Total Synthesis of (±)-8-Aza-9a,9b-dicarbaprostaglandin H_1 [1]

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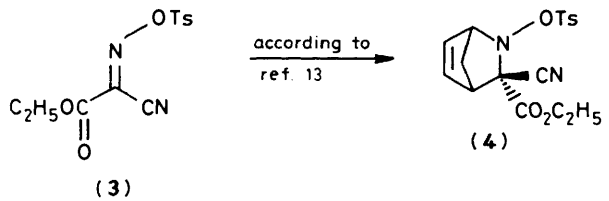
The total synthesis of a stable prostaglandin H_1 analogue in which the bicyclic peroxide system is replaced by a 2-azabicyclo[2.2.1]heptane ring is described. Appropriate functionalization of the heterocycle and de-ethoxycarbonylation of an α-trifluoroacetamido-α-cyano ester were key reactions. Incorporation of side-chains completed the 13-step synthesis.

Among structural modifications which have met with interest in the prostaglandin field is the substitution of the C-8 carbon atom by a nitrogen atom, *i.e.* 8-azaprostaglandins,[2] which should confer more flexibility to the upper side-chain. In addition, increasing efforts have been expended to construct stable analogues[3] of prostaglandin endoperoxides whose discovery[4] has been one of the major events in the elucidation of the arachidonic cascade.[5] Bringing together these two concerns led us to prepare a stable prostaglandin endoperoxide (PGH) analogue, in which the peroxide group is replaced by an ethano bridge and in which the upper side-chain is attached to a nitrogen atom.[6] Such an analogue of PGH_1 (**1**), *i.e.* the title compound, has been obtained, the synthesis of which is now described in detail.†

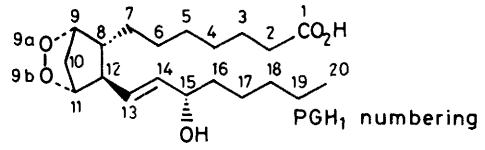
The basic strategy lies upon the construction of a functionalized 2-azabicyclo[2.2.1]heptane upon which branching of lateral side-chains could be subsequently performed. Therefore 3-substituted compounds (**2**) were chosen as suitable intermediates.

There are two main methods of preparation of a 2-azabicyclo[2.2.1]heptane ring system:[7] (i) Diels–Alder reaction between cyclopentadiene and electron-deficient imines,[8] and (ii) ring closure from an appropriately substituted pyrrolidine. Since no rapid access to a suitably functionalized pyrrolidine could be envisaged, the build-up of the bicyclic moiety was best sought in terms of a Diels–Alder cycloaddition. Among the acyclic *C*-substituted activated imines which have been shown to react with cyclopentadiene,[9] ‡ a convenient starting material proved to be the air-stable imine (**3**)[11] which undergoes such a cycloaddition to yield compound (**4**) in 55% yield.[12]

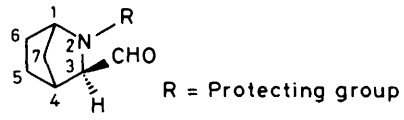


(**3**) (**4**)

Ts = 4 − $CH_3 \cdot C_6H_4 \cdot SO_2$−



(**1**)



(**2**)

Three kinds of operation must be performed before conversion of (**4**) into the desired intermediate (**2**) could be achieved: (i) reduction of the double bond, (ii) transformation of the hydroxylamine tosylate into an amino group, and (iii) replacement of the ethoxycarbonyl substituent by a hydrogen atom. Owing to the sensitivity of the substrate to rearrangement reactions, the order of these operations has been found to be of great importance. Thus, it had been shown that 2-azabicyclo-[2.2.1]heptenes could undergo a retro-Diels–Alder cleavage at temperatures as low as 70 °C,[13] and therefore, considering subsequent reactions to be performed, saturation of the double bond was considered as having priority. Thus, reduction of (**4**) was best accomplished by catalytic hydrogenation with palladium (10% on barium sulphate) in 95% yield, which is clearly superior to the 54% yield previously observed with Raney nickel,[13b] and gave compound (**6**). Next it appeared that (**6**) was very sensitive to the Wagner–Meerwein-type rearrangement[13,14] thus leading to the known[13] 1-azabicyclo-[2.2.1]heptane derivative (**5**), readily identified from a doublet of doublets at δ 5.1 (assigned to 2-H) in its ^1H n.m.r. spectrum. Thus, upon being heated in a polar solvent, (**6**) was totally converted into (**5**).

Removal of the leaving group linked to nitrogen in compound (**6**) before any further manipulation now proved to be mandatory. This could be performed, without rearrangement, by the action of aluminium amalgam in buffered medium, to give the amine (**7**) in 60% isolated yield. In contrast, reduction with sodium cyanoborohydride[15] gave exclusively the rearrangement product (**5**). That the N–O bond, instead of the O–S bond, had been cleaved (amine *vs.* hydroxylamine structures) was demonstrated by the action of tosyl chloride on (**7**) which gave a new tosylated derivative (**8**).

