Synthesis of 9,11-dideoxy-9a-homoprostaglandins[1]

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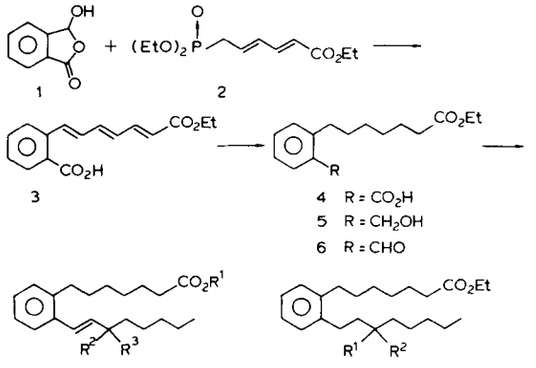
Abstract. The synthesis of three 9,11-dideoxyprostaglandins in which the cyclopentane moiety is replaced by a six-membered ring, is described. Starting from phthalaldehydic acid (**1**) the aromatic PG-analogue, 7-[2-(3-hydroxy-(*E*)-1-octenyl)phenyl]heptanoic acid (**9**), was prepared in 7 steps in 49% overall yield. The *cis*-substituted cyclohexane PG-analogue, ethyl 7-[*cis*-2-(3-hydroxy-(*E*)-1-octenyl)cyclohexyl]heptanoate (**34**), was obtained in 7 steps in 53% overall yield from the same starting material **1**. The *trans*-substituted cyclohexane PG-analogue, ethyl 7-[*trans*-2-(3-hydroxy-(*E*)-1-octenyl)cyclohexyl]heptanoate (**20**), was synthesized from methyl 9-cyano-(*E*)-2-nonenoate (**12**) in 8 steps in 34% yield.

In the last few years many prostaglandin analogues with modifications in the side chains and ring moiety have been synthesized in attempts to obtain prostaglandins with more specific pharmacological properties, free of undesirable side-effects. In this connection hetero atoms (N, O, S) have been introduced into the five-membered ring[2], but only few analogues are known which contain a six-membered ring[3] instead of the cyclopentane moiety. We have synthesized some 9,11-dideoxyprostaglandin analogues in which the side chains are attached to an aromatic or a cyclohexane ring.

Aromatic analogue

Starting from 1-nitroso-2-naphthol *Collet* and *Jacques*[4] synthesized some aromatic prostaglandin analogues, but only compounds with propionic and pentanoic acid side chains were reported. We developed a new general synthesis for the preparation of aromatic analogues with the "natural" heptanoic acid side chain, starting from readily available phthalaldehydic acid **1**.

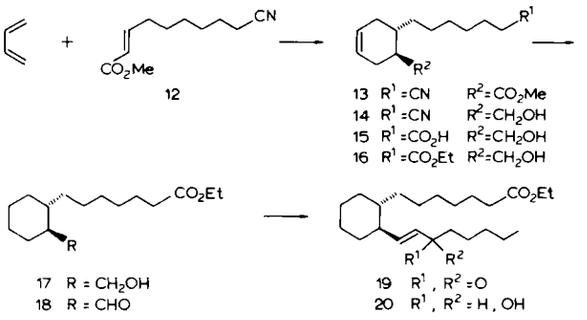


Horner reaction of **1** with triethyl phosphonosorbate **2**[5] in the presence of two equivalents of sodium hydride in tetrahydrofuran gave the triene ester acid **3** in 81% yield. Catalytic hydrogenation of **3** over 10% Pd/C in ethyl acetate furnished **4**. The carboxyl group of **4** could be selectively reduced – without affecting the ester function – to give carbinol **5**. This conversion was accomplished either by direct reduction of the carboxylic acid with diborane[6] in tetrahydrofuran, or by reduction of the mixed carbonic anhydride[7], obtained from **4** with ethyl chloroformate and triethylamine in tetrahydrofuran, with sodium tetrahydridoborate. Oxidation of the benzylic alcohol **5** with manganese dioxide[8] in dichloromethane afforded aldehyde **6**, which was converted with the anion of dimethyl 2-oxoheptylphosphonate[9] in tetrahydrofuran to give enone **7** in 74% yield. Reduction of the oxo function was best achieved with zinc tetrahydridoborate[9] in dimethoxyethane, providing hydroxy compound **8** in quantitative yield. Use of other reducing agents like sodium tetrahydridoborate or lithium hydrido-tri-*tert*-butoxoaluminate led – in addition to **8** – to the formation of conjugate reduction products **10** and **11**. Saponification of the ester group in **8** furnished the aromatic prostaglandin analogue **9** in 49% overall yield from **1**.

Cyclohexane analogues

In the case of the cyclohexane prostaglandin analogues the side chains may be in a *cis* or a *trans* position relative to each other; both isomers were synthesized.

The *trans* analogue **20** was obtained starting from the Diels-Alder adduct of butadiene with *trans* olefine**12**[10]. Reduction of the ester group in adduct **13*** to a hydroxy-



* For racemic compounds only one enantiomer is shown throughout this publication.

