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STEREOSPECIFIC NITROMETHANE CONJUGATE ADDITION TO 4-OXYGENATED-2-SUBSTITUTED-CYCLO PENT-2-ENONES: A SIMPLE APPROACH TO PROSTAGLANDINS

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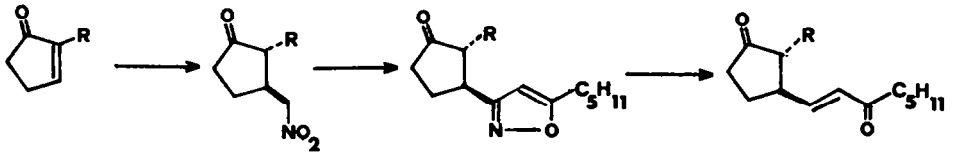
Abstract - The compatibility of nitromethane conjugate addition to 2-cyclopentenones bearing a 4-oxygenated function has been illustrated through a short and practical synthesis of the Corey aldehyde, a key intermediate in prostaglandin synthesis, in both racemic and optically active form. A new synthesis of $PGF_{2\alpha}$ featuring the introduction of the ω-chain via $\left[3+2\right]$ cycloaddition has been also described.

Introduction

A new approach to the total synthesis of prostaglandins recently reported by E.J. Corey[1] eighteen years after his first synthesis, and other recent papers on the same topic from outstanding groups[2,3], have combined to testimonyate that synthetic interest in the field has continuated unabated.

As a part of our continuous interest in this subject, some years ago[4] we envisaged a synthetic strategy to prostanoids featured by an innovative method for the elaboration of the ω-chain, through a $\left[3+2\right]$ dipolar cycloaddition.

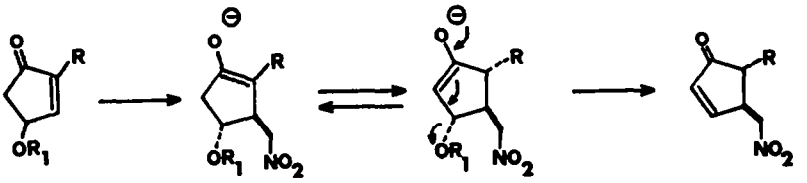
Thus the nitrile oxides generated from primary nitromethyl derivatives resulting from nitromethane conjugate addition to 2-alkylated-2-cyclopent-2-enones were intercepted with n-heptyne to produce 3,5-disubstituted isoxazoles, which could be subsequently elaborated to the corresponding α,β-insaturated ketones as generalized in eq. 1



eq. 1

The major merit of the sequence was the first actual demonstration of the synthetic equivalence of a 3,5-disubstituted isoxazole and a stabilized Wittig reagent. In a broader sense our discovery introduced a new concept for the formation of aldol adducts, through the sequence,cycloaddition followed by suitable elaboration

of the cycloadduct, later widely utilized in natural product synthesis.[5,6]
In reviewing this approach to prostanoids one of our concern was that 4-oxygenated cyclopentenones might easily undergo ß-elimination after Michael addition, in view of the tendency of the initially formed enolate to equilibrate to the regioisomer by easy proton transfer (eq.2), thus limiting the approach to 11-deoxyprostanoids.[7]

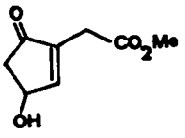


eq. 2

This fear proved well-founded in the case of substituents which are good leaving groups (i.e. OCH_3, $OCOCH_3$).
However, in order to extend our strategy to the synthesis of primary prostaglandins, we have been intrigued by the possibility of overcoming this hurdle by a careful choice of reaction conditions and suitable protective group of the 4-oxygenated function.
We are pleased to report in this paper the results of our studies which demonstrate that the conjugate addition of nitromethane to cyclopentenones bearing a 4-oxygenated function, is perfectly feasible and the latter is not only retained under conditions where Michael addition does occur, but also plays a crucial role in determining the stereochemical outcome of the addition.

The starting material

The preparation of the basic cyclopentenone system 1, required for the initial step, was accomplished in greater than 60% overall yield starting from the readily available 5-oxo-1-cyclopenten-1-acetic acid methyl ester[8,9] through NBS bromination followed by direct replacement of the bromine by an hydroxyl group by treatment with hot water.[10]