The stage was therefore set for the de-ethoxycarbonylation reaction. A number of experimental conditions have been devised for the direct de-ethoxycarbonylation of α-cyano esters.[16] However, use of sodium salts (NaCl, NaI, NaCN) in

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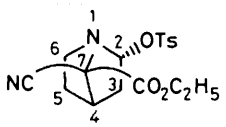
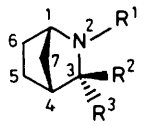
† Independent synthesis of such an analogue has recently been reported: A. Barco, S. Benetti, P. G. Baraldi, F. Modorer, G. P. Pollini, and D. Simoni, *Liebigs Ann. Chem.*, 1982, 960; for the preliminary communication of part of this work see: D. Blondet and C. Morin, *Tetrahedron Lett.*, 1982, **23**, 3681.

‡ Another attractive candidate for the elaboration of functionalized 2-azabicyclo[2.2.1]heptanes has recently been described (see ref. 10).

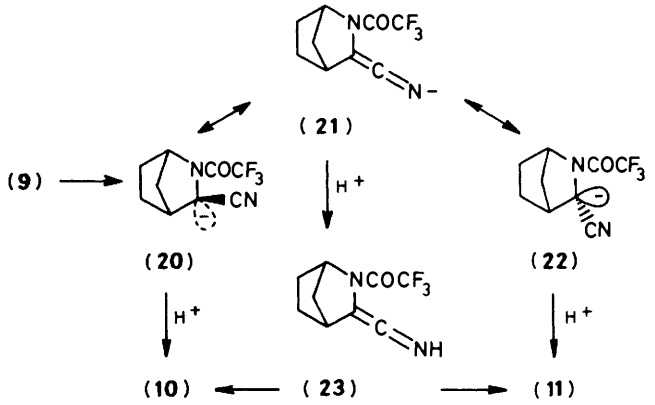




(5)

(6) R^1 = OTs, R^2 = CN, R^3 = $CO_2C_2H_5$
(7) R^1 = H, R^2 = CN, R^3 = $CO_2C_2H_5$
(8) R^1 = Ts, R^2 = CN, R^3 = $CO_2C_2H_5$
(9) R^1 = $COCF_3$, R^2 = CN, R^3 = $CO_2C_2H_5$
(10) R^1 = $COCF_3$, R^2 = CN, R^3 = H
(11) R^1 = $COCF_3$, R^2 = H, R^3 = CN
(12) R^1 = R^2 = H, R^3 = CN
(13) R^1 = R^3 = H, R^2 = CN
(14) R^1 = R^2 = H, R^3: $C(OCH_3)$=NH
(15) R^1 = R^3 = H, R^2: $C(OCH_3)$=NH
(16) R^1 = R^2 = H, R^3 = CO_2CH_3
(17) R^1 = R^3 = H, R^2 = CO_2CH_3
(18) R^1 = $COCF_3$, R^2 = H, R^3 = CHO
(19) R^1 = $COCF_3$, R^2 = CHO, R^3 = H

polar solvents such as dimethylformamide (DMF) or hexamethylphosphoric triamide (HMPT) with or without water at high temperatures (150 °C or above) did not result in any reaction of (7). It was then realized that the presence of an electron-rich α-substituent (nitrogen) might not favour appearance of the intermediate negative charge at C-3 which has to occur whether $B_{AC}2$ or $B_{AL}2$ mechanisms are operating;[17] in fact, a related successful example involved an α-acetamido substituent.[17] Therefore compound (7) was converted (trifluoroacetic anhydride in pyridine) into the trifluoroacetamide (9) in 88% yield, but when submitted to the same de-ethoxycarbonylation conditions as above compound (9) failed to react. We then learnt of the recently described use of Group II metal salts[18] to effect the desired transformation. Obviously, the size and the charge of the cation play a significant role in this reaction and it may be that simultaneous bonding of the cation to both cyano and ester groups results in enhanced electrophilicity of the latter.* Thus, reaction of calcium chloride dihydrate with (9) in DMF (160 °C; 150 min) gave, in 79% yield, a product whose spectral data clearly showed the absence of the ethoxycarbonyl group. Close examination of the n.m.r. spectrum revealed that two signals were accounting for the 3-H resonance. This was at first explained by hindered rotation about the amide bond as has been observed in similar cases[10,19] but variable-temperature n.m.r. experiments, which were expected to bring about coalescence, ruled out this possibility. Then, high-performance liquid chromatography (h.p.l.c.) analysis revealed that the product obtained did, in fact, consist of two compounds whose ratio (60:40) was the same as the one measured from the 3-H relative intensities of the resonances. A high-field n.m.r. spectrum revealed that the 3-H resonance comprised two signals, a doublet (J 4 Hz) at δ 4.4 and a sharp singlet at δ 4.15. In similar bicyclic systems[20] J 4 Hz is characteristic of coupling between 4-H and 3-H_{exo}, whereas J *ca.* 0 Hz denotes that the 4-H is adjacent to the 3-H_{endo}. It was thus concluded that (10) and (11), which are epimeric at C-3, were indeed the de-ethoxycarbonylation products. One is left to explain how a single starting material (9) which bears an *exo*-cyano group gave rise to a mixture of *exo*-cyano (10) and *endo*-cyano (11). If protonation of the intermediate carbanionic species is slow, equilibration *via* planar (21) may account for the observed products. In fact (21) may either give back a mixture of carbanions, (20) and (22), which would lead stereospecifically to (10) and (11) upon protonation (Scheme), or directly protonate to yield the aza-allene (23) which would then equilibrate to (10) and (11).



