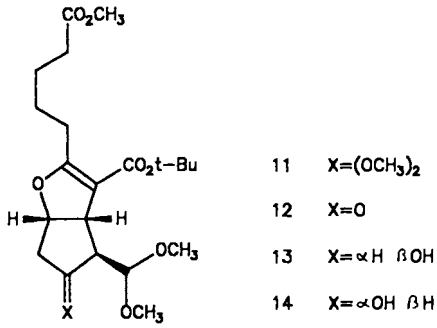
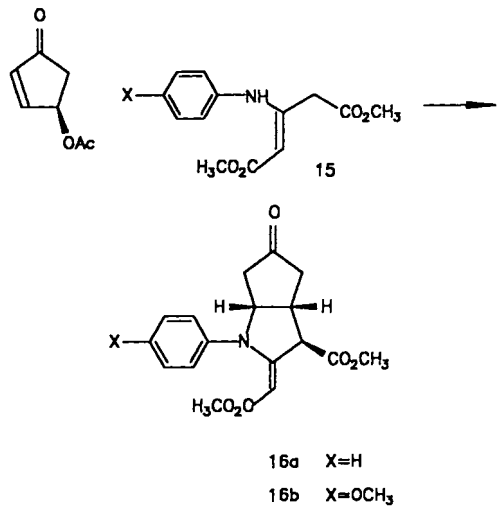
Scheme 3



Scheme 4



Scheme 5



ious prostacyclin derivatives, as aldehydes of type **14** have been used extensively for this purpose.

In addition to the furan series, azaprostacyclins have been shown to be very useful compounds, too[7], and this was the reason for also employing enamines of the general structure **15** as annulating reagents.

Although these starting materials can be prepared very easily and with high stereoselectivity by addition of the corresponding amine to dimethyl allene-1,3-dicarboxylate[8], a comparatively low yield in the annulation process (X = H, 34%; X = OCH_3, 31%) discouraged further work in this direction.

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Experimental

UV spectra were measured in methanol with a Beckman 3600 and IR spectra were taken in chloroform with a Perkin-Elmer 580. For ^{1}H- and ^{13}C-NMR spectra Bruker WH-90, WP-200, AM-300 and WM-400 were used with solvents indicated. Mass spectra were recorded with a Finnigan MAT-312 at an ionization potential of 70 eV, and elemental analyses were done with a Heraeus CHN rapid analyzer. For TLC separation Merck plates 60 F/254 were used and for flash chromatography[9] Baker silica gel 30–60 μm.

tert-Butyl (3aα,6aα)-3a,5,6,6a-Tetrahydro-5,5-dimethoxy-2-(4-methoxycarbonylbutyl)-4H-cyclopenta[b]furan-3-carboxylate (**4**): 1-*tert*-Butyl-8-methyl 3-oxooctanedioate[10] (**3**) (6.8 g, 26.4 mmol) was dissolved in dry tetrahydrofuran (15 mmol) and slowly added to a suspension of lithium hydride (460 mg, 58 mmol) in dry tetrahydrofuran (25 mmol). After leavig this mixture at 0 °C for 1 h, it was slowly added to a solution of 4-acetoxy-2-cyclopenten-1-one (7.38 g, 52.7 mmol) in dry tetrahydrofuran (35 ml), and this reaction mixture was then kept at room temp. for 24 h. It was poured into 2 N citric acid and extracted with ether. This extract was washed with satd. sodium hydrogen carbonate solution, dried with magnesium sulfate, and evaporated. The surplus 4-acetoxy-2-cyclopenten-1-one was removed by Kugelrohr vacuum distillation, and the remaining crude material was dissolved in a mixture of methanol (150 ml) and trimethoxymethane (15 ml) and, after addition of *p*-toluenesulfonic acid (20 mg), stirred at room temp. for 1 h for acetal formation. For workup, the mixture was poured into satd. sodium hydrogen carbonate solution and extracted with dichloromethane. This extract was dried with magnesium sulfate, the solvent evaporated, and the product purified by chromatography with petroleum ether/ether (2:1) to yield 7.3 g (72%) of the bicyclic acetal **4**. – IR ($CHCl_3$): $\tilde{\nu}$ = 1735 cm^{-1}, 1680, 1640, 1370. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 9H), 1.5–1.8 (m, 4H), 1.95–2.25 (m, 4H), 2.34 (t, *J* = 7 Hz, 2H), 2.53 (dd, t, *J* = 14, 1, 7 Hz, 1H), 2.64 (d, t, *J* = 14, 7 Hz, 1H), 3.17 (s, 3H), 3.21 (s, 3H), 3.55 (d, t, *J* = 4.5, 9.5 Hz, 1H), 3.66 (s, 3H), 4.95 (ddd, *J* = 9.5, 6.5, 3.8 Hz, 1H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2 (t), 26.0 (t), 27.0 (t), 28.1 (q), 33.4 (t), 39.0 (t), 40.8 (t), 44.4 (t), 49.2 (q), 49.3 (q), 50.9 (q), 78.9 (s), 83.9 (d), 107.0 (s), 109.7 (s), 164.9 (s), 169.5 (s), 173.3 (s). – MS (70 eV, 20 °C): *m/z* (%) = 384 (2) [M^+], 353 (4), 352 (8), 297 (15), 296 (19), 279 (33), 278 (100).

