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A Novel Approach to Carbacycline

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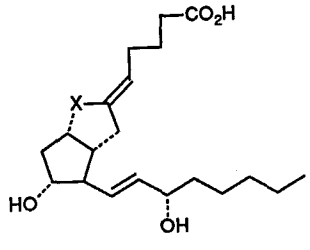
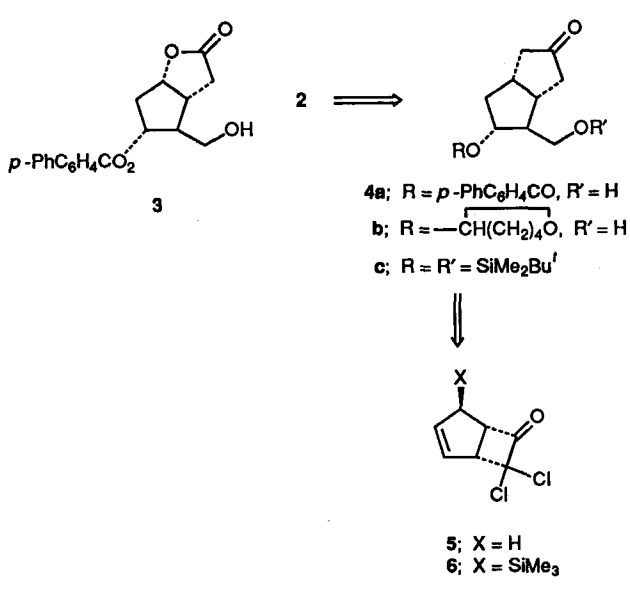
A scheme for (±)-carbacycline synthesis has been developed, based on 7,7-dichlorobicyclo[3.2.0]hept-3-en-7-one.

The 6,9-α-carbanalogues of the highly labile prostacycline **1**, usually called carbacyclines (*e.g.* **2**), are chemically more stable than **1** and are similar to prostacycline in the nature of their bioactivity.[1] After purposeful modification of the side chains and ring framework of the carbacycline, analogues with similar and even greater activities than that of prostacycline have been found in antiaggregation dough. A series of intensive investigations in that field was undertaken to develop carbacycline cardiovascular and antithrombosis preparations.[2–5]



1; X = O
2; X = CH_2

The chemical synthesis of the carbacyclines has been published elsewhere.[1] Most of the ways proposed for the preparation of carbacyclines may be considered as adaptations of a versatile prostaglandin scheme devised by Corey[6] using the key lactone **3**, and they were carried out with perhydropentalene equivalents of **3**: the functionalized bicyclo[3.3.0]octanes **4**. However, the known methods for the synthesis of carbacycline synthons **4a**, **b** are multistage and rather laborious.[7–9] A novel solution of this problem, based on the available bicycloheptenones **5** and **6**, is described in this communication. As shown in the retrosynthetic scheme (Scheme 1), we planned to transform **5** and **6** into the desired bicyclo[3.3.0]octane intermediates **4** in two stages: (*i*) regio- and stereo-controlled 'vicinal oxy-oxymethylation' of the double bonds using the Prins reaction, and (*ii*) insertion of methylene into the cyclobutane rings.



3

4a; R = *p*-PhC_6H_4CO, R′ = H
b; R = —CH(CH$_2$)$_4$O, R′ = H
c; R = R′ = $SiMe_2Bu^t$

5; X = H
6; X = $SiMe_3$

Scheme 1

Initially, according to the established strategy, the possibility of functionalization of alkenes **5** and **6** by the Prins reaction was studied. Boiling a solution of alkene **5** and 15–20 equiv. CH_2O in AcOH and concentrated H_2SO_4 (50:1 by volume) for 70 h produced an oily mixture of compounds **7**, **8**, **9** and **10** in a 20:10:1:1 ratio, respectively, which were isolated separately by crystallization and column chromatography on SiO_2, in a total yield of 90% (Scheme 2).†‡