Scheme.

Although direct diastereoselection during the dealkoxycarbonylation reaction[21] cannot be envisaged here, clearly there is some kind of selectivity during the reaction. In fact, it had been shown that equilibrium of the simpler 2-cyanonorbornane led to equal amounts of *endo*- and *exo*-product under thermodynamic conditions.[22] In the present case, the *endo*:*exo* ratio is 60:40 but was not altered by equilibrium experiments. Preparative separation by chromatography failed although analytical h.p.l.c. separation of the epimers (10) and (11) could be achieved. Consequently it was decided to transform the cyanide group into another function, bearing in mind the requirement for subsequent further transformation into a formyl group.

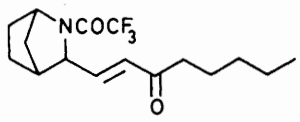
Reaction of the nitriles (10) and (11) proved to be non-trivial.† Acid hydrolysis (acetic acid; trifluoroacetic acid; 1M hydrochloric acid, room temperature or reflux), basic hydrolysis (sodium hydrogen carbonate; sodium hydroxide) or oxidative conditions (hydrogen peroxide–sodium hydroxide[23]) could not bring about any change. Sodium borohydride or lithium triethoxyaluminium hydride[24] yielded only the amino nitriles (12) and (13). Sodium methoxide, at −70 °C, gave the latter compounds but permitted, when the reaction was performed at room temperature, additional isolation of the imino ethers (14) and (15) in poor yield; acidic hydrolysis[25] of these derivatives gave an inseparable mixture of the esters (16) and (17).‡ Di-isobutylaluminium hydride treatment[26] of the protected amino nitriles (10) and (11) resulted in a complex mixture presumably arising from over-reduction or degradation of intermediate α-amino aldehydes. The only successful and synthetically acceptable reaction was found to be the direct reduction of (10) and (11) to the protected α-amino aldehydes (18) and (19) by means of Raney nickel–sodium hypophosphite.[27] This proceeded in *ca.* 60% yield and the crude product, which was characterized by an absorption at δ 9.6 in its ^1H n.m.r. spectrum and a positive 2,4-dinitrophenylhydrazine colour test, had to be used immediately in the next step, owing to its instability.

* However, one cannot exclude cyclic participation[19] of the trifluoroacetyl group in the process; (7) does not react under these conditions.

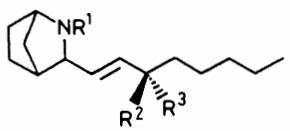
† This might be attributed to the presence of an α-amino functionality as a similar case can be found in the literature: R. D. Gless and H. Rapoport, *J. Org. Chem.*, 1979, **44**, 1324; we thank Dr. D. Grierson for bringing this work to our attention.

‡ Saponification of the esters gave the corresponding new amino acids whose structure is reminiscent of the newly discovered methanoproline: E. A. Bell, M. Y. Qureshi, R. J. Pryce, D. H. Janzen, P. Lemke, and J. Clardy, *J. Am. Chem. Soc.*, 1980, **102**, 1409.

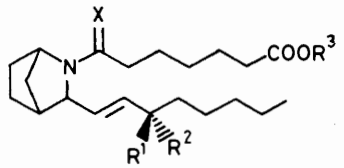
Having thus obtained the projected type-(**2**) intermediate, branching of lateral side-chains could then be considered. These operations rest on standard prostaglandin chemistry and the lower side-chain was thus introduced by a Wittig–Horner reaction. Treating the freshly prepared aldehydes (**18**) and (**19**) with the phosphorane[28] derived from dimethyl 2-oxoheptylphosphonate[29] gave the enones (**24**) in 60% yield. The ^{1}H n.m.r. spectrum showed two overlapping AB parts of ABMX systems (J_{AB} 17 Hz) in the olefinic region which can be explained by the presence of *endo* and *exo* isomers of *trans*-enones. Analytical h.p.l.c. showed their ratio to be 55:45, which is slightly different from the 60:40 ratio of the starting nitriles; this might have arisen from enolisation of the aldehydes; further equilibration (acetic acid; sodium acetate; sodium carbonate; sodium hydroxide; potassium t-butoxide) failed and since this mixture could not be preparatively resolved, it was decided to carry on the final stages of the synthesis without separation of the *endo* and *exo* isomers.