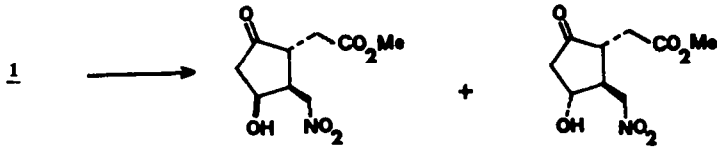


1

Conjugate nitromethane addition to 4-oxygenated-2-substituted-cyclopent-2-enones

Having an excellent source of the building block 1 in hand, we began to examine the conjugate addition of nitromethane, utilizing previously experienced experimental conditions. When 1 was allowed to react at 0°C using nitromethane itself as solvent and tetramethyl guanidine (TMG)[11] as catalyst, an easy addition took place affording with high stereoselectivity a 90% yield of a 3:1 mixture of the crystal-

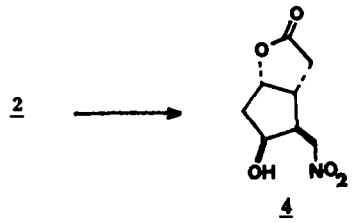
line adduct 2 and the oily isomer 3, easily separated by flash-chromatography.



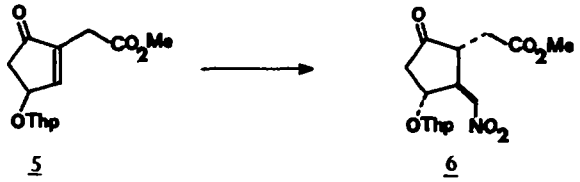
Differentiation for the two isomers was readily made by ^1H NMR spectroscopy by observing for 2 a pair of double doublets centered at δ 4.6 (J=13.8Hz, J=5Hz) and 4.8 (J=13.8Hz, J=9Hz) and for 3 a doublet at δ 4.72 (J=6Hz) due to the nitromethylene protons. The isolated 2 cannot be converted to 3 by basic equilibration both in TMG/CH_3NO_2 or MeONa/MeOH from 0°C to room temperature for 2h.

The fact that the entering nitromethyl moiety added preferentially cis to the hydroxy group indicated the partecipation of the neighbouring free hydroxyl function as chelating ligand during the nitronate anion attack, which proceeds in a "pseudointramolecular" fashion. This hypothesis is supported by the prevalent formation of 3 when the reaction was performed in methanol containing 1.1 equiv. of nitromethane in the presence of catalytic amounts of sodium methylate. However the reaction proceeded more sluggishly giving rise to by-products due to concomitant elimination.

Stereochemical assignement of 2 and 3 rests also on the X-ray analysis of the corresponding crystalline lactone 4 obtained by direct reduction of the carbonyl derivative 2 with $LiAlH(OBu)_3$ at 0°C followed by heating at 50°C for 2h of the resulting reaction mixture.



The major role played by the free hydroxyl group in determining the observed preference received further support performing the nitromethane addition on the tetrahydropyranyl ether 5, available from 1 by treatment with dihydropyran in the presence of an acid catalyst.



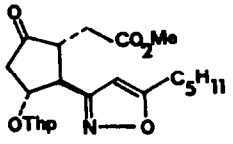
In fact the TMG-catalyzed Michael addition of nitromethane to 5 proceeded at 0°C giving rise to the stereospecific formation of the adduct 6 in 85% yield, in which the three ring substituents are present in the thermodynamically most stable

all-trans configuration. It is noteworthy that despite the poor leaving group ability of the tetrahydropyranyloxy group, trace amount of ß-elimination product can be detected by T.L.C.

Synthesis of $(\pm)$-$PGF_{2\alpha}$

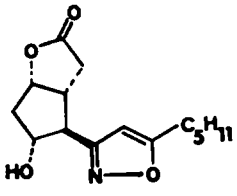
The successful accomplishment of nitromethane conjugate addition to 4-oxygenated cyclopenten-2-enones paved the way to the extension of our original strategy to natural prostaglandins, such as $PGF_{2\alpha}$, chosen as an illustrative example.

With the intermediate 6 in hand, the stage was set to assemble the carbon skeleton of the ω-chain. Thus the primary nitromethyl moiety acts as source of nitrile oxide generated under Mukaiyama conditions[12], which is trapped by 1-heptyne in the crucial carbon-carbon bond forming cycloaddition step to produce the isoxazole derivative 7 in good yield.



7

With the ω-chain masked in form of a stable heterocycle, 7 could represent a useful substrate for the introduction of the upper chain. To this end 7 was treated with $LiAlH(OBu^t)_3$ in THF at 0°C followed by keeping the reaction mixture at 60°C for 3h. Subsequent treatment with 5% aqueous hydrochloric acid afforded a 1:3 mixture of the solid lactone 8 and the hydroxy-ester 9a, easily separated by column chromatography.