$C_{20}H_{32}O_7$ (384.5) Calcd. C 62.48 H 8.39
Found C 62.39 H 8.49
Calcd. 384.2148 Found 384.2155 (MS)

Enol ethers **5**[11] *and* **8**[12] were prepared according to standard techniques.

5: IR ($CHCl_3$): $\tilde{\nu}$ = 1740 cm^{-1}, 1680, 1650, 1635, 1360. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.47 (s, 9H), 1.5–1.75 (m, 4H), 2.33 (t, *J* = 7 Hz, 2H), 2.45 (dddd, *J* = 17, 3, 2, 1.5 Hz, 1H), 2.70 (ddd, *J* = 17, 8, 1.5 Hz, 1H), 2.5–2.8 (m, 2H), 3.66 (s, 3H), 3.67 (s, 3H), 3.7–3.8 (m, 1H), 4.64 (dt, *J* = 2, 1.5 Hz, 1H), 5.54 (ddd, *J* = 9, 2, 2 Hz, 1H). – MS (70 eV, 20°C): *m/z* (%) = 352 (6) [M^+], 296 (21), 279 (30), 278 (100), 136 (52).

$C_{19}H_{28}O_6$ Calcd. 352.1886 Found 352.1886 (MS)

8: IR ($CHCl_3$): $\tilde{\nu}$ = 1730 cm^{-1}, 1675, 1645, 1630, 1470, 1450, 1440, 1370. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.46 (s, 9H), 1.4–1.7 (m, 4H), 2.32 (t, *J* = 7 Hz, 2H), 2.4–2.7 (m, 2H), 3.65 (s, 3H), 3.66 (s, 3H), 3.65–3.75 (m, 1H), 4.13 (d, *J* = 1 Hz, 1H), 4.78 (dd, *J* = 1, 1 Hz, 1H), 4.98 (d, *J* = 8 Hz, 1H), 7.25–7.40 (m, 5H).

$C_{25}H_{32}O_6S$ Calcd. 460.1920 Found 460.1937 (MS)