The Prins reaction of allylsilane **6** proceeded in a different way. Under similar conditions as for **5** (10 h boiling), the main reaction products were monoacetates **11** and **12** in a 4:1 ratio (40%), alkenes **5** (20%) and polycyclic compounds **10** (15%); the minor diacetates **14** and **15** were formed in an 8:2 ratio in insignificant amounts (5%). It should be noted that in an alternative approach, electrophilic oxymethylation of **6** gave only the tricyclic adduct **16** in 50% yield on treatment with 1,3,5-trioxane–$TiCl_4$ (CH_2Cl_2, −78 °C→20 °C, 1 h) (Scheme 3).

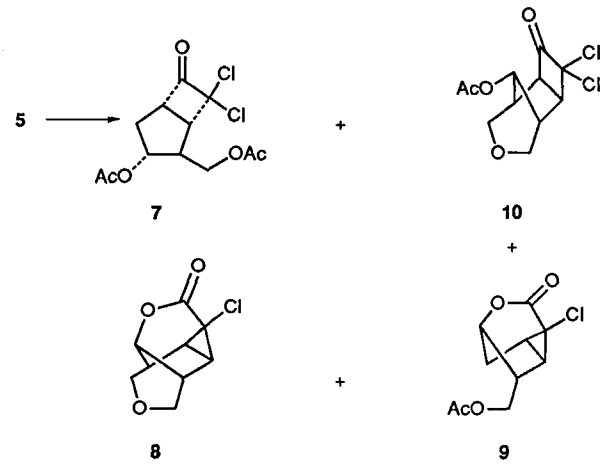
† *Characterization data* for 3α-acetoxy-2β-acetoxymethylene-7,7-dichlorobicyclo[3.2.0]heptan-6-one **7**: IR ν_{max}/cm^{-1} 1240, 1720–1750, 1805; ^{1}H NMR ($CDCl_3$) δ 1.95 (s, 3H, OAc), 2.95 (t, 1H, *J* 6.35 Hz, C^{5}H), 3.25 (dd, 1H, *J* 6.28, 2 Hz, C^{1}H), 4.10–4.40 (m, 2H, CH_2O), 5.20 (m, 1H, C^{3}H); ^{13}C NMR ($CDCl_3$) δ 20.77 (Me), 20.90 (Me), 34.93 (C^4), 48.15 (C^5), 55.20 (C^2), 60.35 (C^1), 63.89 (CH_2O), 78.73 (C^3), 86.92 (C^7), 169.85 (OAc), 170.57 (OAc), 195.52 (C=O).

7,9-Carbolactone-3-oxa-7-chlorotricyclo[3.3.1.0^{6,8}]nonane **8**: m.p. 122–123 °C; IR ν_{max}/cm^{-1} 1750, 3010, 3070; ^{1}H NMR ($CDCl_3$) δ 2.40–2.43 (m, 4H, C^{1}H, C^{5}H, C^{6}H, C^{8}H), 3.58 (d, 2H, C^{2}H, C^{4}H, $^3J_{AB}$ 12 Hz), 3.98 (dd, 2H, C^{2}H, C^{4}H, $^2J_{BA}$ 12, $^3J_{RX}$ 2.5 Hz), 4.34–4.37 (m, 1H, C^{9}H); ^{13}C NMR ($CDCl_3$): δ 29.48 (C^1, C^5), 39.22 (C^6, C^8), 40.46 (C^7), 67.74 (C^2, C^4), 73.37 (C^9), 167.65 (CO_2); MS *m/z* 200 (M^+), 172 (M − CO), 170 (M − CH_2O), 165 (M − Cl), 142 (M − CH_2CO_2), 126, 107, 100, 81, 79, 77, 55, 44 (CO_2).