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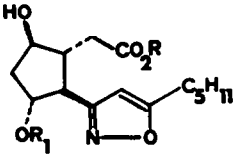
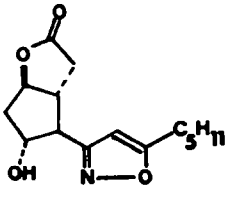


9a R=Me; R_1=H

9b R=H; R_1=Thp

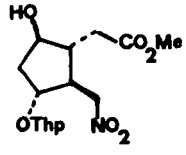


10

Saponification of 9a with methanolic lithium hydroxyde at room temperature produced quantitatively the corresponding acid 9b, which could be transformed to the nicely crystalline trans-lactone 10 only by heating in refluxing benzene in the presence of toluene-p-sulphonic acid.

Faced with the disappointingly low stereoselectivity of the reduction of the ketonic function of 7, which could be easily attributed to the presence of the bulky heterocyclic moiety, we turned our attention to the initial adduct 6. We decided to perform the reduction of the ketone group before the cycloaddition step, being convinced that the hydride approach from the ß-side could be less

hindered by the nitromethylene substituent. Thus reaction of 6 with $LiAlH(OBu^t)_3$ in THF at 0°C, followed by heating at 50°C for 2h of the crude reaction mixture, led to the formation of a 3:1 mixture of the oily lactone 11a and the hydroxy--ester 12 , which were readily separated by flash-chromatography. Removal of the protecting group from 11a by mild aqueous acid treatment furnished the crystalline nitro-lactone 11b.



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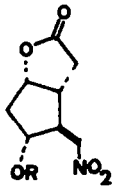
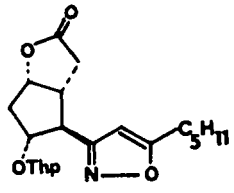


11a R=Thp

11b R=H

Subjecting 11a to the usual Mukaiyama conditions[12] in the presence of n-heptyne, the expected isoxazole 13 was obtained in excellent yield.



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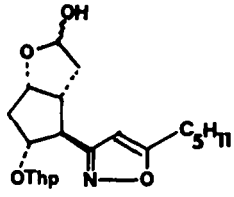
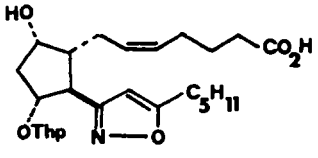


14

At this point the stage was set to assemble the carbon skeleton of α-chain. Reduction of the lactone 13 to the lactol 14 was easily obtained in 70% yield by treatment with DIBAH in toluene at -78°C. The crude lactol was then allowed to react with a five-fold excess of (4-carboxybutylidene)triphenylphosphorane in DMSO in the presence of potassium tert-butoxide to give the acid 15 in 60% yield after column chromatography.



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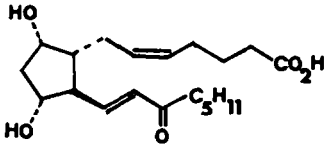


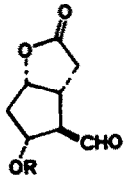
16

The latent α,ß-unsaturated moiety contained in 15 was uncovered by exposure to sodium in liquid ammonia containing tert-butyl alcohol as a proton source, followed by heating the derived rather unstable ß-amino-ketone in $CHCl_3$ solution in the presence of silica gel to promove complete elimination of ammonia[13].

Final treatment of the crude reaction product with dilute hydrochloric acid cleaved the protective group to furnish in 44% overall yield the known[14] 16, which has been already taken to $PGF_{2\alpha}$ by routine procedures.

Synthesis of the optically active Corey intermediates

With the aim at further illustrate the significative importance of the successfully achieved nitronate addition to 4-oxygenated cyclopent-2-enones as a convenient route to prostanoids, independently from our cycloadditive strategy, we decided to synthesize the most classical intermediate for prostaglandins, namely the Corey aldehyde (17)[15].



17a R=H

17b R=Thp

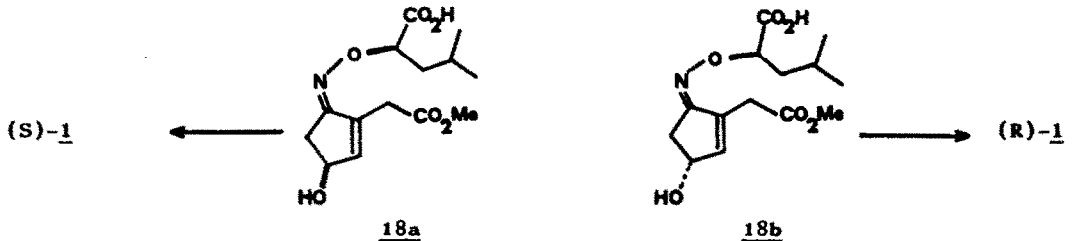
This popular target has been the object of several synthetic endeavours, deriving much of its importance from the fact that is the usual starting material for the synthesis of prostaglandins.