(**24**)



(**25**) R^1 = $COCF_3$, R^2 = OH, R^3 = H
(**26**) R^1 = $COCF_3$, R^2 = H, R^3 = OH
(**27**) R^1 = $COCF_3$, R^2 = $OSi(CH_3)_2C(CH_3)_3$, R^3 = H
(**28**) R^1 = $COCF_3$, R^2 = H, R^3 = $OSi(CH_3)_2C(CH_3)_3$
(**29**) R^1 = R^3 = H, R^2 = $OSi(CH_3)_2C(CH_3)_3$
(**30**) R^1 = R^2 = H, R^3 = $OSi(CH_3)_2C(CH_3)_3$



(**31**) R^1 = $OSi(CH_3)_2C(CH_3)_3$, R^2 = H, R^3 = C_2H_5, X = H_2
(**32**) R^1 = H, R^2 = $OSi(CH_3)_2C(CH_3)_3$, R^3 = C_2H_5, X = H_2
(**33**) R^1 = OH, R^2 = R^3 = H, X = H_2
(**34**) R^1 = R^3 = H, R^2 = OH, X = H_2
(**35**) R^1 = $OSi(CH_3)_2C(CH_3)_3$, R^2 = H, R^3 = CH_3, X = O
(**36**) R^1 = H, R^2 = $OSi(CH_3)_2C(CH_3)_3$, R^3 = CH_3, X = O
(**37**) R^1 = OH, R^2 = R^3 = H, X = O
(**38**) R^1 = R^3 = H, R^2 = OH, X = O

Selective 1,2-reduction of the enone, to yield (in 95% yield) the allylic alcohols (**25**) and (**26**), was best accomplished by use of sodium borohydride in the presence of cerium(III) chloride;[30] performing the reaction at −40 °C for 5 min avoided any reaction of the trifluoroacetamido group. Protection of alcohols (**25**) and (**26**), epimeric at C-15 (prostaglandin numbering), before introduction of the upper side-chain, was accomplished by use of t-butyl(chloro)dimethylsilane–imidazole in DMF[31] to yield the silyl ethers (**27**) and (**28**) in 90% yield.

Conversion of the trifluoroacetamide into the secondary amines (**29**) and (**30**) was done with freshly prepared sodium methoxide, and proceeded in 85% (isolated) yield. Once again, chromatographic separation of the isomers could not be accomplished although slight enrichment into the *exo* compounds was revealed by high-field n.m.r. spectroscopy (3-H_{endo} at δ 3.85 and 3-H_{exo} at δ 4.05); therefore alkylation of nitrogen was performed on the mixture of diastereoisomers.

The final steps of the synthesis were straightforward; thus, completion of the skeleton by alkylation with ethyl 7-iodoheptanoate[32] (prepared just before use from the corresponding 7-bromo derivative[33]) produced compounds (**31**) and (**32**) in 40% yield. Acidic treatment [acetic acid–water–tetrahydrofuran (THF)] followed by saponification (sodium hydroxide) afforded the acids (**33**) and (**34**) as a mixture of diastereoisomers in 58% isolated yield.

Similarly, interest in the 7-oxo series[34,35] prompted the preparation of the corresponding 7-oxo derivatives. Thus, acylation of the mixture of (**29**) and (**30**) with the imidazolide[34] derived from 6-methoxycarbonylhexanoyl chloride gave compounds (**35**) and (**36**) in 79% yield. Final deprotection reactions were carried out as described earlier to give a mixture of diastereoisomeric acids (**37**) and (**38**) in 54% yield. These did not induce contractions of rabbit aorta strip. Similarly, they were not active in platelet aggregation tests nor did they show significant inhibitory activity against arachidonic acid-induced platelet aggregation.

Experimental

M.p.s were obtained with a Thomas-Hoover Unimelt apparatus and are uncorrected. I.r. spectra were recorded for KBr pellets or chloroform solutions on a Perkin-Elmer 221 or 237 spectrophotometer, with polystyrene film calibration. U.v. spectra were determined on a Perkin-Elmer 5505 spectrophotometer for solutions in ethanol. ^{1}H N.m.r. spectra were recorded in $CDCl_3$ (with tetramethylsilane as internal standard, δ 0) on Varian EM-360, Varian HA 100, or Cameca TSN 250 spectrometers. Coupling constants (*J*) are given in Hz. Multiplicity abbreviations (s, d, dd, t, m) stand for singlet, doublet, doublet of doublets, triplet, and multiplet respectively. Mass spectra were recorded on a VG-Micromass 70–70 F apparatus. Only peaks yielding structural information are reported. H.p.l.c. was obtained on a Perkin-Elmer series 3B apparatus coupled with a Hewlett-Packard 3390 A integrator. Column and thin-layer chromatography was performed on silica gel 60 (Merck). When needed dry, THF, diethyl ether, toluene, and 1,2-diethoxyethane were distilled under nitrogen from sodium using sodium benzophenone ketyl as indicator. Pyridine was distilled from calcium hydride, and methanol from magnesium methoxide.