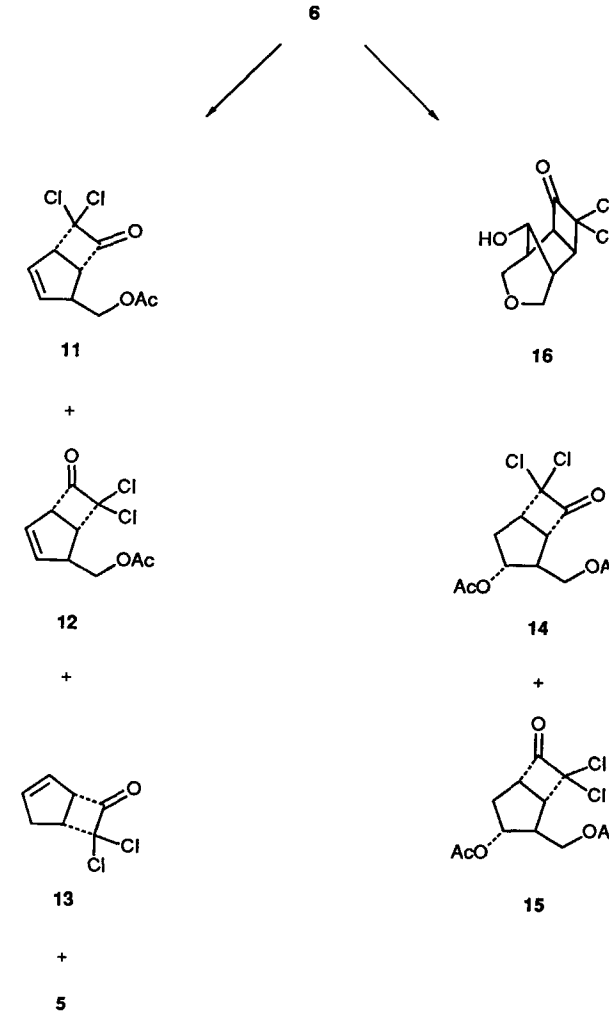
6,3-Carbolactone-2β-acetoxymethylene-6-chlorobicyclo[3.1.0]hexane **9**: IR ν_{max}/cm^{-1} 1240, 1730, 3020, 3080; ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H, OAc), 4.55 (m, 1H, OCHO); ^{13}C NMR ($CDCl_3$) δ 20.69 (Me), 29.57 (C^1), 29.57 (C^4), 31.46 (C^5), 42.95 (C^6), 43.41 (C^2), 67.14 (CH_2O), 76.63 (C^3), 167.11 (CO), 170.56 (OAc).

2β-Acetoxymethylene-6,6-dichlorobicyclo[3.2.0]hept-3-en-7-one **11**: IR ν_{max}/cm^{-1} 1270, 1750, 1810, 3080; ^{1}H NMR ($CDCl_3$) δ 1.96 (s, 3H, OAc), 3.26 (m, 1H, C^{2}H), 3.86 (dd, 1H, *J* 11.1, 6.6 Hz, C^{8}H), 3.93 (dd, 1H, *J* 11.1, 5.9 Hz, C^{8}H), 4.02 (m, 1H, C^{5}H), 4.09 (d, 1H, *J* 7.06 Hz, C^{1}H), 5.82 (m), 5.90 (m, 2H, CH=CH); ^{13}C NMR ($CDCl_3$) δ 20.53 (OAc), 47.95 (C^2), 58.77 (C^5), 61.67 (C^1), 88.44 (C^6), 64.95 (CH_2O), 130.65 (C^4), 136.75 (C^3), 170.34 (OAc), 195.72 (C=O). MS *m/z*: 248 (M^+), 206 (M − $COCH_2$), 188 (M − AcOH).

‡ Satisfactory elemental analyses were obtained for compounds **8** and **16**.



Scheme 2



Scheme 3

Thus, as a result of our investigation of the Prins reaction of alkenes **5** and **6**, a series of adducts was prepared, from which diacetate **8** and the isomeric monoacetates **11** and **12** were easily isolated from the reaction mixtures by single column chromatography on SiO_2 in 40–50% yields.† These three compounds were of interest for further study.