In order to obtain this compound in optically active form, we adopted a synthetic strategy which involved the optical resolution of the starting 4-hydroxy-2--substituted-cyclopentenone 1. This task was achieved through derivatization of the carbonyl group utilizing as chiral derivatizating agent (R)-2-aminoxy-4-methylvaleric acid, following the interesting method developed by Pappo.[16]

Application of this technique to racemic 1 gave an 80% yield of the diastereoisomeric oximes 18a and 18b, which were easily separated by silica gel column chromatography and subsequently treated with $TiCl_3$ to regenerate the corresponding ketones (S)-1 and (R)-1 in 80 and 85% yield respectively. Their configuration has been determined by converting each one to the corresponding nitromethane adduct, obtained as above described for the racemic compound through the sequence 1⟶5⟶6, followed by removal of the protecting group by mild acid treatment.

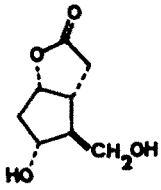
The positive Cotton effect ($\vartheta_m \times 10^{-3}$ =+6.4 at 292.5 nm) exhibited by the adduct derived from (S)-1 has resulted contrary to the circular dichroism curves of natural prostaglandins.

Therefore the adduct derived from (R)-1 was converted by treatment at 60°C with $LiAlH(OBu^t)_3$ into the corresponding optically active lactone 11a, an immediate precursor of the popular Corey intermediate 17a.



The Nef reaction performed on the optically active 11a in methanol with buffered aqueous titanium (III) chloride proceeded smoothly to provide the labile aldehyde

17b, which was correlated to more stable crystalline compound 19[15], upon reduction with sodium borohydride followed by aqueous acid removal of the protective group.



19

Conclusions

The demand for PG synthesis has been well served in recent years by a prodigious intellectual effort. However the feasibility of the conjugate addition of nitromethane to cyclopent-2-enones bearing a 4-oxygenated function, has opened a new route to natural prostaglandins which may offer some advantages in terms of simplicity, cheap and safe reagents and satisfactory overall yield.

As an optional, the ω-chain can be constructed both via the classical Wittig reaction or via [3+2] dipolar cycloaddition.

EXPERIMENTAL

Melting points and boiling points are uncorrected. Reaction courses and product mixtures were routinely monitored by thyn-layer chromatography (TLC) on silica gel precoated F_{254} Merck plates. Infrared (IR) spectra were measured on a Perkin Elmer 297 spectrometer. Nuclear magnetic resonance (^{1}H NMR) spectra were obtained with a Brucker 200 spectrometer for solutions in $CDCl_3$ and peak positions are given in parts per million downfield from tetramethylsilane as an internal standard. Optical rotations were determined with a Perkin Elmer 141 polarimeter, concentration c=1 in the appropriate solvent at a temperature in the range 24-25°C. All drying operations were carried out with anhydrous magnesium sulphate. Light petroleum refers to the fractions boiling range 40-60°C and ether to diethyl ether.

Starting materials. 5-Oxo-1-cyclopenten-1-acetic acid methyl ester was prepared starting either from cyclopentanone[8] or cyclopent-2-en-1-one[9] through published procedures developed in our laboratories. The preparation of 1 has been detailed elsewhere.[10]

(1α,2β,3β)-3-Hydroxy-2-nitromethyl-5-oxo-cyclopentane acetic acid methyl ester 2 and 3α-Hydroxy Epimer 3.

A solution of 1 (4g, 23.53 mmol) in CH_3NO_2 (50 ml) containing tetramethylguanidine (0.5 ml) was stirred at 0°C for 2h. The mixture was diluted with ether (25 ml), washed with 5% HCl, then with saturated $NaHCO_3$ and brine. The organic extracts were dried and concentrated in vacuo. The residue was flash-chromatographed over silica gel using ether as eluent to give 2 (3.56g; 66% yield) as a crystalline solid m.p. 95-97°C (ether). IR ($CHCl_3$): 3600, 3100, 1740, 1720 and 1550 cm^{-1}; ^{1}H NMR:δ 2.2-3.2 (compl.m, 7H), 3.67 (s,3H), 4.25-4.6 (m, 1H), 4.6 (dd, 1H, J=13.8 and 5Hz), 4.8 (dd, 1H, J=13.8 and 9Hz) and 3, oil, (1.18g, 22% yield). IR ($CHCl_3$): 3600, 3100, 1740, 1720 and 1550 cm^{-1}; ^{1}H NMR:δ 2.17-3.12 (compl.m, 6H), 3.6 (broad, 1H), 3.67 (s, 3H), 4.0-4.55 (m, 1H), 4.77 (d, 2H, J=6Hz).