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[2] *G. P. Rozing, T. J. H. Moinat, H. de Koning* and *H. O. Huisman*, Heterocycles **4**, 719 (1976) and references cited therein.
[3] *J. Fried, T. S. Santhanakrishnan, J. Himizu, C. H. Lin, S. H. Ford, B. Rubin* and *E. O. Grigas*, Nature **223**, 208 (1969); *N. S. Crossley*, Tetrahedron Lett. 3327 (1971); *J. M. Muchowski* and *E. Velarde*, Prostaglandins **10**, 297 (1975).
[4] *A. Colllet* and *J. Jacques*, Chim. Ther. **5**, 163 (1970).
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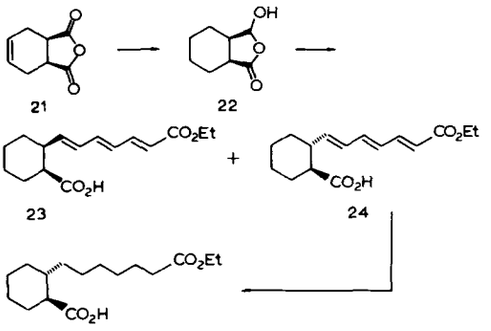
[6] *H. C. Brown, P. Heim* and *N. M. Yoon*, J. Amer. Chem. Soc. **92**, 1637 (1970).
[7] *K. Ishizumi, K. Koga* and *S. Yamada*, Chem. Pharm. Bull. (Tokyo) **16**, 492 (1968).
[8] *J. S. Pizey*, "Synthetic Reagents", Vol. II, John Wiley & Sons Inc., New York, 1974, p. 143.
[9] *E. J. Corey, N. M. Weinshenker, T. K. Schaaf* and *W. Huber*, J. Amer. Chem. Soc. **91**, 5675 (1969).
[10] Prepared by Horner reaction of 7-cyanoheptanal[11] with trimethyl phosphonoacetate.
[11] Org. Synth. **49**, 27 (1969).

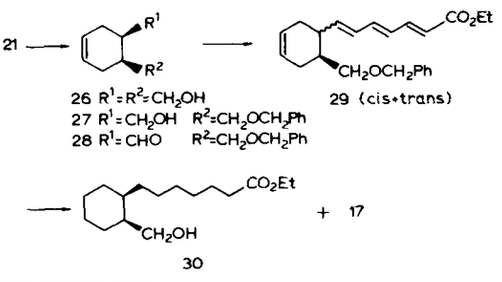
methyl function was accomplished with lithium tetrahydridoborate in refluxing dimethoxyethane. Saponification of the cyano group in **14** afforded carboxylic acid **15**, which was esterified with ethanol in the presence of sulfuric acid to give **16**. Catalytic hydrogenation of the double bond in **16** produced **17** which, upon Moffatt oxidation[12], afforded aldehyde **18**. Horner reaction of **18** with the anion of dimethyl 2-oxoheptylphosphonate gave enone **19**. Subsequent reduction of the oxo function with zinc tetrahydridoborate provided prostaglandin analogue **20** as an inseparable mixture of C(15)-epimeric alcohols in 34% overall yield from **12**.

For the synthesis of the corresponding *cis* analogue, the Diels-Alder adduct **21** of butadiene with maleic anhydride seemed initially an obvious choice. This adduct had to be functionalized in order to introduce the side chains *via* condensation reactions.



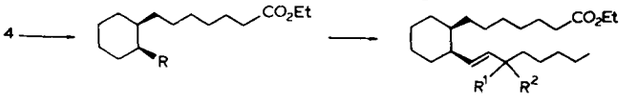
In accordance with our experiences in the reduction of other cyclic anhydrides[13], catalytic hydrogenation of **21** in ethanol[14] over 10% Pd/C catalyst reduced both the olefinic double bond and the anhydride part of the molecule, leading to the formation of the saturated hemi-acylal **22**. Upon prolonged hydrogenation more than two equivalents of hydrogen were consumed, producing hexahydrophthalide and/or 2-methylcyclohexanecarboxylic acid, depending on the reaction time. Horner reaction of **22** with triethyl phosphonosorbate **2** in tetrahydrofuran with two equivalents of sodium hydride gave a mixture of **23** and **24**, due to partial isomerization of the aldehyde during the reaction. The isomers could neither be separated at this stage, nor at later stages of the synthesis. If hemi-acylal **22** was stirred in the presence of sodium ethoxide in ethanol, prior to addition of the phosphonosorbate to the reaction mixture, only *trans* isomer **24** was isolated. This compound could be converted into the alcohol **17** by catalytic hydrogenation, affording **25**, followed by subsequent reduction of the carboxyl function by the mixed carbonic anhydride method.

In another approach adduct **21** was functionalized by reduction of the anhydride with lithium tetrahydridoaluminate to give diol **26**.



After protection of one of the hydroxyl functions as benzyl ether (**27**), the remaining carbinol was converted into an aldehyde by Moffatt oxidation. Horner reaction of aldehyde **28** with triethyl phosphonosorbate, however, again gave an inseparable mixture of *cis-trans* isomers **29** because of partial isomerization of the aldehyde during the reaction. The mixture of saturated alcohols **30** and **17**, obtained by catalytic hydrogenation of **29**, could equally not be separated. The *trans* compound **17** could be obtained exclusively if the *cis* aldehyde **28** was isomerized with sodium ethoxide in ethanol before the Horner reaction.

A successful approach to the synthesis of the *cis* prostaglandin analogue was found *via* aromatic intermediate **4**, which could be hydrogenated stereospecifically over PtO_2 in acetic acid to give exclusively *cis* compound **31**.



The *cis* stereochemistry was deduced from the ^{1}H-NMR spectrum, exhibiting a multiplet at δ 2.5–2.75, indicating an equatorial position for the ring proton adjacent to the carboxyl group; the corresponding (axial) proton in the *trans* compound **25** was found at δ 1.9–2.15. Selective conversion of the carboxyl function in **31** to give the *cis*-carbinol **30** was accomplished by reduction with sodium tetrahydridoborate of the mixed carbonic anhydride. Moffatt oxidation of **30** furnished aldehyde **32**, which reacted with the anion of dimethyl 2-oxoheptylphosphonate in tetrahydrofuran at ambient temperature to provide enone **33**. According to the ^{1}H-NMR spectrum no isomerization of the aldehyde had occurred during the reaction. Reduction of the oxo function with zinc tetrahydridoborate gave a mixture of the C(15)-epimeric prostaglandin analogues **34** in 53% overall yield from **1**.

