The α-hydroxyphosphonate-phosphate rearrangement of a noncyclic substrate – some new observations

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Racemic ethyl hydrogen (1-hydroxy-2-methylsulfanyl-1-phenylethyl)phosphonate was resolved with (R)-1-phenylethylamine. The (R)-configuration of the (−)-enantiomer was determined by chemical correlation. Esterification of the (−)-enantiomer with a substituted diazomethane derived from 3-hydroxy-1,3,5 (10)-estratrien-17-one delivered two epimeric phosphonates separated by HPLC. Methylation with methyl fluorosulfate at the sulfur atom and treatment with a strong base induced an α-hydroxyphosphonate-phosphate rearrangement with formation of dimethyl sulphide and two enantiomerically pure enol phosphonates. Their oily nature interfered with a single crystal X-ray structure analysis to determine the stereochemistry at the phosphorus atom.

Introduction

When phosphoric acid derivatives (±)-1 are treated with strong bases in stoichiometric amounts such as alkyl lithiums or lithium amides at low temperatures, they are deprotonated to give short-lived organolithiums (±)-2 containing dipole-stabilised1 carbanions (Scheme 1). These undergo rearrangements via (±)-3 to lithiated α-substituted phosphonates (±)-4 and on work up to α-hydroxy-, α-sulfanyl- and α-aminophosphonates (±)-5. This isomerisation discovered for X = O by Sturtz and Corbel2 is called phosphate–phosphonate or more specifically phosphate-α-hydroxyphosphonate rearrangement. This3–5 and the versions for X = S6,7 and N8 have extensively been studied by Hammerschmidt’s group. The reverse process with many examples9–17 for X = O, the α-hydroxyphosphonate-phosphate rearrangement, also termed [1,2]-phospha-Brook rearrangement, has been found by Pudovik and Konovalova17 before the phosphate–phosphonate rearrangement. This isomerisation is normally catalysed by a variety of catalytic bases such as e.g. NaOH, NaOEt and DBU. While the transformation of (±)-1 into (±)-5 for X = O is feasible even for R2 = alkyl and R3 = H, the reverse process not. At least one of the substituents, R2 or R3, should stabilise the developing negative charge on the carbon atom in (±)-3 upon cleavage of the C–P bond. An aromatic substituent suffices to stabilise the intermediate carbanion. The driving force for the phosphate–phosphonate rearrangements is the stronger Li–O than Li–C bond. The reverse process (O–H + P–C → C–H + P–O) is dominated by the much higher P–O than P–C bond energy. These isomerisations are related to the Brook and retro-Brook rearrangements in silicon chemistry.18

The phosphate–phosphonate rearrangement for X = O,3–5 S7 and N8 and the reverse process for X = O follows a retenti
tive course at the respective carbon atoms. The stereochemistry at the phosphorus atom upon the a-hydroxyphosphonate-phosphate rearrangement follows a retentive course too, proven only for α-hydroxyphosphonates with the phosphorus atom as part of a six-membered ring.11,16 It was found that dia
t stereo
eremic α-hydroxyphosphonates (R,S)– and (R,R)–7 obtained by esterification of enantiomer (R)-6 and fractional crystallisation rearrange stereospecifically (Scheme 2).10 Here the phosphorus atom was not part of a ring system and the developing negative charge on the α-carbon atom upon

Scheme 1 Phosphate–phosphonate rearrangements and reverse processes.

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cleavage of the P–C bond eliminated a β-chloride, resulting in enantiomerically pure enol phosphates +− and −−. As they were oils, their absolute configuration could not be determined by X-ray structure analysis and the stereochemistry at the phosphorous atom had to remain unanswered.

## Results and discussion

The highly enantioselective synthesis of acyclic phosphate triesters is difficult and challenging. While Hall and Inch built their syntheses on 5- and 6-membered cyclic phosphorus compounds derived from −−-ephedrine and −−-glucose, Nakayama and Thompson applied −−-proline derivatives. We reasoned that the α-hydroxyphosphonate-phosphate rearrangement of acyclic substrates with a stereogenic P-atom of known configuration would give chiral, nonracemic phosphate triesters (Scheme 2).