The next stage of our investigation included a study of the homologation of the cyclobutane fragment of these compounds. Because of the anomalously high reactivity of diacetate **7** towards CH_2N_2 (the reaction is difficult to control), the direct transformation **7**→**17** was accomplished in only a moderate yield (40%), hence, at the ring-expansion stage the less reactive monochloro derivative **18** was used. After complete dechlorination of the intermediate **19**, the yield of the final diacetate **17** was more than 60% with respect to **7**. In contrast to diacetate **7**, the isomeric bicycloheptenones **11** and **12** reacted readily with CH_2N_2 to form the corresponding homologues **16** and **20** which, after treatment with Zn in AcOH, led to the same acetate **22** in a total yield of 80%. Stereo- and regio-selective addition of an OH-group at position 3 of alkene **22** was carried out by an initial transformation of the latter to the bromhydrin **23** and then by radical dehalogenation with Bu_3SnH to monoacetate **24**, and further to diacetate **17** (Scheme 4).§

Of the two approaches developed, the preparation of the key diacetate **17** from **7** was shown to be more efficient. The diacetate **17** is considered to be a novel equivalent of retrones **4**, and its preparation facilitated the final stages of the synthesis by providing a solution to the problem of forming side chains. Further, we have described a short and chemorational way to transform diacetate **17** into carbacycline **2**. For this purpose, using versatile procedures, diacetate **17** was transformed into bis(triethylsilyl) ether **25** and an acid **27** (identified as the methyl ester **28**) was prepared by alkenation with phosphorane **26** (Scheme 5).[10] The application of our recently developed method for direct oxidation of silyl ethers by the $(COCl)_2$–dimethylsulfoxide (DMSO) system[11] generated siloxyaldehyde **29**, which was then condensed with dimethyl-2-oxoheptylphosphonate[12] according to Emmons–Horner to form a 5(*Z*,*E*)-isomeric (2:1) mixture of enones **30** in a total yield of 20% based on ether **25**. After the removal of the silane protecting group, the isomeric oxyenones **31** were separated by HPLC. Reduction of an individual enone **30a** by the Yamamoto reagent,[13] followed by saponification, gave carbacycline **2** and its 15β-isomer in a ratio of 7:3, which were separated by column chromatography on SiO_2.§

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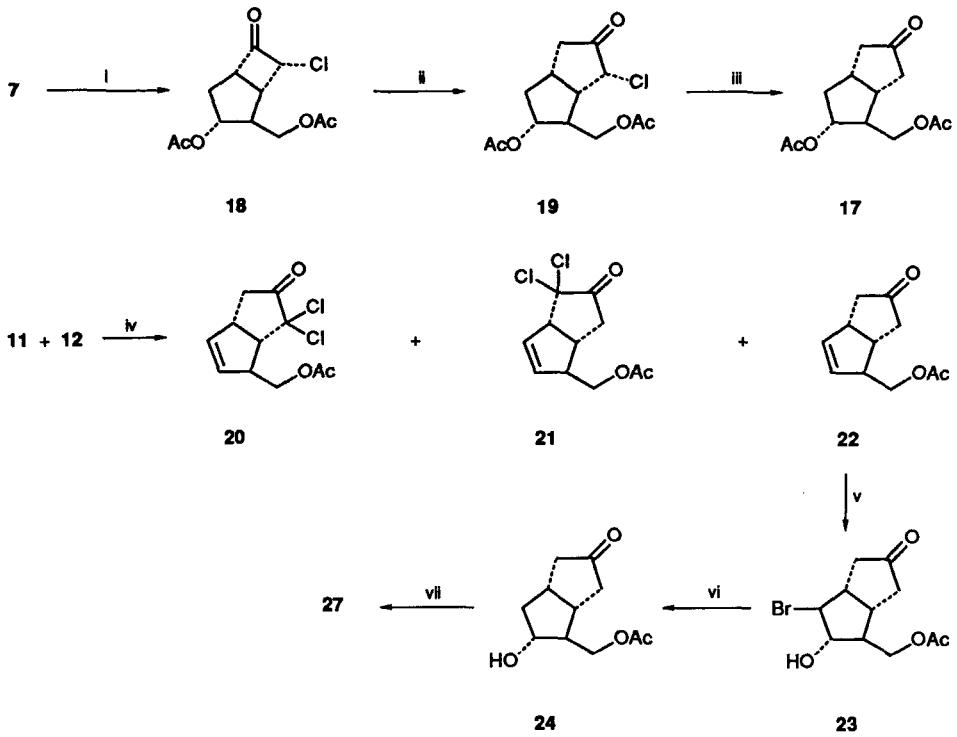
§ *Characterization data* for 3α-acetoxy-2β-acetoxymethylene-7-*endo*-chlorobicyclo[3.2.0]heptan-6-one **18**: IR ν_{max}/cm^{-1} 1750, 1790; ^1H NMR ($CDCl_3$) δ 1.99 (s, 3H, OAc), 2.09 (3H, OAc), 4.10 (d, 2H, *J* 6.6 Hz, CH_2O), 5.26 (m, 1H, C^3H); ^{13}C NMR ($CDCl_3$) δ 20.30 (Me), 20.56 (Me), 34.40 (C^4), 39.69 (C^5), 44.72 (C^2), 59.73 (C^1), 63.78 (CH_2O), 62.60 (C^7), 78.64 (C^3), 169.59 (OAc), 203.27 (C^6).