An interesting difference was observed between the ^{1}H-NMR spectra of the *cis* and the *trans* isomers. The vinyl proton adjacent to the cyclohexane ring in the *cis* compounds **33** and **34** was deshielded ~ 0.4 ppm relative to the corresponding proton in the *trans* isomers **19** and **20**, respectively.

Pharmacological data

The prostaglandin analogues **8**, **20** and **34** were submitted to several biological tests*, but showed no noteworthy activity (see Table I).

Table I

Compound	$PGF_{2\alpha}$ antibody binding[a]	15-OH-PG-dehydrogenase[b] ($PGF_{2\alpha}$ = 100)	Inhibition of Indomethacin induced gastric ulcers[c] (ED 50; ug/kg)
8	40,000	4	>1000
20	40,000	24	>1000
34	50,000	14	800

[a] Relative mass of an analogue required to displace labelled $PGF_{2\alpha}$ from a $PGF_{2\alpha}$ antibody, equivalent to 1.0 pg of $PGF_{2\alpha}$ when measured at the 100 pg $PGF_{2\alpha}$ displacement level.

[b] Initial velocities of the analogues (all tested as free carboxylic acids) relative to an equimolar amount of $PGF_{2\alpha}$ as measured at 340 nm.

[c] Indomethacin (100 mg) was administered subcutaneously to mice and a dispersion of drug from an alcohol solution in gum acacia was given every 30 min for 6 h. The stomach was examined at 6 h and the presence or absence of ulceration and haemorrhage was graded.

* Kindly performed by Hoffmann–La Roche Inc., Nutley, U.S.A.; we thank Dr. *W. Leimbruber* for making these results available to us.

[12] *K. E. Pfitzer* and *J. G. Moffatt*, J. Amer. Chem. Soc. **87**, 5661, 5670 (1965).

[13] *T. A. Eggelte, H. de Koning* and *H. O. Huisman*, Tetrahedron **29**, 2445 (1973).

[14] In ethyl acetate or acetone as solvent, only the olefinic double bond was reduced.

At 10^{-5} M they were inactive in PG-synthetase inhibition[15] and caused no aggregation of human platelets or inhibition of collagen-induced aggregation.

Experimental part

Melting points (uncorrected) were determined on a Leitz hot stage microscope. Spectral measurements were performed on the following instruments: IR (absorption maxima given in cm^{-1}), Unicam SP-200 and Perkin-Elmer 125 spectrophotometers with $CHCl_3$ as solvent; UV, Cary-14 recording spectrophotometer with ethanol as solvent; ^{1}H-NMR, Varian A-60, A-60 D and HA-100 spectrometers, using $CDCl_3$ as solvent. Line positions for NMR spectra are given in the δ scale as ppm downfield from internal tetramethylsilane; coupling constants are given in Hz. Elemental analyses were performed by Mr. *H. Pieters* of this laboratory. Reactions were carried out at room temperature, unless otherwise stated.

Ethyl 7-(2-carboxyphenyl)-(E,E,E)*-2,4,6-heptatrienoate* **3**

A solution of hydroxyphthalide **1** (6.0 g, 40 mmol) and phosphonate **2** (11.2 g, 41 mmol) in THF (75 ml) was added drop by drop to a dispersion of sodium hydride (2.1 g, 87 mmol) in THF (75 ml). After stirring for 18 h, the mixture was acidified with dilute HCl and extracted with ether. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give crude, crystalline **3**. Crystallization from cyclohexane/ethyl acetate afforded 8.8 g (81%) of triene **3**, m.p. 146–148°: IR (KBr) 3400–2400 (CO_2H), 1700 (CO_2Et), 1670 (CO_2H), 1620, 1600 and 1560 (triene, aromatic ring); NMR 1.30 (t, J = 7, CH_3), 4.23 (q, J = 7, OCH_2), 5.91 (d, J = 15.5, C(2)–H), 6.25–6.60 (m, C(4)–H), 6.60–7.00 (m, C(5)–H), 6.79 (d, J = 14.5, C(7)–H), 7.20–7.90 (m, C(3)–H, C(6)–H and 3 aromatic H) and 7.95–8.15 (m, aromatic C(3)–H); UV, 247 (ε 15200) and 340 nm (ε 66900). $C_{16}H_{16}O_4$ (272.29); calcd. C 70.57 H 5.92; found C 70.6 H 6.0.

Ethyl 7-(2-carboxyphenyl)heptanoate **4**

A mixture of **3** (10.7 g), 10% palladium on carbon (0.50 g) and ethyl acetate (150 ml) was hydrogenated in a Parr apparatus for 5 h. The reaction mixture was filtered and the solvent removed *in vacuo* to yield 10.7 g (98%) of **4**: IR, 3500–2500 (CO_2H), 1730 (CO_2Et), 1700 (CO_2H), 1605 and 1580 (aromatic ring); NMR, 1.22 (t, J = 7, CH_3), 1.0–2.0 [m, $(CH_2)_4$], 2.30 (t, J = 6.5, CH_2CO_2Et), 3.05 (t, J = 7, $ArCH_2$), 4.13 (q, J = 7, OCH_2), 7.1–7.65 (m, 3 aromatic H), 7.9–8.1 (aromatic C(3)–H) and 11.1–11.5 (COOH). $C_{16}H_{22}O_4$ (278.34); calcd. C 69.04 H 7.97; found C 68.9 H 7.8.