The next step was the determination of absolute configuration of (−−)-10, it was transformed into the known α-hydroxyphosphonate (−−)-12 (Scheme 4). This was achieved by desulphuration of the respective potassium salt with aged Raney-nickel, followed by passage through Dowex 50 W, H+ to get the free acid. Esterification with diazoethane furnished phosphonic acid diethyl ester (−−)-12 (in 22% overall yield), which has (−−)-configuration based on the comparison of the specific optical rotation with the literature value. When freshly prepared RANEY-nickel was used, the CH3S and OH groups were both reductively removed. This experiment proved that phosphonic acid (−−)-10 has (−−)-configuration. The change of the descriptor is caused by the change in the priority for the substituents according to the CIP rules for (−−)-12: P > Ph > CH3; for (−−)-10: P > CH3SCH2 > Ph.

The stereoisomer of phosphonic acid (−−)-10 with a diazoalkane under mild conditions, which should give (1) separable diastereomeric α-hydroxyphosphonates and (2) at least one crystalline phosphate upon α-hydroxyphosphonate-phosphate rearrangement. Previously, a variety of bromoaryl diazoethanes were tested, but they delivered inseparable mixtures of α-hydroxyphosphonates and oily phosphates unfortunately. We reasoned that a steroid such as the fairly easily available 1,3,5(10)-estratrien-3-yl diazoethane (19) could fulfill the outlined requirements (Scheme 5). The centres of chirality of the steroid are too far away from the phosphorus atom to have an influence on the rearrangement. 1,3,5(10)-Estratrien-3-ol (12) prepared by a literature procedure from 3-hydroxy-1,3,5(10)-estratrien-17-one was esterified with triflic anhydride in the presence of 2,4,6-collidine and DMAP at −30 °C to give triflate 14 in 85% yield. Alkoxycarbonylation catalysed by Pd(OAc)2-1,3-bis(diphenylphosphino)propane of the phenolic triflate with CO/MeOH/

[Scheme 2: α-Hydroxyphosphonate-phosphate rearrangement of diastereomeric α-hydroxyphosphonates 7 to enantiomerically pure enol phosphates 8.]

[Scheme 3: Preparation and resolution of ethyl hydrogen phosphate (±)-10.]

[Scheme 4: Determination of absolute configuration of (−−)-10.]
Et$_3$N at 70 °C delivered benzoate 15 in 80% yield, which was
quantitatively reduced to benzyl alcohol 16 with LiAlH$_4$. Swern
oxidation of 16 to the aldehyde 17 was less effective (54%
yield) than PCC oxidation (91%) in the presence of 3 Å mole-
cular sieves, which facilitated a smooth reaction and workup.

Heating a mixture of aldehyde 17 with tosyl hydrazine in
MeOH at 40 °C, furnished in 95% yield tosyl hydrazone 18,
the starting material for the preparation of the substituted dia-
zomethane. Refluxing a mixture of the hydrazone and sodium
bis(trimethylsilyl)amide in dry THF for 90 min gave the substi-
tuted diazomethane 19.

Crude 19 was not purified, but immediately used for the
esterification of phosphonic acid (R)-(−)-10 in CH$_2$Cl$_2$ at room
temperature (Scheme 6). Flash chromatography of the crude
product provided a 1 : 1 mixture of epimers 20 and 23 (by $^1$H
NMR; epimers displayed the same polarity) in 90% yield.

Separation by preparative HPLC delivered the less polar 20 of
88% de and the more polar 23 of 96% de. Crystallisation of epimer 20 from hexanes or cyclohexane furnished crystals of
>98% de, which contained solvent (20/hexanes, 3.13 : 1; 20/
cyclohexane, 2 : 1, by $^1$H NMR). The more polar epimer 23 was
crystallised from hexanes/i-PrOH to give crystals of also de
>98%, which were suitable for an X-ray crystal structure. It
allowed to assign $(R,R_p)$-configuration (Fig. 1) to the phos-
phonic acid part of 23 and consequently $(R,S_p)$-configuration to
that of 20 (the P=O bond is considered a single bond when
the sequence rule is used!). Both epimers were methylated at
the sulfur atom with methyl fluorosulfate at −35 °C. The
respective sulfonium salts 21 and 24 were deprotonated at the
hydroxyl groups with phosphazene base P$_1$-t-Bu, a stronger
base than DBU, to induce α-hydroxyphosphonate-phosphate
rearrangements as detailed for 24 in Scheme 7.

The alkoxide 26 has two options. Firstly (pathway A), it can
disintegrate (retro-Abramov reaction) into phosphite anion
29 and sulfonium salt 28, which in turn react with each other
to sulfonium ylide 30 and H-phosphonate 31. The carbonyl
group of the ylide is not electrophilic enough to allow addition

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**Scheme 5** Preparation of substituted diazomethane 19.