(3aα,4α,5α,6aα)-Hexahydro-5-hydroxy-4-nitromethyl-2H-cyclopenta [b] furan-2-one 4.

To an ice-cooled and stirred suspension of $LiAlH(OBu^t)_3$ (2g, 7.87 mmol) in THF (20 ml) a solution of 2 (1.24g, 5.36 mmol) in THF (5 ml) was added dropwise. When the reaction was complete as judged by TLC (eluent: ether), the mixture was heated at 50°C for 2h, then poured into water, treated with 10% HCl, and extracted several times with $CHCl_3$. The organic extracts were dried and evaporated to give the crystalline lactone-alcohol 4: 0.9g (85%); m.p. 104-105°C (ether). IR (KBr): 3600, 3400, 1770 and 1550 cm^{-1}; ^{1}H NMR:δ 2.1-2.9 (compl.m, 5H), 3.8-4.1 (m, 1H), 4.2-4.4

(m, 2H), 5.05 (m, 1H).

3-[(Tetrahydro-2H-pyran-2-yl)oxy]-5-oxo-1-cyclopentene-1-acetic acid methyl ester 5.

To an ice-cooled solution of 1 (3.4g, 20 mmol) and freshly distilled dihydropyran (1.8g) in CH_2Cl_2 (50 ml) p-toluene sulphonic acid (0.1g) was added. The mixture was allowed to warm to room temperature until completion (6h), then quenched by the addition of saturated $NaHCO_3$ solution. Usual workup afforded 5 in quantitative yield. IR (neat): 1740, 1710, 1640 and 1580 cm^{-1}; ^1H NMR: δ1.2-1.9 (m, 6H), 2.1-2.9 (m, 2H), 3.2 (s, 2H), 3.65 (s, 3H), 3.4-4.0 (m, 2H), 4.6-5.0 (m, 2H), 7.45 (s, 1H).

(1α, 2β-3α)-2-Nitromethyl-3-[(tetrahydro-2H-pyran-2-yl)oxy]-5-oxo-cyclopentane acetic acid methyl ester 6.

This compound was obtained from 5 as an oil in 85% yield by tetramethylguanidine-catalyzed addition of nitromethane as above described. IR(Kbr): 1750, 1740 and 1560 cm^{-1}; ^1H NMR: δ 1.35-1.85 (compl.m, 6H), 2.0-3.1 (compl.m, 4H), 2.7 (d,2H, J=5.6) 3.3-3.95 (compl.m, 2H), 3.62 (s, 3H), 4.0-4.8 (compl.m, 4H).

(1α,2β-3α)-2-(5-Pentyl-3-isoxazolyl)-3-[(tetrahydro-2H-pyran-2-yl)oxy]-5-oxocyclopentane acetic acid methyl ester 7.

To a stirred mixture of 6 (1.9g, 6 mmol) and 1-heptyne (1.15g, 12 mmol) in benzene (10 ml) containing several drops of Et_3N a solution of PhNCO (1.8g, 15 mmol) in benzene (10 ml) was added dropwise at 25°C. The mixture was stirred overnight at room temperature and then heated at 50°C for 1h. The cooled mixture was filtered and the filtrate washed with dilute 5% NH_4OH, dried and evaporated under reduced pressure. The residue was purified by flash-chromatography on silica gel (eluent: ether:light petroleum 1:1) to give (7) as an oil (1.9g, 80%). IR (neat): 1750, 1740 and 1600 cm^{-1}; ^1H NMR: δ 0.9 (broad t, 3H), 1.2-2.0 (compl.m, 15h), 2.5-3 (compl.m, 5H), 3.4-3.7 (m, 2H), 3.65 (s, 3H), 4.3-4.75 (m, 2H), 6.08 (s, 1H).

(3aα,4α,5β-6aα)-Hexahydro-5-hydroxy-4-(5-pentyl-3-isossazolyl)-2H-cyclopenta[b]-furan-2-one 8 and (1α, 2β,3α, 5β)-5-hydroxy-2-(5-pentyl-3-isoxazolyl)-cyclopentane acetic acid methyl ester 9a.