Ethyl 7-[2-(hydroxymethyl)phenyl]heptanoate **5**

(i) Ethyl chloroformate (225 mg, 2.07 mmol) in THF (5 ml) was added to a solution of carboxylic acid **4** (560 mg, 2.01 mmol) and triethylamine (205 mg, 2.03 mmol) in THF (10 ml) at −5°. After stirring for 30 min at −5° the reaction mixture was filtered and the solution added slowly to $NaBH_4$ (200 mg) in water (10 ml) at 15°. The mixture was stirred for 2 h at room temperature, and then, after cooling, the excess $NaBH_4$ was decomposed with dilute HCl. The mixture was extracted with ether and the combined extracts were washed with saturated solutions of $NaHCO_3$ and NaCl. Drying ($MgSO_4$) and evaporation of the solvent gave 510 mg (96%) of **5**.

(ii) A 1 *M* solution of diborane in THF (2 ml) was added slowly at −5° to a solution of **4** (400 mg, 1.44 mmol) in THF (5 ml). After stirring for 5 min at −5° water was added and the reaction mixture extracted with ether. Following the washing procedure described under *(i)* 370 mg (97%) of carbinol **5** were obtained: IR, 3500 (OH), 1720 (CO_2Et), 1600 and 1580 (aromatic ring); NMR, 1.23 (t, J = 7, CH_3), 2.29 (t, J = 7, CH_2CO_2Et), 2.63 (t, J = 7, $ArCH_2$), 4.13 (q, J = 7, OCH_2), 4.71 (s, $ArCH_2O$) and 7.15–7.45 (m, 4 aromatic H). $C_{16}H_{24}O_3$ (264.35); calcd. C 72.69 H 9.15; found C 72.5 H 9.3.

Ethyl 7-(2-formylphenyl)heptanoate **6**

A mixture of alcohol **5** (150 mg, 0.57 mmol) and manganese dioxide (2.0 g) in dichloromethane (10 ml) was stirred for 18 h. The manganese oxides were filtered off and washed with dichloromethane. Evaporation of the solvent furnished 148 mg (99%) of aldehyde **6** (oil): IR, 1720 (CO_2Et), 1695 (CHO), 1605 and 1580 (aromatic ring); NMR, 1.22 (t, J = 7, CH_3), 2.26 (t, J = 7, CH_2CO_2Et), 3.01 (t, J = 7, $ArCH_2$), 4.10 (q, J = 7, OCH_2), 7.1–7.6 (m, 3 aromatic H), 7.6–7.8 (aromatic C(3)–H) and 9.66 (s, CHO). 2,4-Dinitrophenylhydrazone, m.p. 113–115°: $C_{22}H_{26}N_4O_6$ (442.46); calcd. C 59.72 H 5.92; found C 59.7 H 5.9.

Ethyl 7-[2-(3-oxo-(E)*-1-octenyl)phenyl]heptanoate* **7**

Dimethyl 2-oxoheptylphosphonate (800 mg, 3.60 mmol) in THF (5 ml) was added to sodium hydride (96 mg, 4.0 mmol) in THF (10 ml) under N_2, and stirred for 10 min. To this solution aldehyde **6** (830 mg, 3.17 mmol) in THF (10 ml) was added and stirring continued for 2 h. After addition of water, the reaction mixture was extracted with ether. The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give 1.35 g of crude product which was purified on a silica gel column (cyclohexane: ethyl acetate = 3 : 1), yielding 840 mg (74%) of enone **7** as an oil: IR, 1720 (CO_2Et), 1685 (C=O), 1660 (C=C), 1610 and 1600 (aromatic ring); NMR, 0.91 (t, J = 6, CH_3), 1.23 (t, J = 7, ester CH_3), 2.26 (t, J = 7, CH_2CO_2Et), 2.62 and 2.72 (2 t, both J = 7, $COCH_2$ and $ArCH_2$), 4.10 (q, J = 7, OCH_2), 6.65 (d, J = 16, C=CHCO), 7.10–7.55 (m, 3 aromatic H), 7.50–7.70 (aromatic C(3)–H) and 7.81 (d, J = 16, ArCH=C); UV, 226 (ε 9000) and 292 nm (ε 15800). $C_{23}H_{34}O_3$ (358.50); calcd. C 77.05 H 9.56; found C 77.0 H 9.5.

Ethyl 7-[2-(3-hydroxy-(E)*-1-octenyl)phenyl]heptanoate* **8**

To a solution of enone **7** (2.05 g, 5.72 mmol) in dimethoxyethane (20 ml) was added dropwise a solution of $Zn(BH_4)_2$ in dimethoxyethane (8 ml; 0.5 *M*). After stirring for 2 h, the excess reagent was destroyed with a saturated solution of potassium sodium tartrate. Then water was added and the reaction mixture was extracted with ether. Drying ($MgSO_4$) and evaporation of the extracts gave 2.05 g (99%) of alcohol **8** (oil): IR, 3550 (OH) and 1720 (CO_2Et); NMR, 0.89 (t, J = 6, CH_3), 1.21 (t, J = 7, ester CH_3), 2.12 (OH), 2.26 (t, J = 7, CH_2CO_2Et), 2.64 (t, J = 8, $ArCH_2$), 4.09 (q, J = 7, OCH_2), 4.12–4.4 (m, C*H*OH), 6.06 (dd, J = 16 and 6.5, ArC=CH), 6.80 (d, J = 16, ArCH=C), 7.1–7.3 (m, 3 aromatic H) and 7.3–7.5 (m, aromatic C(3)–H). $C_{23}H_{36}O_3$ (360.52); calcd. C 76.62 H 10.07; found C 76.4 H 10.1.