**Scheme 6** Esterification of (R)-10 to give epimeric α-hydroxyphosphonates 20 and 23 for the rearrangement to phosphates 22 and 25.

**Scheme 7** Reaction pathways for alkoxide 26.
of the phosphate anion, which would lead to epimeric α-hydroxyphosphonates. Additionally, sulfur ylide 30 is not basic enough to deprotonate 31 to give 29. The H-phosphate 31 was detected in the crude reaction mixture by 1H NMR spectroscopy [P(O)H: δH = 6.84, d, JHP = 698.0 Hz]. Secondly (pathway B), alkoxide 26 can undergo the rearrangement to enol phosphate 25 via cyclic species 27, which might be either an intermediate or a transition state.13 We assume that 27 has a trigonal bipyramidal structure formed by an apical attack of the alkoxide anion on the electrophilic phosphorus atom from the less hindered side opposite to the EstCH2O substituent. The P-C bond will be equatorially orientated. The negative charge building up on the α-carbon atom in 25 upon cleavage of the P-C bond eliminates dimethyl sulphide. The two enol phosphates 22 and 25 were obtained in yields of 46% and 48%, respectively. Their specific optical rotations were [α]D 25 22 + 46.8 and + 41.9, respectively. These compounds contain beside the stereogenic phosphorus atom some stereogenic carbon ones in the steroidal substituent. Therefore the specific optical rotations cannot have the same absolute values with opposite signs, NMR spectroscopically, they are virtually identical (1H, 13C, 31P) except for the resonances of EstCH2OP group (AB parts of ABP systems) in the 1H NMR spectrum (Fig. 2).

Inspection of the three segments of the relevant 1H NMR spectra reveal that the two enol phosphates 21 and 25 are enantiomerically pure. Unfortunately, none of the two oils could be induced to crystallise and the absolute configuration of the stereogenic phosphorus atom could not be determined by single X-ray structure analysis. The stereochemical course of the α-hydroxyphosphate-phosphate rearrangements remains to be determined. However, it must be a stereospecific reaction yielding enantiomerically pure enol phosphates.

Conclusions

In summary, we prepared a racemic ethyl hydrogen α-hydroxyphosphonate, resolved it with (R)-1-phenylethylamine and esterified it with a diazomethane derived from 3-hydroxy-1,3,5(10)-estratrien-17-one. Each epimer obtained by HPLC separation was methylated at the methylsulfanyl substitutent and treated with base to induce α-hydroxyphosphate-phosphate rearrangements. We found that the rearrangement is stereospecific. However, the stereochemistry could not be determined as the obtained phosphate was not crystalline to perform a single crystal X-ray structure analysis. The sequence allows to prepare enantiomerically pure enol phosphates.

Experimental

General

1H, 13C (J-modulated) and 31P NMR spectra were recorded in CDCl3 on Bruker Avance AV 400 (1H: 400.13 MHz, 13C: 100.61 MHz, 31P: 161.97 MHz) and AV III 600 (1H: 600.25 MHz, 13C: 150.93 MHz, 31P: 242.94 MHz) spectrometers at 25 °C. Chemical shifts (δ) are reported in parts per million (ppm) relative to CHCl3/CDCl3 (δH 7.24, δC 77.00) and external H3PO4 (85%; δP 0.00) and coupling constants (J) in Hz. Data for 1H NMR spectra are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet), coupling constants, and integration.

IR spectra were run as films between NaCl plates or on a silicon disc using a PerkinElmer 1600 FT-IR spectrometer. Optical rotations were measured on a PerkinElmer 351 polarimeter in a 1 dm cell. Analytical HPLC was performed on a Jasco System (PU-980 pump, UV 975 and RI 930) using a Nucleosil 50-4 column (Macherey-Nagel), Φ 0.4 cm × 25 cm. Preparative HPLC was performed on a Rainin System (Dynaxm Model SD-1 pump, Model UV-1 UV detector, 254 nm) using a Nucleosil 50-7 column, Φ 6.3 cm × 28.8 cm. Melting points were measured on a Leica Galen III Thermovar instrument and are uncorrected. Flash (column) chromatography was performed with silica gel 60 (230–400 mesh) and monitored by TLC conducted on glass-backed 0.25 mm thick silica gel 60 F254. Spots were visualised by UV and/or dipping the plate into a solution of (NH4)2MoO4·3H2O (23.0 g) and Ce(SO4)2·4H2O (1.0 g) in 10% aqueous H2SO4 (500 mL), followed by heating with a heat gun.