exo-3-*Cyano*-endo-3-*ethoxycarbonyl*-2-p-*tosyloxy*-2-*azabicyclo*[2.2.1]*heptane* (**6**).—Adduct (**4**), obtained from cyclopentadiene[36] and ethyl 2-cyano-2-tosyloxyiminoacetate (**3**)[11] according to published procedures[12] (15.0 g, 41.4 mmol), was hydrogenated at 1 atm in ethyl acetate (250 ml) over a catalytic quantity of 10% palladium on barium sulphate. After the mixture had been stirred for 2 h, the catalyst was filtered off, the filtrate evaporated, and the residue crystallized to afford the title compound (**6**) (14.4 g 95.5%), m.p. 99—100 °C (lit.,[12] 100 °C).

exo-3-*Cyano*-endo-3-*ethoxycarbonyl*-2-*azabicyclo*[2.2.1]*heptane* (**7**).—In a 1-l three-necked flask maintained at 4 °C, freshly prepared aluminium amalgam[37] (15 g) was covered with THF (*ca.* 100 ml) and then sodium hydrogencarbonate (7 g) was added. Dropwise addition, so as to maintain the internal temperature below 30 °C, of compound (**6**) (47 g, 129 mmol) in THF–water (9:1) (250 ml) was then performed while the contents of the flask were vigorously agitated. After 2 h, more aluminium amalgam (15 g) and sodium hydrogencarbonate (7

g) were added; this was repeated after a further 2 h. The reaction was over 1 h later. After filtration, the residue was thoroughly washed with THF. After evaporation of the filtrate, the crude product was taken up in dichloromethane, washed with water, and dried (Na_2SO_4). After evaporation of the solvent, chromatography of the residue upon silica gel afforded the ester (**7**) (15.0 g, 60%); after crystallization from toluene, it had m.p. 33—34 °C (Found: C, 61.45; H, 7.6; N, 14.6. $C_{10}H_{14}N_2O_2$ requires C, 61.83; H, 7.26; N, 14.43%); $\nu_{max.}$(KBr) 3 300 (NH), 2 210 (CN), and 1 730 cm^{-1} ($CO_2C_2H_5$); δ 1.4 (3 H, t, *J* 8, $CO_2CH_2CH_3$), 1.6—2.0 (6 H, m, 5-, 6-, and 7-H_2), 2.6 (1 H, br s, exch. with D_2O, NH), 3.7 (1 H, br s, 1-H), and 4.3 (2 H, q, *J* 8, $CO_2CH_2CH_3$).

exo-3-*Cyano*-endo-3-*ethoxycarbonyl*-2-*trifluoroacetyl*-2-*azabicyclo*[2.2.1]*heptane* (**9**).—To an agitated solution of the amine (**7**) (15.0 g, 77.3 mmol) in pyridine at 4 °C was added dropwise trifluoroacetic anhydride (116 mmol, 1.5 equiv.) and the cooling bath was removed. After 2.5 h, methanol (10 ml) was added and the solvents were removed under reduced pressure. The residue was taken up in dichloromethane and this organic layer was washed with water and dried (Na_2SO_4). After evaporation, the crude product was chromatographed on silica gel and elution with dichloromethane afforded the trifluoro compound (**9**) (19.7 g, 88%); after crystallization from ethanol it had m.p. 56 °C (Found: C, 49.85; H, 4.6; N, 10.0. $C_{12}H_{13}F_3N_2O_3$ requires C, 49.66; H, 4.51; N, 9.66%); $\nu_{max.}$(KBr) 1 760 (C=O ester) and 1 690 cm^{-1} (C=O amide); δ 1.35 (3 H, t, *J* 8, $CO_2CH_2CH_3$), 1.5—2.4 (6 H, m, 5-, 6-, and 7-H_2), 3.05 (1 H, br s, 4-H), 4.3 (2 H, q, *J* 8, $CO_2CH_2CH_3$), and 4.7 (1 H, br s, 1-H).

exo- *and* endo-3-*Cyano*-2-*trifluoroacetyl*-2-*azabicyclo*[2.2.1]-*heptane* (**10**) *and* (**11**).—To a solution of the cyano ester (**9**) (19.0 g, 65.5 mmol) in DMF (350 ml) was added calcium chloride dihydrate (49 g, 5 equiv.). The mixture was gently swirled at 160 °C for 2.5 h and filtered. The precipitate was washed with DMF. After evaporation of the filtrate at reduced pressure the residue was taken up in dichloromethane and filtered. After evaporation of the solvent, silica gel chromatography [cyclohexane–dichloromethane (1:1) afforded a mixture of the title compounds (**10**) and (**11**) (11.3 g, 79%) which crystallized from methanol (Found: C, 49.4; H, 4.25; N, 12.45. $C_9H_9F_3N_2O$ requires C, 49.54; H, 4.16; N, 12.84%); $\nu_{max.}$(KBr) 2 250 (CN) and 1 690 cm^{-1} (C=O); δ 1.2—2.3 (6 H, m, 5-, 6-, and 7-H_2), 3.1 (1 H, br s, 4-H), 4.2 and 4.45 (together 1 H, 2 s, 3-H), and 4.6 (1 H, br s, 1-H).