To a stirred and ice-cooled suspension of $LiAlH(OBu^t)_3$ (1.07g, 4.2 mmol) in THF (15 ml) was added dropwise a solution of 7 (1.6g, 4.07 mmol) in THF (5 ml). After additional stirring for 2h at room temperature, the mixture was heated at 60°C for 3h, then cooled and carefully acidified with 5% hydrochloric acid to pH=3. The reaction mixture was stirred for 1h, then extracted several times with CH_2Cl_2 (5x15 ml). The dried organic extracts were evaporated to leave a residue which was chromatographed on silica gel (eluent AcOEt:light petroleum 1:1, then AcOEt) to give 8 (0.2g, 18% yield), m.p. 91-92°C (Ether:light petroleum 1:1); IR ($CHCl_3$): 3500-3100, 1770, 1640, 1600 cm^{-1}; ^1H NMR ($CDCl_3$):δ 0.97 (broad t, 3H), 1.15-1.9 (m, 7H), 2.0-3.0 (m, 6H), 3.1-3.47 (m, 2H), 4.25-4.55 (m, 1H), 4.9-5.2 (m, 1H), 5.9 (s, 1H) and 9a (0.67g, 53%), oil; IR (neat): 1740, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): 0.9 (broad t, 3H), 1.1-1.5 (m, 6H), 1.5-3.0 (m, 10H), 3.65 (s, 3H), 4.0-4.35 (m, 2H), 5.95 (s, 1H).

(1α,2β-3α,5β)-5-Hydroxy-2-(5-pentyl-3-isoxazolyl)-3-[(tetrahydro-2H-pyran-2-yl)oxy]-cyclopentane acetic acid 9b.

A solution of 9a (0.9g, 2.9 mmol) in CH_3OH (40 ml), water (4 ml) containing LiOH (0.2g) was stirred at room temperature for 6h. Most of the solvent was removed in vacuo, then the mixture was acidified with 5%HCl and extracted with AcOEt (3x20 ml). The dried organic extracts were evaporated in vacuo to give 9b as a solid, m.p. 89-91°C (AcOEt:light petroleum 1:1). IR ($CHCl_3$): 3500-2500, 1720, 1600 cm^{-1}; ^1H NMR ($CDCl_3$):δ 0.9 (broad t, 3H), 1.05-1.5 (m, 6H), 1.5-3.2 (m, 8H), 3.95-4.3 (m, 2H), 5.85 (s, 1H), 5.9-6.3 (broad, 3H).

(3aα,4α,5β,6aβ)-Hexahydro-4-(5-pentyl-3-isoxazolyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-cyclopenta[b]furan-2-one (10).

A solution of 9b (0.6g, 2.00 mmol) in benzene (20 ml) containing $TsOH.H_2O$ (30 mg) was heated at reflux for 3h with provision for the removal of water (Dean and Stark). The organic layer was washed with saturated $NaHCO_3$ solution, dried and concentrated in vacuo. The residue, purified by flash-chromatography on silica gel, gave 10 as white solid, m.p. 88-90°C (ether:light petroleum 1:2) in 71% yield. IR ($CHCl_3$): 3500-3100, 1770, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.95 (broad t, 3H), 1.15-2.25 (m, 7H), 2.55-3.05 (m, 7H), 3.4 (broad s, 1H), 4.1-4.45 (m, 1H), 4.95 (m, 1H), 6.07 (s, 1H).

(3aα,4α,5β-6aα)-Hexahydro-4-nitromethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-cyclopenta[b]furan-2-one 11a and (1α,2β,3α,5β)-5-hydroxy-2-nitromethyl-3-[(tetrahydro-2H-pyran-2-yl)-oxy]-cyclopentane acetic acid methyl ester 12.

To an ice-cooled and stirred suspension of $LiAlH(OBu^t)_3$ (2.2g, 8.9 mmol) in anhydrous THF (15 ml), a solution of 6 (1.4g, 4.4 mmol) in THF (5 ml) was added dropwise. Stirring was continued for 18h at room temperature and then for 3h at 60°C. The cooled mixture was poured in water (10 ml),

carefully acidified at pH=6 with 5% HCl and extracted with CH_2Cl_2 (4x20 ml). The dried extracts were evaporated to give an oily residue which was chromatographed on silica gel (eluent:ether) to afford 11a as an oil (0.96g, 75.6%). IR (neat): 1770, 1550 cm^{-1}; ^1H NMR: δ 1.35-1.85 (compl.m, 6H), 2.0-3.1 (compl.m, 4H), 2.7 (m, 2H), 3.3-3.95 (compl.m, 2H), 4.0-4.8 (compl.m, 5H), and 12 (0.35g, 25%) as an oil. IR (neat): 3600-3100, 1740, 1550 cm^{-1}; ^1H NMR: δ 1.35-1.85 (m, 6H), 2.0-3.1 (m, 5H), 2.7 (m, 2H), 3.3-3.95 (compl.m, 2H), 3.65 (s, 3H), 4.0-4.9 (compl.m, 5H).