(1*R**,5*S**,6*R**,9*S**,10*R**)-8,8-dichloro-10-hydroxy-3-oxatricyclo-[7.2.1^{1,5}.O^{6,9}]undecan-7-one **16**: m.p. 131–132 °C (hexane); IR ν_{max}/cm^{-1} 1790; ^1H NMR ($CDCl_3$) δ 2.97 (br s, 1H, C^1H), 3.01 (br s, 1H, C^5H), 3.58 (d, 1H, *J* 7.72 Hz, C^9H), 3.93 (dd, 1H, *J* 11.1, 3.07 Hz, C^4H), 3.78 (dd, 1H, *J* 11.1, 2.56 Hz, C^2H), 3.62 (br s, 0.5H), 3.69 (br s, 1H), 3.79 (br s, 0.5H, C^9H_2); ^{13}C NMR ($CDCl_3$) δ 48.95 (C^1), 57.17 (C^6), 55.51 (C^2), 63.02 (C^5), 65.06 (C^{10}), 73.04 (C^9), 74.74 (C^7).

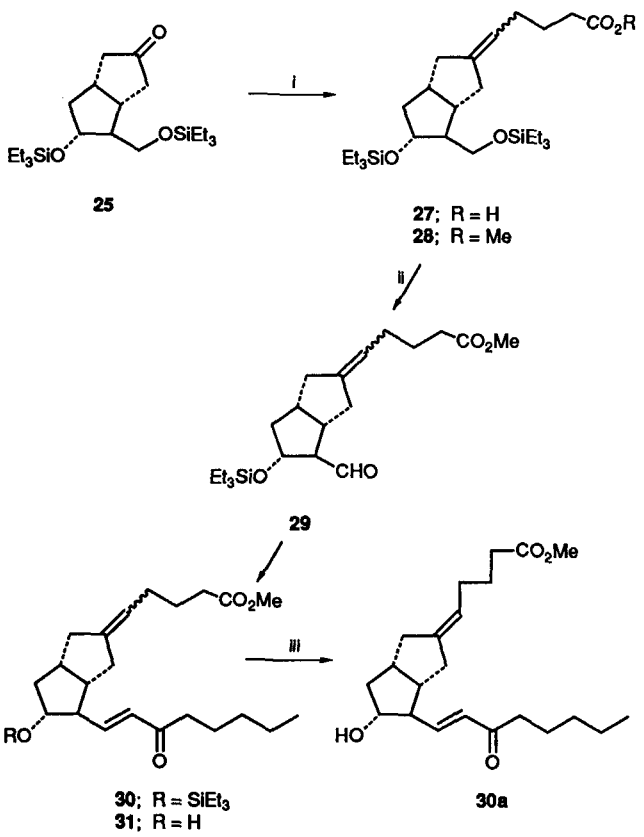
3α-Acetoxy-2β-acetoxymethylenebicyclo[3.3.0]octan-7-one **17**: IR ν_{max}/cm^{-1} 1240, 1736; ^1H NMR ($CDCl_3$) δ 1.60 (dt, 1H, C^4H, ^2J 14, ^3J 6 Hz), 2.03 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.08–2.63 (m, 7H, $2CH_2$, C^4H, C^1H, C^5H), 2.86 (m, 1H, C^2H), 4.12 (d, 2H, *J* 6.2 Hz, CH_2O), 5.38 (dt, 1H, C^3H, ^3J 6.1, ^3J 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 20.17 (Me), 20.43 (Me), 36.31 (C^5), 37.85 (C^4), 40.56 (C^1), 43.25 (C^6), 43.98 (C^8), 51.47 (C^2), 63.61 (CH_2O), 77.01 (C^3), 169.75 (OAc), 170.12 (OAc), 218.01 (C^7). MS *m*/*z* M^+ 254.