7-[2-(3-Hydroxy-(E)*-1-octenyl)phenyl]heptanoic acid* **9**

Ester **8** (330 mg, 0.92 mmol) was saponified by stirring for 1 h with NaOH (100 mg) in ethanol/water 2 : 1 (10 ml). Then water was added and the mixture extracted with ether. The aqueous phase was acidified with dilute HCl to pH 3–4 and extracted with ether. After drying ($MgSO_4$), the organic phase was concentrated *in vacuo* to afford 265 mg (87%) of acid **9** as an oil: NMR, 0.83 (t, J = 6, CH_3), 2.32 (t, J = 7, CH_2CO_2H), 2.64 (t, J = 7.5, $ArCH_2$), 4.2–4.5 (C*H*OH), 6.05 (dd, J = 15.5 and 6, ArC=CH), 6.5–7.05 (COOH), 6.70 (d, J = 15.5, ArCH=C), 7.05–7.25 (m, 3 aromatic H) and 7.30–7.55 (m, aromatic C(3)–H). $C_{21}H_{32}O_3$ (332.47); calcd. C 75.86 H 9.70; found C 75.7 H 9.5.

Ethyl 7-[2-(3-hydroxyoctyl)phenyl]heptanoate **11**

IR, 3500 (OH) and 1720 (CO_2Et); NMR, 0.89 (t, J = 7, ester CH_3), 1.92 (OH), 2.28 (t, J = 7, CH_2CO_2Et), 2.9–3.5 (2 × $ArCH_2$), 3.45–3.60 (m, C*H*OH), 4.11 (q, J = 7, OCH_2) and 7.10 (4 aromatic H). $C_{23}H_{38}O_3$ (362.53); calcd. C 74.51 H 11.32; found C 74.8 H 11.0.

*7-[*trans*-6-(Methoxycarbonyl)-3-cyclohexenyl]heptanenitrile* **13**

A mixture of ester[10] (12.0 g), butadiene (50 ml) and xylene (30 ml) was heated for 40 h at 240° in an autoclave. The solvent was evaporated and the residue distilled to give 10.5 g (69%) of **13**, b.p. 130–135° at 0.02 Torr: IR, 2240 (CN) and 1725 (CO_2Me); NMR, 2.36 (t, J = 7.5, CH_2CN), 3.74 (s, OCH_3) and 5.50–5.80 (C(3)–H, C(4)–H). $C_{15}H_{23}NO_2$ (249.34); calcd. C 72.25 H 9.30 N 5.62; found C 72.1 H 9.2 N 5.5.

*7-[*trans*-6-(Hydroxymethyl)-3-cyclohexenyl]heptanenitrile* **14**

A solution of ester **13** (1.23 g, 4.93 mmol) and $LiBH_4$ (0.25 g, 11 mmol) in THF (25 ml) was refluxed under N_2 for 48 h. After

[15] Assayed as described by *W. L. Smith* and *W. E. M. Lands*, J. Biol. Chem. **246**, 6700 (1971).

cooling, water was added carefully and the mixture extracted with ether. The organic phase was dried ($MgSO_4$) and evaporated to yield 950 mg (87%) of carbinol **14**: IR, 3500 (OH) and 2240 (CN); NMR, 2.27 (t, J = 7.5, CH_2CN), 3.40–3.75 (m, CH_2O) and 5.4–5.75 (C(3)–H, C(4)–H). $C_{14}H_{23}NO$ (221.33); calcd. C 75.97 H 10.47 N 6.33; found C 75.8 H 10.4 N 6.3.

*Ethyl 7-(*trans*-6-hydroxymethyl-3-cyclohexenyl)heptanoate* **16**

A solution of nitrile **14** (1.20 g, 5.43 mmol) and KOH (0.40 g) in methanol (2 ml) and water (10 ml) was refluxed for 40 h. After addition of water (15 ml) the mixture was extracted with ether. The aqueous phase was acidified and extracted with ether. This ethereal extract was dried ($MgSO_4$) and concentrated *in vacuo* to give 1.1 g (84%) of crude acid **15**: IR, 3500–2500 and 1705 (CO_2H). The acid (1.1 g) was refluxed for 18 h in ethanol (50 ml) in the presence of H_2SO_4 (0.5 ml). After partial evaporation of the solvent, water was added and the mixture was extracted with ether. The ether extracts were washed with $NaHCO_3$ solution, dried and concentrated *in vacuo* to afford 1.18 g (96%) of ester **16**: IR, 3500 (OH) and 1720 (CO_2Et); NMR, 1.28 (t, J = 7, CH_3), 2.29 (t, J = 7, CH_2CO_2Et), 3.45–3.80 (CH_2OH), 4.16 (OCH_2) and 5.60 (C(3)–H, C(4)–H). $C_{16}H_{28}O_3$ (268.38); calcd. C 71.60 H 10.52; found C 71.6 H 10.5.

*Ethyl 7-[*trans*-2-(hydroxymethyl)cyclohexyl]heptanoate* **17**

(i) Catalytic hydrogenation of **16** gave the saturated compound **17** in quantitative yield.
(ii) Reduction of the carboxyl function in **25** (5.7 g) *via* the mixed carbonic anhydride, following the procedure described for the preparation of **30**, afforded **17** in 60% yield after column chromatography.
(iii) Catalytic hydrogenation and debenzylation of *trans*-**29** (700 mg) over 10% Pd/C (0.10 g) in ethyl acetate (10 ml) and acetic acid (5 ml) for 18 h yielded 510 mg (95%) of **17**: IR, 3600 and 3450 (OH), 1720 (CO_2Et); NMR, 1.23 (t, J = 7, CH_3), 2.28 (t, J = 7.5, CH_2CO_2Et), 2.47 (s, OH), 3.4–3.7 (m, CH_2OH and 4.12 (q, J = 7, OCH_2). $C_{16}H_{30}O_3$ (270.40); calcd. C 71.07 H 11.18: found C 70.9 H 11.0.