(3aα,4α,5β,6aα)-Hexahydro-5-Hydroxy-4-(5-pentyl-3-isoxazolyl)-2H-cyclopenta[b]furan-2-one 13.

To a stirred mixture of the nitrolactone 11 (1.0g, 3.5 mmol) and 1-heptyne (0.67g, 7 mmol) in benzene (10ml) containing several drops of Et_3N was added a solution of PhNCO (1.44g, 12 mmol) in benzene (10 ml) dropwise at 25°C. The solution was stirred overnight at room temperature and then heated at 50°C for 1h. The cooled mixture was filtered and the filtrate washed with dilute 5% NH_4OH, dried and evaporated under reduced pressure. The residue was purified by flash-chromatography on silica gel to give an oil, which was hydrolysed with dilute HCl (15%) and THF by stirring at 25°C until starting material was consumed. The THF was removed at reduced pressure and the aqueous residue was extracted with AcOEt. Evaporation in vacuo of the organic solvent left 13 (70%) as a solid after chromatographic purification (eluent/ AcOEt:light petroleum 1:1), m.p. 91-92°C (ether:light petroleum 1:1); IR ($CHCl_3$): 3500-3100, 1770, 1640, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ0.97 (broad t, 3H), 1.15-1.9 (m, 7H), 2.0-3.0 (m, 6H), 3.1-3.47 (m, 2H), 4.25-4.55 (m, 1H), 4.9-5.2 (m, 1H), 5.9 (s, 1H).

(1α,2β,3α,5α)-7- 2-(5-pentyl-3-isoxazolyl)-3-(tetrahydro-2H-pyran-2-yl)-oxy-5-hydroxy cyclopentyl--hept-5(Z)enoic acid 15.

To a solution of the lactone 13 (1.81g, 0.5 mmol) in anhydrous toluene (15 ml) cooled to -78°C neat diisobutylaluminum hydride (1.42g, 10 mmol) was added dropwise.
When the addition was completed, the mixture was stirred for 2h, and while still at -78°C, methanol was added cautiously to quench excess reagent. The mixture was allowed to warm to room temperature, and, after 1h, a 10% solution of sodium potassium tartrate was added. Usual work-up led to the oily lactol (1.5g, 85% yield), homogeneous by TLC (ether), which was employed without further purification.
To a solution of potassium tert-butoxide (6.72g, 60 mmol) in freshly distilled dimethyl sulfoxide (15 ml) was added solid (4-carboxybutyl)triphenylphosphonium bromide (13.29g, 30 mmol). A solution of the lactol 14 (5 mmol) in dimethyl sulfoxide (10 ml) was then added to the red solution of the ylide and stirring was continued until the reaction was complete (TLC). The mixture was poured into ice water (40 ml) and extracted with EtOAc. The aqueous phase was acidified with sodium dihydrogen phosphate and extracted with CH_2Cl_2 (4x50 ml). The extracts were washed with brine, dried and evaporated to give a residue, which was triturated with ethyl acetate to induce solidification of (4-carboxybutyl)-diphenylphosphine oxide. Filtration and removal of the solvent from the filtrate led to an oily residue which was chromatographed on silica gel using light petroleum containing increasing quantitaties of ether. The acid 15 was obtained as an oil (1.3g, 60% yield). IR ($CHCl_3$): 3600-2700, 1700, 1600 cm^{-1}; ^1H NMR: δ 0.9 (br t, 3H), 1.2-2.0 (compl.m, 19H), 2.5-3.0 (compl.m, 7H), 3.4-3.8 (m, 2H), 4.1-4.75 (m, 3H), 5.5 (m, 2H), 6.0 (s, 1H), 6.5 (broad, 2H).

(1α,2β,3α,5α)-3,5 Dihydroxy-2-(3-oxo-trans-octenyl)cyclopentane-1-cis-hept-2-enoic acid 16

A solution of acid 15 (2.24g, 5 mmol) in THF (15 ml) containing tert-butyl alcohol (1.11g, 15 mmol) was added to liquid ammonia (100 ml). Sodium (0.6g) was then added portionwise until the solution remained blue. After additional stirring for 15 min, solid NH_4Cl was added until decolorization, and ammonia was allowed to evaporate. The residue was treated with saturated NH_4Cl solution (15 ml), carefully acidified in an ice-bath to pH=5, and extracted with $CHCl_3$ (3x25 ml). The dried extracts were concentrated in vacuo to half of their volume and silica gel (5g) preheated overnight at 150°C was added. The mixture was refluxed overnight, then filtered and the filtrate concentrated in vacuo. The residue was dissolved in THF (15 ml) and stirred at room temperature with 5% HCl (15 ml) until starting material was consumed. Most of the solvent was removed under reduced pressure, and the residue was treated with water (15 ml) and extracted with $CHCl_3$. Evaporation of the dried extracts left a residue which was chromatographed on silica gel (eluent EtOAc/MeOH, 99:1), to give the known[14] 16.