endo- *and* exo-3-*Formyl*-2-*trifluoroacetyl*-2-*azabicyclo*[2.2.1]-*heptane* (**18**) *and* (**19**).—To a solution of the nitriles (**10**) and (**11**) (2.0 g, 9.2 mmol) in water–acetic acid–pyridine (1:1:2) (30 ml) was added sodium hypophosphite (4 g), followed by freshly prepared Raney nickel[27] (*ca.* 0.5 g). After 2 h, the reduction was over and the residue was filtered off and washed in turn with dichloromethane and water. Separation of the layers and extraction of the aqueous phase with dichloromethane gave an organic phase which was dried (Na_2SO_4). The solvents were evaporated (no heat) under reduced pressure and co-evaporation several times with toluene afforded a mixture of the unstable crude aldehydes (**18**) and (**19**) (1.3 g, 63%) which was used immediately in the next step.

3-(3′-*Oxo*-*oct*-1′-*enyl*)-2-*trifluoroacetyl*-2-*azabicyclo*[2.2.1]-*heptane* (**24**).—To a stirred suspension of the sodium salt of dimethyl 2-oxoheptylphosphonate [prepared[28] from sodium hydride (57.5% in mineral oil; 276 mg, 6.62 mmol) and dimethyl 2-oxoheptylphosphonate[29] (1.43 ml, 6.89 mmol)] in dry 1,2-dimethoxyethane (80 ml) under nitrogen at 4 °C was added dropwise a solution of the crude aldehydes (**18**) and (**19**) in dry 1,2-dimethoxyethane (15 ml). After being stirred for 30 min at 4 °C and 150 min at room temperature, the reaction mixture was poured into 5% aqueous sodium diphosphate (NaH_2PO_4) (200 ml) and extracted with dichloromethane. The extract was dried and the solvents were removed. The crude residue was best purified by chromatography on silica gel [cyclohexane–dichloromethane (1:1)] to afford the enone (**24**) (880 mg, 30% from nitriles) as an oil (Found: C, 60.5; H, 7.05; N, 4.8. $C_{16}H_{22}F_3NO_2$ requires C, 60.55; H, 6.99; N, 4.41%); $\lambda_{max.}$ 211 nm (log ε 3.8); $\nu_{max.}$($CHCl_3$) 1 685 cm^{-1} (2 C=O); δ 0.6—2.0 (15 H, m, 5-, 5′-, 6-, 6′-, 7-, 7′-H_2 and 8′-H_3), 2.6 (3 H, m, 4-H and 4′-H_2), 4.1—4.6 (2 H, m, 1- and 3-H), and 5.7—6.8 (2 H, 2 AB parts of ABMX systems, J_{AB} 17, 1′- and 2′-H).

3-[(3′S)- *and* (3′R)-3′-*Hydroxyoct*-1′-*enyl*]-2-*trifluoroacetyl*-2-*azabicyclo*[2.2.1]*heptane* (**25**) *and* (**26**).—To a solution of the enone (**24**) (260 mg, 0.82 mmol) in methanol (2 ml) was added cerium(III) chloride hexahydrate (283 mg). After the mixture had been cooled to −40 °C, sodium borohydride (30 mg, 0.79 mmol) was added all at once. After the mixture had been stirred for 5 min, acetone (1 ml), then 5% aqueous sodium diphosphate (2 ml) were added. The mixture was extracted with dichloromethane and the extract was dried (Na_2SO_4). After evaporation of the solvents, the residual alcohols (**25**) and (**26**) were purified by column chromatography [dichloromethane–methanol (98:2)] to give an oil (250 mg, 95%) (Found: C, 59.9; H, 7.5; N, 4.15. $C_{16}H_{24}F_3NO_2$ requires C, 60.16; H, 7.57; N, 4.39%); $\nu_{max.}$($CHCl_3$) 3 500 (OH) and 1 690 cm^{-1} (C=O); δ 0.8—2.0 (17 H, m, 5-, 6-, and 7-H_2 and $[CH_2]_4CH_3$), 2.6 (1 H, m, 4-H), 4.0—4.5 (3 H, m, 1-, 3-, and 3′-H), and 5.65 [3 H, m (1 H exch. with D_2O), 1′- and 2′-H and OH].

3-[(3′S)- *and* (3′R)-3′-*t*-*Butyldimethylsilyloxyoct*-1′-*enyl*]-2-*trifluoroacetyl*-2-*azabicyclo*[2.2.1]*heptane* (**27**) *and* (**28**).—To a solution of the alcohols (**25**) and (**26**) (280 mg, 0.89 mmol) in DMF (3 ml) were added imidazole (604 mg, 8.9 mmol) and t-butyl(chloro)dimethylsilane (670 mg, 4.45 mmol). After the mixture had been stirred for 1 d at room temperature, water (5 ml) was added and the mixture was extracted with dichloromethane. After the extract had been dried (Na_2SO_4) and the solvents evaporated off, the crude product was purified by chromatography [dichloromethane–cyclohexane (6:4)] to give the silyl ethers (**27**) and (**28**) (340 mg, 90%) (Found: C, 61.2; H, 8.95; N, 3.15. $C_{22}H_{38}F_3NO_2Si$ requires C, 60.93; H, 8.83; N, 3.23%); $\nu_{max.}$($CHCl_3$) 1 690 cm^{-1} (C=O); δ 0.05 [6 H, s, $Si(CH_3)_2$], 0.98 [9 H, s, $SiC(CH_3)_3$], 0.98—2.15 (17 H, m, 5-, 6-, and 7-H_2 and $[CH_2]_4CH_3$), 2.6 (1 H, m, 4-H), 4.0—4.6 (3 H, m, 1-, 3-, and 3′-H), and 5.5 (2 H, m, 1′- and 2′-H).