*Ethyl 7-(*trans*-2-formylcyclohexyl)heptanoate* **18**

Carbinol **17** (3.27 g, 12.1 mmol) and dicyclohexylcarbodiimide (8.24 g) were dissolved in anhydrous dimethyl sulfoxide (20 ml) and benzene (20 ml) containing pyridine (1.04 g) and trifluoroacetic acid (0.75 g). The mixture was stirred for 18 h. After addition of ether (100 ml), oxalic acid (4.3 g) was added carefully. After evolution of gas had ceased (about 0.5 h), water was added and dicyclohexylurea was removed by filtration. The organic layer was washed with saturated bicarbonate and brine, and dried ($MgSO_4$). Evaporation of the solvent gave 4.0 g of crude aldehyde **18**, which was not purified: NMR, 1.25 (t, J = 7, CH_3), 2.25 (t, J = 7, CH_2CO_2Et), 4.10 (q, J = 7, OCH_2) and 9.54 (d, J = 3, CHO).

*Ethyl 7-[*trans*-2-(3-oxo-*(E)*-1-octenyl)cyclohexyl]heptanoate* **19**

Crude aldehyde **18** (3.8 g) in THF (10 ml) was added dropwise to a solution of the phosphonate carbanion, prepared from sodium hydride (0.36 g; 15 mmol) and dimethyl 2-oxoheptylphosphonate (2.67 g; 12 mmol) in THF (40 ml), under a nitrogen atmosphere. The mixture was stirred for 2 h and, after addition of water, extracted with ether. The organic phase was dried ($MgSO_4$) and concentrated to give 5.6 g of crude product, which was purified by column chromatography using silica gel (cyclohexane/ethyl acetate 5 : 1), to afford 3.06 g (73% from **17**) of enone **19**: IR, 1720 (CO_2Et), 1660 (C=O) and 1615 (C=C); NMR, 0.94 (t, J = 6, CH_3), 1.29 (t, J = 7, ester CH_3), 2.31 (t, J = 7.5, CH_2CO_2Et), 2.56 (t, J = 7.5, $COCH_2$), 4.15 (q, J = 7, OCH_2), 6.09 (d, J = 16, C=CHCO) and 6.59 (dd, J = 16 and 9, CH=CCO). $C_{23}H_{40}O_3$ (364.55); calcd. C 75.77 H 11.06; found C 75.9 H 11.2.

*Ethyl 7-[*trans*-2-(3-hydroxy-*(E)*-1-octenyl)cyclohexyl]heptanoate* **20**

Enone **19** (2.2 g, 6.0 mmol) was reduced with $Zn(BH_4)_2$ (4 mmol), as described for **8**, to give 2.15 g (97%) of prostaglandin analogue **20**: IR, 3500 (OH) and 1720 (CO_2Et); NMR, 0.93 (t, J = 6, CH_3), 1.30 (t, J = 7, ester CH_3), 2.29 (t, J = 7.5, CH_2CO_2Et), 3.95–4.20 ($CHOH$), 4.18 (q, J = 7, OCH_2) and 5.35–5.50 (CH=CH).

Hexahydrohydroxyphthalide **22**

Tetrahydrophthalic anhydride **21** (15.0 g) was hydrogenated over 10% Pd/C catalyst (1.0 g) in ethanol (100 ml) in a Parr apparatus. After uptake of 2 mol. equivs. of hydrogen the reaction was terminated and the catalyst was filtered off. Evaporation of the solvent gave an oil which slowly crystallized. Recrystallization from cyclohexane/ethyl acetate afforded 10.7 g (70%) of hemi-acylal **22**, m.p. 80–81°: IR (KBr), 3400 (OH) and 1760 (C=O); NMR, 2.8–3.2 (m, >CHC=O), 5.54 and 5.72 (both s, $CHOH$). $C_8H_{12}O_3$ (156.18); calcd. C 61.52 H 7.75; found C 61.7 H 7.8.

*Ethyl 7-(*trans*-2-carboxycyclohexyl)-*(E,E,E)*-2,4,6-heptatrienoate* **24**

Hemi-acetal **22** (4.7 g, 30 mmol) was stirred for 1 h with a solution of sodium (1.5 g, 65 mmol) in dry ethanol (75 ml) under N_2. Then phosphonate **2** (8.4 g, 30 mmol) was added drop by drop and stirring was continued for 3.5 h. The mixture was acidified with dilute HCl and extracted with ether. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give 7.9 g of crude material which was purified by column chromatography over silica gel (eluent ethyl acetate) affording 5.7 g (68%) of triene **24**: IR, 3500–2500 (CO_2H), 1700 (CO_2Et, CO_2H) and 1615 (triene); NMR, 1.29 (t, J = 7, CH_3), 4.19 (q, J = 7, OCH_3), 4.19 (q, J = 7, OCH_3) and 5.6–7.6 (6 vinylic H).