[R-(R*,S*)] -5- [(1-Carboxy-3-methylbutoxy)imino] -3-hydroxy-1-cyclopentene-1-acetic acid methyl ester 18a and its [R-(R*,R*)]-epimer 18b.

To a solution of 1 (1.6g, 9.4 mmol) in MeOH (20 ml) containing pyridine (1.8 ml, 20 mmol) was added (R)-2-aminoxy-4-methylvaleric acid (2g, 10 mmol). The mixture was stirred at room temperature for 20 minutes, then acidified with 5% HCl and extracted with AcOEt (3x25 ml). The dried organic extracts were evaporated in vacuo and the oily residue chromatographed on silica gel (eluent CH_2Cl_2:MeOH:AcOH 9.4:0.5:0.1 mixture) to give 18a (35% yield) and 18b (35% yield) as oils with similar spectroscopic characteristics. IR ($CHCl_3$): 3600-2500, 1740-1690, 1630 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.92 (d, 6H, J=7Hz), 1.47-1.32 (m, 3H), 2.3-3.02 (m, 2H), 3.2 (s, 2H), 3.65 (s, 3H), 4.5 (m, 1H), 4.8 (m, 1H), 5.9-6.25 (m, 2H), 6.4 (m, 1H).

(S)-3-Hydroxy-5-oxo-1-cyclopentene-1-acetic acid (S)-1 and its enantiomer (R)-1 - General procedure: a solution of the oxime (0.5g, 1.7 mmol) in THF:H_2O 1:1 (20 ml) was treated with $AcONH_4$ (3g) and 15% aqueous $TiCl_3$ (6 ml) and heated at 60°C for 1h. After filtration on Celite, the filtrate was extracted with AcOEt (3x40 ml) and the dried extracts evaporated in vacuo. The oily residue was chromatographed on silica gel column (eluent:ether) to give the corresponding ketones (IR and NMR as reported for the racemic compound 1) with the following additional spectroscopic data:
(S)-1: $[\alpha]_D$= -34.28 (MeOH); (R)-1: $[\alpha]_D$= +33.54 (MeOH).

[3aR-(3aα,4α,5β,6aα)]-Hexahydro-4-nitromethyl-5-hydroxy-2H-cyclopenta[b]furan-2-one **11b** This compound, obtained as described above for the racemic compound, has the following characteristics: m.p. 78-79°C (AcOEt:n-hexane 1:1). $[\alpha]_D$=-42.3 (MeOH). Its enantiomer 3aS-(3aß, 4ß, 5 ,6aß) -Hexahydro-4-nitromethyl-5-hydroxy-2H-cyclopenta b furan-2-one has m.p. 78-79°C (AcOEt-:n-Hexane 1:1) $[\alpha]_D$=+42.6 (MeOH).

[3aR-(3aα,4α,5β,6aα)]-Hexahydro-2-oxo-5-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-cyclopenta[b]furan-4--carboxaldehyde **17a**

To a buffered $TiCl_3$ solution, prepared by adding NH_4OAc (3g) in 10 ml of water to 15% aqueous $TiCl_3$ (6.8 ml) under nitrogen the nitrolactone (15) (0.5g) in 8 ml of THF was added rapidily and the mixture was stirred overnight at room temperature. The reaction mixture was extracted several times with Et_2O; the organic extracts were washed with 5% $NaHCO_3$ solution, dried and concentrated in vacuo. The crude aldehyde **17a** was obtained as an amber oil (0.31g, 70%) and utilized without further purification.

[3aR-(3aα,4α,5β,6aα)]-Hexahydro-5-hydroxy-4-hydroxymethyl-2H-cyclopenta[b]furan-2-one **19**

To a solution of **17a** (0.3g, 1.18 mmol) in CH_3OH (4 ml) was added $NaBH_4$ (0.05g, 1.3 mmol) at room temperature and the mixture was stirred for 2h. Water was added and the solution was extracted with $CHCl_3$ (3x10 ml). The residue obtained by removal of the solvent in vacuo was dissolved in THF (5 ml) containing 5% HCl (5 ml) and the solution was stirred at 25°C until the starting material was consumed (generally 3h; monitored by TLC). The THF was removed on a rotary evaporator and the aqueous residue was extracted with $CHCl_3$. Evaporation in vacuo of the organic solvent left **19** (0.2g; 75%), m.p. 115-116°C; identical in all respects, including optical activity, with that reported in the literature.

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