tert-Butyl (3aα,4α,6aα)-4-(Dimethoxymethyl)-3a,6a-dihydro-5-methoxy-2-(4-methoxycarbonylbutyl)-4H-cyclopenta[b]furan-3-carboxylate (**10**): Enol ether **5** (730 mg, 2.07 mmol) was dissolved in trimethoxymethane (40 ml), Et_2O-BF_3 (0.76 ml, 6.22 mmol) was added under dried nitrogen, and the mixture stirred at room temp. for 10 min. The brown solution was then poured into ice/water, and the product was extracted with ether. The ether solution was dried with magnesium sulfate, evaporated, and the remaining crude material purified by flash chromatography with petrol ether/ether (2:1). Acetal **10** is eluted as the main reaction product in a yield of 488 mg (55%). – IR ($CHCl_3$): $\tilde{\nu}$ = 1728 cm^{-1}, 1680, 1640, 1625, 1370. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.48 (s, 9H), 1.5–1.7 (m, 4H), 2.32 (t, *J* = 7 Hz, 2H), 2.5–2.65 (m, 2H), 3.03 (dddd, *J* = 3, 3, 2, 1 Hz, 1H), 3.45 (s, 3H), 3.47 (s, 3H), 3.55 (d, *J* = 8.5 Hz, 1H), 3.66 (s, 3H), 3.67 (s, 3H), 4.41 (d, *J* = 3 Hz, 1H), 4.69 (dd, *J* = 2, 1 Hz, 1H), 5.51 (ddd, *J* = 8.5, 2, 2 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.4 (t), 26.3 (t), 27.6 (t), 28.5 (q), 33.8 (t), 46.1 (d), 51.4 (q), 54.2 (d), 56.2 (q), 56.8 (q), 57.5 (q), 79.5 (s), 88.4 (d), 96.8 (d), 106.3 (s), 107.2 (d), 164.4 (s), 165.4 (s), 169.5 (s), 173.9 (s). – MS (70 eV, 50°C): *m/z* (%) = 426 (2) [M^+], 394 (6), 338 (7), 320 (17), 306 (4), 382 (4), 251 (6), 195 (8), 75 (100).

$C_{22}H_{34}O_8$ Calcd. 426.2254 Found 426.2254 (MS)

tert-Butyl (3aα,4α,5α,6aα)-4-(Dimethoxymethyl)-3a,5,6,6a-tetrahydro-5-hydroxy-2-(4-methoxycarbonylbutyl)-4H-cyclopenta[b]furan-3-carboxylate (**13**): Enol ether **10** (1.2 g, 2.82 mmol) was dissolved in a 0.01% solution of sulfuric acid in dry methanol (150 ml), stirred for 18 h at room temp., neutralized with satd. sodium hydrogen carbonate solution, and extracted with ether. After evaporation of the solvent, the residue was dissolved in a mixture of dioxan (60 ml) and water (20 ml) and treated with oxalic acid (500 mg, 5.56 mmol). TLC control proves the acetal hydrolysis to be complete after 18 h, but, as ketone **12** is not stable owing to a retro Michael process, it is immediately reduced by adding sodium borohydride (350 mg) at 0°C. After addition of the hydride, the reaction mixture is allowed to warm to room temp., poured into satd. sodium hydrogen carbonate solution, and extracted with dichloromethane. Evaporation of the solvent is followed by chromatography [ether/petroleum ether (2:1)] to yield 750 mg (65%) of β-hydroxy compound **13** as a colourless oil. – IR ($CHCl_3$): $\tilde{\nu}$ = 3500 cm^{-1}, 2860, 1730, 1680, 1625, 1390. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.50 (s, 9H), 1.5–1.75 (m, 4H), 1.83 (ddd, *J* = 14, 5, 5 Hz, 1H), 2.18–2.35 (m, 2H), 2.33 (t, *J* = 7 Hz, 2H), 2.58 (t, *J* = 7 Hz, 2H), 3.48 (s, 3H), 3.54 (s, 3H), 3.5–3.65 (m, 1H), 3.67 (s, 3H), 4.48 (q, *J* = 5 Hz, 1H), 4.85 (d, *J* = 4 Hz, 1H), 5.13 (ddd, *J* = 10, 7, 5 Hz, 1H). – MS (70 eV, 20°C): *m/z* (%) = 414 (3) [M^+], 382 (6), 338 (32), 326 (27), 325 (32), 295 (29), 282 (100), 250 (47).