*Ethyl 7-(*trans*-2-carboxyxyclohexyl)heptanoate* **25**

Triene **24** (5.7 g) in ethyl acetate (100 ml) was hydrogenated over 10% Pd/C catalyst (0.5 g) in a Parr apparatus, yielding 5.7 g (98%) of the saturated compound **25**: IR, 3500–2500 (CO_2H), 1725 (CO_2Et) and 1705 (CO_2H); NMR, 1.26 (t, J = 7, CH_3), 2.29 (t, J = 7.5, CH_2CO_2Et), 1.9–2.15 ($CHCO_2H$), 4.13 (q, J = 7, OCH_2) and 9.2–9.6 (CO_2H). $C_{16}H_{28}O_4$ (284.38); calcd. C 67.57 H 9.93; found C 67.6 H 10.0.

cis-*4,5-Bis(hydroxymethyl)cyclohexene* **26**

To $LiAlH_4$ (9.0 g, 0.24 mol) in THF (250 ml) was added dropwise at 0° (under N_2) a solution of anhydride **21** (25.8 g, 0.17 mol) in THF (100 ml). After stirring for 18 h at room temperature, the mixture was cooled in ice and treated carefully with subsequently water (9 ml), 10% NaOH (9 ml) and water (27 ml). Stirring was continued for 20 min and then the precipitate was filtered off and washed with ether. The combined filtrates were dried and evaporated *in vacuo* to give 21.6 g (90%) of diol **26**: IR, 3380 (OH); NMR, 2.04 (C(3)- and C(6)–H_2, C(4)- and C(5)–H), 3.2–3.9 (CH_2O), 4.79 (OH) and 5.60 (C(1)- and C(2)–H). $C_8H_{14}O_2$ (142.19); calcd. C 67.57 H 9.93; found C 67.5 H 10.1.

cis-*4-(Benzyloxymethyl)-5-(hydroxymethyl)cycldhexene* **27**

Diol **26** (14.2 g, 0.10 mol) in dimethylformamide (50 ml) was added dropwise (under N_2) to sodium hydride (2.7 g, 0.11 mol) in dimethylformamide (50 ml). The mixture was stirred for 20 min, then benzyl bromide (19.0 g, 0.11 mol) was added and stirring was continued for 18 h at 70°. After removing dimethylformamide *in vacuo*, water was added and the mixture was extracted with ether. The extracts were dried ($MgSO_4$) and the solvent was evaporated to give the crude product, which was distilled to afford 14.5 g (62%) of the monobenzyl ether **27**, b.p. 140–145° at 0.02 Torr: IR, 3480 (OH); NMR, 1.7–2.5 (C(3)- and C(6)–H_2, C(4)- and C(5)–H), 3.0 (OH), 3.2–3.7 (2 × CH_2O), 4.47 ($PhCH_2$), 5.59 (C(1)- and C(2)–H) and 7.29 (aromatic H). $C_{15}H_{20}O_2$ (232.31); calcd. C 77.55 H 8.68; found C 77.5 H 8.7.

*Ethyl 7-[*trans*-6-(benzyloxymethyl)-3-cyclohexenyl]-*(E,E,E)*-2,4,6-heptatrienoate* **29** (trans)

Moffatt oxidation of hydroxymethyl compound **27** (350 mg, 1.51 mmol), carried out as described for the synthesis of **18**, gave crude aldehyde **28**: IR, 1700 (CHO); NMR, 3.3–3.6 (2 × CH_2O), 4.43 ($PhCH_2$), 5.64 (C(1)- and C(2)–H), 7.29 (aromatic H) and 9.80 (s, CHO).
This crude aldehyde was stirred for 25 min with sodium ethoxide (2 mmol) in dry ethanol (5 ml) and then triethyl phosphonosorbate **2** (600 mg, 2.17 mmol) was added. After stirring for 24 h water was added and the mixture was extracted with ether. The extract was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was chromatographed over silica gel (cyclohexane/ethyl acetate 5 : 1) to afford 390 mg (73% from **27**) of *trans*-**29**: IR, 1695 (CO_2Et) and 1610 (triene).

*Ethyl 7-(*cis*-2-carboxycyclohexyl)heptanoate* **31**

A solution of aromatic compound **4** (300 mg) in acetic acid (15 ml) was hydrogenated over PtO_2 (50 mg) in a Parr apparatus. The reaction time was dependent on the activity of the catalyst. The mixture was filtered through hyflo and the filtrate was evaporated *in vacuo* to give 307 mg (100%) of cyclohexane derivative **31** as an oil: IR, 3500–2500 (CO_2H), 1720 (CO_2Et) and 1700 (CO_2H); NMR, 1.28 (t, J = 7, CH_3), 2.31 (t, J = 7.5, CH_2CO_2Et), 2.5–2.75 ($CHCO_2H$), 4.15 (q, J = 7, OCH_2) and 8.1–8.6 (CO_2H). $C_{16}H_{28}O_4$ (284.38); calcd. C 67.57 H 9.93; found C 67.3 H 9.8.

*Ethyl 7-[*cis*-2-(hydroxymethyl)cyclohexyl]heptanoate* **30**

A solution of ethyl chloroformate (1.20 g, 11.1 mmol) in THF (5 ml) was added to a solution of triethylamine (1.13 g, 11.2 mmol) and carboxylic acid **31** (2.84 g, 10.0 mmol) in THF (20 ml) at −5°. After stirring for 45 min at −45° the reaction mixture was filtered and the filtrate was added drop by drop to a solution of $NaBH_4$ (1.5 g) in ethanol (50 ml) at 0°. The reaction mixture was stirred for 3 h, after which the excess $NaBH_4$ was decomposed with dilute HCl. Water was then added and the mixture was extracted with ether. The ethereal extracts were washed with water, saturated solutions of $NaHCO_3$ and NaCl, and dried over $MgSO_4$. Evaporation of the solvent gave 2.71 g of crude product, which was chromatographed on silica gel (cyclohexane/ethyl acetate 5 : 1) to yield 2.23 g (83%) of carbinol **30**: IR, 3600 and 3450 (OH), and 1720 (CO_2Et); NMR, 1.28 (t, J = 7, CH_3), 2.32 (t, J = 7, CH_2CO_2Et), 2.44 (s, OH), 3.4–3.7 (CH_2OH) and 4.14 (q, J = 7, OCH_2). $C_{16}H_{30}O_3$ (270.40); calcd. C 71.07 H 11.18; found C 70.9 H 11.0.