3α-Triethylsilyloxy-2β-triethylsilyloxymethylenebicyclo[3.3.0]-octan-7-one **25**: IR ν_{max}/cm^{-1} 740, 800, 1000, 1240, 1410, 1460, 1740; ^1H NMR ($CDCl_3$) δ 4.05–4.15 (m, 1H, C^3H), 3.59 (d, 2H, *J* 5 Hz, CH_2O); ^{13}C NMR ($CDCl_3$), 4.50 (t, $SiCH_2$), 4.83 (t, $SiCH_2$), 14.16 (Me), 36.55 (C^4), 40.14 (C^5), 42.29 (C^1), 44.51 (C^8), 45.53 (C^6), 57.70 (C^2), 62.86 (C^9), 75.26 (C^3), 220.70 (C^7).

(±)-6,9α-Methanoprostaglandin I_2 **2**: ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, *J* 6.3 Hz, Me), 1.20–2.50 (m, 23H, $10CH_2$, 3CH), 3.50–4.30 (m, 2H, 2CH), 5.16 (m, 1H, C^5H), 5.40–5.60 (m, 2H, CH=CH); ^{13}C NMR ($CDCl_3$) δ 177.01 (C^1), 33.14 (C^2), 24.68 (C^3), 28.63 (C^4), 121.01 (C^5), 142.84 (C^6), 36.03 (C^7), 45.39 (C^8), 37.63 (C^9), 41.68 (C^{10}), 77.30 (C^{11}), 57.00 (C^{12}), 133.07 (C^{13}), 135.51 (C^{14}), 73.49 (C^{15}), 37.22 (C^{16}), 25.29 (C^{17}), 31.81 (C^{18}), 22.69 (C^{19}), 14.08 (C^{20}), 38.26 ($C^{9\alpha}$).



Scheme 4 *Reagents and conditions*: i, Zn–AcOH, 20 °C; ii, 5 equiv. CH_2N_2; iii, Zn–AcOH, 40 °C; iv, excess of CH_2N_2; v, 1.2 equiv. *N*-bromosuccinimide (NBS), tetrahydrofuran (THF)–H_2O (9:1); vi, 2 equiv. Bu_3SnH, azoisobutyronitrile, C_6H_6, 70%; vii, Ac_2O, py



Scheme 5 *Reagents and conditions*: i, (1) $Ph_3P{=}CH(CH_2)_3CO_2Na$ **26**, (2) CH_2N_2; ii, see ref. 11; iii, HPLC

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