(±)-Ethyl hydrogen (1-hydroxy-2-methylsulfonyl-1-phenyl)-phosphonate ([±]-10)

A solution of ethyl bis(trimethylsilyl) phosphate3 (36.13 g, 142 mmol) and methylsulfonylmethyl phenyl ketone (9)21 (23.61 g, 142 mmol) in dry toluene (100 mL) was heated for 18 h at 70 °C under exclusion of moisture, cooled and then diluted with water (200 mL). After stirring vigorously for 30 min the mixture was neutralised with NaOH (2 M, phenolphthalein). The organic phase was separated and discarded. The aqueous one was continuously extracted with Et2O for 2 h and the extract was discarded. The aqueous layer was acidified with diluted H2SO4 (10 mL conc. H2SO4 and 30 mL H2O) and again continuously extracted with Et2O for 1 h. This extract was concentrated under reduced pressure and dried to yield crystalline phosphonic acid ([±]-10) (28.0 g). Continuous extraction for another 2 h gave another 1 g phosphonic acid. The combined products were crystallised from Et2O (with cooling at −20 °C) to yield phosphonic acid ([±]-10) (23.0 g,
95%) as colourless crystals. The analytical sample was recrystallised from EtOAc/Et2O; mp 95–98 °C.

IR (nujol): ν 3409, 3100–2000, 1620, 1550, 1300, 1190, 1170, 1160, 1050 cm⁻¹; ¹H NMR (600.25 MHz, CDCl₃); δ 11.6 (t, J = 7.1 Hz, 3H), 8.10 (s, 3H), 3.33 (AB part of ABP system, JAB = 14.1 Hz, J = 8.2, 6.6 Hz, 2H), 3.86–4.00 (m, 2H), 7.25–7.29 (m, 1H), 7.34 (t, J = 7.7 Hz, 2H), 7.40 (br. s, 2H), 7.54–7.60 (m, 2H); when excess (R)-(+)1-phenylethylamine was added to the NMR sample, two diasteromeric salts formed with the methylsulfanyl groups resonating at 1.77 and 1.79 ppm. The singlet at lower field corresponds to the CH₃S of the salt of the dextrorotary acid. ¹³C NMR (150.93 MHz, CDCl₃); δ 16.2 (d, J = 5.9 Hz), 17.1, 43.1 (d, J = 6.8 Hz), 63.8 (d, J = 8.6 Hz), 74.2 (d, J = 165.4 Hz), 126.4 (d, J = 4.2 Hz), 127.8 (d, J = 2.8 Hz), 128.1 (d, J = 2.5 Hz), 138.6; ³¹P NMR (242.99 MHz, CDCl₃); δ 23.4. Anal. calcd for C₁₉H₂₈NO₄PS: C, 57.42; H, 7.10; N, 3.52; calcd for C₁₉H₂₈NO₄PS: C, 57.42; H, 7.10; N, 3.52.

Optical resolution of (±)-ethyl hydrogen (1-hydroxy-2-methylsulfanyl-1-phenylethyl)phosphonate with (R)-1-phenylethylamine ([R]-11)

Racemic phosphonic acid (±)-10 (16.56 g, 60 mmol) was dissolved in CH₂Cl₂ (30 mL) and (R)-(+)1-phenylethylamine (7.72 g, 60 mmol, 7.68 mL) was dropwise added with cooling. After the addition of Et₂O (300 mL) and seeding crystals obtained by slow evaporation of solvent from a CHCl₃ solution of this salt, the solution was left for 24 h at 4 °C. The formed crystals were collected, washed with cold CH₂Cl₂ and dried; 8.03 g, de 98%. The crystals were recrystallised from CHCl₃ as before and furnished phosphonic acid salt (R)-(+)1-phenylethylammonium salt hemihydrate ([R]-11) × (0.11 g, 22%) as a colourless powder.

Desulphurisation of potassium salt of (±)-ethyl hydrogen (1-hydroxy-2-methylsulfanyl-1-phenylethyl)phosphonate (±)-10

Raney-nickel prepared by a literature procedure²² was washed with water (10 × 250 mL portions) and stored in water for 72 h at room temperature prior to use (it has to be handled quickly when moist as it is pyrophoric).