$C_{21}H_{34}O_8$ Calcd. 414.2254 Found 414.2253 (MS)

tert-Butyl (3aα,4α,5α,6aα)-4-(Dimethoxymethyl)-3a,5,6,6a-tetrahydro-5-hydroxy-2-(4-methoxycarbonylbutyl)-4H-cyclopenta[b]furan-3-carboxylate (**14**): β-Alcohol **13** (550 mg, 1.33 mmol) in dry tetrahydrofuran (20 ml) was treated with triphenylphosphine (523 mg, 1.99 mmol) and *p*-nitrobenzoic acid (333 mg, 1.99 mmol); at 0°C a solution of diethyl azodicarboxylate (347 mg, 1.99 mmol) in dry tetrahydrofuran (5 ml) was slowly added. After 90 min at 0°C the clear solution was allowed to reach room temp., kept at this temperature for another 30 min, and evaporated. The residue on chromatography [ether/petroleum ether (1:2)] yielded 640 mg (86%) of the *p*-nitrobenzoate which without further characterization was hydrolyzed with a 10 mol-% solution of barium hydroxide in methanol. TLC proved the reaction to be finished after 5 min at room temp., and workup gave rise to a quantitative yield of α-hydroxy compound **14** which differed from **13** particularly in its ^1H-NMR data. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.50 (s, 9H), 1.5–1.75 (m, 4H), 1.90 (ddd, *J* = 14, 6, 5 Hz, 1H), 2.2–2.7 (m, 4H), 2.33 (t, *J* = 7 Hz, 2H), 3.29 (dd, *J* = 9.5, 5 Hz, 1H), 3.46 (s, 3H), 3.49 (s, 3H), 3.66 (s, 3H), 4.36 (q, *J* = 6 Hz, 1H), 4.57 (d, *J* = 4 Hz, 1H), 4.92 (ddd, *J* = 9.5, 7, 5 Hz, 1H).

General Procedure for the Annulation of Enamines **15**: The corresponding enamine (1 mmol) was dissolved in dry tetrahydrofuran (4 ml) and, after addition of lithium tetramethylpiperidid (1 mmol) at −78°C, the mixture was stirred for 2 h at this temp. Then, 4-acetoxy-2-cyclopenten-1-one (1 mmol), dissolved in dry tetrahydrofuran (2 ml), was added, and the reaction mixture was then allowed to warm to room temp. After 15 h at room temp., the solution was poured into satd. ammonium chloride solution and extracted with dichloromethane. The extracts are washed with brine, dried with magnesium sulfate, and after evaporation, the crude product was purified by flash chromatography (ether).

Methyl (3α3aα,6aα)-Perhydro-2-methoxycarbonylmethylen-5-oxo-1-phenylcyclopenta[b]pyrrole-3-carboxylate (**16a**): Yield 34%, yellow oil. – UV (CH_3OH): λ_{max} = 288 nm (qual.). – IR ($CHCl_3$): $\tilde{\nu}$ = 1740 cm^{-1}, 1680, 1610, 1590. – ^1H NMR (90 MHz, $CDCl_3$): δ = 1.0–3.0 (m, 4H), 3.0–3.5 (m, 1H), 3.56 (s, 3H), 3.82 (s, 3H), 4.55 (m, 1H), 4.70 (m, 2H), 7.3 (m, 5H). – MS (70 eV, 60°C): *m/z* (%) = 329 (10) [M^+], 297 (10), 270 (6), 254 (7), 210 (7), 168 (9), 85 (63), 83 (100).

$C_{18}H_{19}NO_5$ Calcd. 329.1263 Found 329.1263 (MS)

Methyl (3α3aα,6aα)-1-Anisyl-perhydro-2-methoxycarbonylmethylen-5-oxocyclopenta[b]pyrrole-3-carboxylate (**16b**): Yield 31%, yellow foam. – UV (CH_3OH): λ_{max} = 285 nm (qual.). – IR ($CHCl_3$): $\tilde{\nu}$ = 1740 cm^{-1}, 1685, 1620, 1600, 1510. – ^1H NMR (90 MHz, $CDCl_3$): δ = 2.0–2.8 (m, 4H), 2.8–3.5 (m, 1H), 3.56 (s, 3H), 3.82 (s, 6H), 4.53 (s, 1H), 4.60 (s, 1H), 7.0 (m, 4H). – MS (70 eV, 80°C): *m/z* (%) = 359 (9) [M^+], 328 (5), 300 (4), 284 (4), 268 (3), 239 (4), 225 (3), 205 (4), 120 (26), 106 (32), 105 (74), 92 (26), 91 (100), 77 (23).

$C_{19}H_{21}NO_6$ Calcd. 359.1369 Found 359.1368 (MS)

CAS Registry Numbers

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