3-[(3′S)- *and* (3′R)-3′-*t*-*Butyldimethylsilyloxyoct*-1′-*enyl*]-2-*azabicyclo*[2.2.1]*heptane* (**29**) *and* (**30**).—To a solution of the trifluoroacetamides (**27**) and (**28**) (380 mg, 0.87 mmol) in dry methanol was added a freshly prepared 1M solution of sodium methoxide in methanol (1.1 ml, 1.2 equiv.) and the reaction mixture was stirred at room temperature for 5 h and poured into a pH 6 buffer (sodium diphosphate–citric acid). After extraction with dichloromethane, the extract was washed with water, dried, and evaporated, and chromatography [dichloromethane–methanol (95:5)] of the residue afforded the amines (**29**) and (**30**) (250 mg, 85%) (Found: C, 70.8; H, 11.25; N, 4.35. $C_{20}H_{39}NOSi$ requires C, 71.15; H, 11.64; N, 4.14%); $\nu_{max.}$($CHCl_3$) 3 600 cm^{-1} (NH); δ 0.05 [6 H, s, $Si(CH_3)_2$], 0.98 [9 H, s, $SiC(CH_3)_3$], 0.9—1.8 (17 H, m, 5-, 6-, and 7-H_2 and $[CH_2]_4CH_3$), 2.3 (1 H, m, 4-H), 3.25—3.75 (2 H, m, 1- and 3-H), 3.8—4.15 (1 H, m, 3′-H), and 5.55 (2 H, m, 1′- and 2′-H); *m/z* (200 °C; 70 eV) 337($M^{+\cdot}$), 322 ($M - CH_3$)$^+$, 280 [$M - C(CH_3)_3$]$^+$ 266 ($M - (C_5H_{11})$)$^+$, 206 ($M - OSi(CH_3)_2C(CH_3)_3$)$^+$, and 122 ($M - (CH_3)_3CSi(CH_3)_2OCHC_5H_{11}$)$^+$.

(15R)- *and* (15S)-15-O-*t*-*Butyldimethylsilyl*-8-*aza*-9a,9b-*dicarbaprostaglandin* H_1 *Ethyl Ester* (**31**) *and* (**32**).*—To a stirred solution of the amines (**29**) and (**30**) (40 mg, 120 μmol) in methanol (0.5 ml) was added ethyl 7-iodoheptanoate [32] (40 mg, 140 μmol) followed by potassium hydrogencarbonate (20 mg, 200 μmol.) After 2 d at room temperature the mixture was poured into pH 6 buffer (3 ml) and extracted with dichloromethane and the extract was dried. After evaporation, the crude residual product was chromatographed to yield the esters (**31**) and (**32**) (12 mg) and unchanged starting material (20 mg recovery) (yield 40% based on amines consumed) (Found: C, 70.9; H, 10.95; N, 2.75. $C_{29}H_{55}NO_3Si$ requires C, 70.53; H, 11.23; N, 2.84%); $\nu_{max.}$($CHCl_3$) 1 740 cm^{-1} (C=O); δ† 0.02 [6 H, s, $Si(CH_3)_2$], 0.98 (9 H, s, $SiC(CH_3)_3$], 1.0—2.6 (31 H, m, 2-, 3-, 4-, 5-, 6-, 9a-, 9b-, and 10-H_2, 11-H, $[CH_2]_4CH_3$, and $CO_2CH_2CH_3$), 3.3—3.75 (3 H, m, 7-H_2 and 12-H), 3.8—4.3 (4 H, m, 9- and 15-H and $COOCH_2CH_3$), and 5.7—6.1 (2 H, m, 13- and 14-H); *m*/*z* (200 °C; 70 eV) 493 (M^+), 448 (M − $(OC_2H_5)^+$, 436 [M − $C(CH_3)_3$]$^+$, 420 (M − C_5H_{11})$^+$, 362 [M − $OSi(CH_3)_2C(CH_3)_3$]$^+$, 350 (M − upper side-chain)$^+$, and 278 (M − lower side-chain)$^+$.