*Ethyl 7-[*cis*-2-(3-oxo-*(E)*-1-octenyl)cyclohexyl]heptanoate* **33**

Mofatt oxidation of hydroxymethyl compound **30** (2.23 g, 8.26 mmol), carried out as described for the preparation of **18**, gave crude aldehyde **32** (2.76 g): IR, 1715 (CHO, CO_2Et); NMR, 1.26 (t, J = 7, CH_3), 2.0–2.25 ($CHCHO$), 2.30 (t, J = 7.5, CH_2CO_2Et), 4.13 (q, J = 7, OCH_2) and 9.88 (d, J = 1.5, CHO). Crude aldehyde **32** (2.56 g) was converted with dimethyl 2-oxo-heptylphosphonate, following the procedure described for the synthesis of **19**. The crude product (3.5 g) was chromatographed on silica gel (cyclohexane/ethyl acetate 5 : 1), yielding 2.31 g (83% from **30**) of enone **33**: IR, 1720 (CO_2Et), 1660 (C=O) and 1615 (C=C); NMR, 0.96 (t, J = 6.5, CH_3), 1.30 (t, J = 7, ester CH_3), 2.33 (t, J = 7.5, CH_2CO_2Et), 2.59 (t, J = 7.5, $COCH_2$), 2.40–2.70 (CHC=C), 4.16 (q, J = 7, OCH_2), 6.14 (d, J = 16, C=CHCO) and 7.04 (dd, J = 16 and 8.5, CH= =CCO). $C_{23}H_{40}O_3$ (364.55); calcd. C 75.77 H 11.06; found C 75.7 H 11.1.

*Ethyl 7-[*cis*-2-(3-hydroxy-*(E)*-1-octenyl)cyclohexyl]heptanoate* **34**

Reduction of enone **33** (2.23 g) with $Zn(BH_4)_2$ as described for **8**, afforded 2.15 g (96%) of prostaglandin analogue **34**: IR, 3500 (OH) and 1720 (CO_2Et); NMR, 0.96 (t, J = 6.5, CH_3), 1.30 (t, J = 7, ester CH_3), 2.34 (t, J = 7.5, CH_2CO_2Et), 2.25–2.50 (CHC=C), 4.0–4.25 ($CHOH$), 4.14 (q, J = 7, OCH_2), 5.49 (dd, J = 16.5 and 7.5, C=CHC–O) and 5.84 (dd, J = 16.5 and 8, CH=C–C–O).

Boron trifluoride catalysed rearrangement and decarbonylation of quinoid γ-oxo-α,β-unsaturated thiolesters. α-Alkylthio-γ-lactones*

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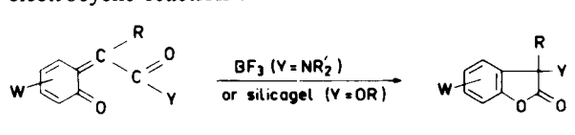
Abstract. Under the influence of boron trifluoride quinoid γ-oxo-α,β-unsaturated thiolesters (**5**) and (**10**) rearrange into α-alkylthio-γ-lactones (**6**) and (**9**), respectively, in yields of 50–90%. In the case of *S*-alkyl 2-(10-oxo-9-phenanthrenylidene)alkanethioates (**13**) decarbonylation occurs with formation of α,β-unsaturated ketones (**14**). Mechanisms are proposed. The γ-oxo-α,β-unsaturated thiolesters were prepared *in situ* from a 1-alkynyl sulfide and 3,5-di-*tert*-butyl-*o*-benzoquinone or 9,10-phenanthroquinone, under the influence of boron trifluoride.

Introduction

Recently we reported on rearrangements of quinoid γ-oxo-α,β-unsaturated amides (**1**: Y = NR_2) into α-dialkylamino-γ-lactones (**2**: Y = NR_2) under the influence of boron trifluoride[1]. The corresponding esters (**1**: Y = OR) could be rearranged under the influence of silica gel into α-alkoxy-γ-lactones (**2**: Y = OR)[2]. The same products (**2**: Y = OR) could be obtained photochemically *via* a [4 + 2] electrocyclic reaction[2].



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In order to get a better insight into the scope and the mechanism of the boron trifluoride catalysed rearrangements, we studied the behaviour of γ-oxo-α,β-unsaturated thiolesters towards boron trifluoride.

Results

α,β-Unsaturated thiolesters can be prepared by boron trifluoride catalysed addition of carbonyl compounds to (alkylthio)acetylenes[3–6]. In order to prepars γ-oxo-α,β-unsaturated thiolesters like (**5**) and (**10**) we treated mixtures of an *o*-quinone and an (alkylthio)acetylene in chloroform with boron trifluoride/diethyl ether.

*Boron trifluoride catalysed addition of 3,5-di-*tert*-butyl-o-benzoquinone to Alk–C≡C–SR;* γ-lactones

Boron trifluoride catalysed reaction of 3,5-di-*tert*-butyl-*o*-benzoquinone (**3**) to 1-alkynyl sulfides (**4**) appeared to afford 3-(alkylthio)benzofuran-2-one derivatives (**6**) in good yield. The structures of the lactones (**6**) were deduced from their spectral data (see Experimental part). Obviously the

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