(15R)- *and* (15S)-8-*Aza*-9a,9b-*dicarbaprostaglandin* H_1 (**33**) *and* (**34**).—A solution of the silyl ethers (**31**) and (**32**) (21 mg, 40 μmol) in a mixture of acetic acid–water–THF (3:2:2; 1 ml) was stirred at room temperature for 22 h. The product was extracted with dichloromethane and the extract was washed with saturated brine, dried, and evaporated. The product was chromatographed on silica gel [dichloromethane–methanol (98:2)] to give the intermediate 15*R* and 15*S* alcohols. These were then dissolved in ethanol (250 μl) and 0.6M aqueous sodium hydroxide (80 μl, 1.2 equiv.) was added. After 16 h at room temperature, the mixture was extracted with diethyl ether and the aqueous layer was acidified to pH 4, saturated with sodium chloride, and extracted with diethyl ether. After the second extracts had been dried and evaporated, chromatography of the residue on silica gel [dichloromethane–methanol (95:5)] afforded the title compounds (9 mg, 58%) as an oil, $\nu_{max.}$($CHCl_3$) 3 500 (OH) and 1 710 cm^{-1} (C=O); δ† 0.9—2.5 (28 H, m, 2-, 3-, 4-, 5-, 6-, 9a-, 9b-, and 10-H_2, 11-H, and $[CH_2]_4CH_3$), 3.2—3.6 (3 H, m, 7-H_2 and 12-H), 3.9—4.4 (2 H, m, 9- and 15-H), 5.7—6.3 [4 H, m (2 H are exch. with D_2O), 13- and 14-H, OH, and C(O)OH]).

(15R)- *and* (15S)-15-O-*t*-*Butyldimethylsilyl*-7-*oxo*-8-*aza*-9a,9b-*dicarbaprostaglandin* H_1 *Methyl Esters* (**35**) *and* (**36**).—To a stirred solution of the amines (**29**) and (**30**) (60 mg, 180 μmol) in dichloromethane (0.5 ml) under nitrogen was added *N*-(6-methoxycarbonylhexanoyl)imidazole [34] (40 mg, 200 μmol) all at once. The mixture was stirred for 20 h at room temperature and methanol (2 ml) was added. After evaporation of the solvents, chromatography on silica gel [dichloromethane–methanol (98:2)] afforded the oxo esters (**35**) and (**36**) (70 mg, 79%) (Found: C, 68.1; H, 10.4; N, 2.8. $C_{28}H_{51}NO_4Si$ requires C, 68.10; H, 10.41; N, 2.84%); $\nu_{max.}$($CHCl_3$) 1 745 (C=O ester) and 1 640 cm^{-1} (NC=O); δ† 0.05 [6 H, s, $Si(CH_3)_2$], 0.95 [9 H, s, $C(CH_3)_3$], 0.9—2.0 (23 H, m, 3-, 4-, 5-, 9a-, 9b-, and 10-H_2 $[CH_2]_4CH_3$), 2.1—2.5 (5 H, m, 2- and 6-H_2 and 11-H), 3.7 (3 H, s, CO_2CH_3), 4.1—4.4 (3 H, m, 9-, 12-, and 15-H), and 5.4—5.7 (2 H, m, 13- and 14-H); *m*/*z* (200 °C; 70 eV) 492 (M − 1)$^+$, 461 (M − CH_3OH)$^+$, 435 [M − 1 − $C(CH_3)_3$]$^+$, 252 (M − lower side-chain)$^+$, and 143 [$CH_3OCO(CH_2)_4C{\equiv}O^+$].

(15R)- *and* (15S)-7-*Oxo*-8-*aza*-9a,9b-*dicarbaprostaglandin* H_1 (**37**) *and* (**38**).—A solution of the preceding compounds (25 mg, 50 μmol) in a 3:2:2 mixture of acetic acid–water–THF (1.5 ml) was stirred for 18 h at room temperature and extracted with dichloromethane, and the extract was washed with brine. The extract was dried and evaporated, and the product was chromatographed [dichloromethane–methanol (98:2)] to afford the intermediate 15*R* and 15*S* alcohols. These were then taken up in ethanol (300 ml) and 0.6M aqueous sodium hydroxide (70 μl) was added. After the mixture had been stirred for 20 h it was extracted with diethyl ether. Then the aqueous phase was adjusted to pH 4, saturated with sodium chloride, and extracted with diethyl ether. After the second extract had been dried and evaporated, the crude residual product was chromatographed on silica gel [dichloromethane–methanol (95:5)] to give the acids (**37**) and (**38**) as an oil (9 mg) (Found: C, 69.1; H, 9.85; N, 3.45. $C_{21}H_{35}NO_2$ requires C, 69.00; H, 9.65; N, 3.83%); $\nu_{max.}$($CHCl_3$) 3 500 (OH), 1 710 (C=O acid), and 1 640 cm^{-1} (NC=O); δ† 0.8—2.0 (23 H, m, 3-, 4-, 5-, 9a-, 9b-, and 10-H_2 and $[CH_2]_4CH_3$), 2.1—2.6 (5 H, m, 2- and 6-H_2 and 11-H), 4.1—4.4 (3 H, m, 9-, 12-, and 15-H), 5.9—6.1 (2 H, m, 13- and 14-H), and 7.7 (2 H, br s, exch. with D_2O, OH, and CO_2H).

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