Diazoethane.²¹ To a solution of KOH (15 g) in water (45 mL) and Et₂O (30 mL) cooled at −35 °C (bath temperature) N-nitroso-N-ethylurea²³ (4.0 g) was added in portions within 5 min. The mixture was stirred until the urea had dissolved (20 min). The yellow ethereal solution of diazoethane was used directly for esterification.

The free phosphonic acid obtained by general procedure A from (R)-1-phenylethylammonium salt hemihydrate ([R]-11) × (−)10 × 0.5H₂O (0.80 g, 1.97 mmol) was dissolved in a mixture of ethanol (12 mL) and water (8 mL) and neutralised with KOH (10%, phenolphthalein). After the addition of moist RANEY-nickel (5.3 g) the mixture was stirred for 15 h at room temperature and filtered. The RANEY® nickel was washed with a mixture of EtOH/water (the spent RANEY®-nickel was inactivated by storage under CH₂Cl₂). The filtrate was passed through Dowex 50 W × 8, (H⁺) and eluted with water until neutral. The eluate was concentrated under reduced pressure, dissolved in EtOH and esterified with diazoethane. The solution was concentrated under reduced pressure. The oily residue was flash chromatographed (CH₂Cl₂/EtOAc, 5:1; R, 0.17 and 0.07). The less polar product (0.060 g) although evidently homogeneous by TLC was an inseparable mixture of diethyl 1-hydroxy-2-methylsulfanyl-1-phenylethylphosphonate and diethyl 1-phenylethylphosphonate (ratio ¹H NMR: 19:81). The more polar product was flash chromatographed a second time (CH₂Cl₂/EtOAc, 2:1; R, 0.17) to give diethyl 1-hydroxy-1-phenylethylphosphonate (−)-12 (0.11 g, 22%) as a colourless oil; [α]D²⁰ = −36.4 (c 3.4, CHCl₃), after distillation (115–120 °C/0.005 mm) [α]D²⁰ = −35.67 (c 1.8, CHCl₃) (lit.³ [α]D²⁰ = −37.2 (c 2.12, CHCl₃) for known 1-hydroxy-1-phenylethylphosphonate (3)-(−)-12).

Conversion of (R)-1-phenylethylammonium salt of ethyl hydrogen (1-hydroxy-2-methylsulfanyl-1-phenylethyl)phosphonate to free phosphonic acid (−)-10 (general procedure A)

The (R)-1-phenylethylammonium salt hemihydrate ([R]-11) × (−)10 × 0.5H₂O (1.105 g, 2.72 mmol), CH₂Cl₂ (20 mL), water (20 mL) and ammonia solution (2 mL, 25%) were mixed. The organic phase was separated and the aqueous one was extracted with CH₂Cl₂ (2 × 15 mL). The organic phases containing the amine were discarded and the aqueous phase was concentrated under reduced pressure. The residue was dissolved in water and applied to a Dowex 50W × 8, H⁺ column and eluted with water until neutral. The eluate was concentrated under reduced pressure and dried (0.5 mbar/RT) to give phosphonic acid (−)-10 (0.710 g, 94%) as colourless gum, which crystallised; mp 61–63 °C (i-Pr₅O/few drops of CH₂Cl₂); [α]D²⁰ = −16.9 (c 1.45, dry EtOH). Anal. calcd for C₁₉H₂₈NO₄PS: C, 47.82; H, 6.20; O, 23.16; S, 11.60. Found: C, 47.83; H, 6.20; O, 23.40; S, 11.71.

1.3.5(10)-Estratrien-3-yl trifluoromethanesulfonate (14)

1.3.5(10)-Estratrien-3-ol₂⁵ (13) (11.7 g, 45.6 mmol, crystalline product, freed from EtOH by dissolution in toluene and concentration under reduced pressure) was dissolved in

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dry CH₂Cl₂ (150 mL) under argon atmosphere. 2,4,6-Trimethylpyridine (9.53 g, 78.7 mmol, 10.4 mL, 1.73 equiv.) and 4-dimethylaminopyridine (1.30 g, 10.6 mmol, 0.23 equiv.) were added, followed by cooling at −30 °C and dropwise addition of triflic anhydride (19.4 g, 69 mmol, 11.3 mL, 1.5 equiv.). The mixture was stirred for 10 min at −30 °C and 2 h at room temperature. The mixture was washed with 2 M HCl, water and a saturated aqueous solution of NaHCO₃ (each with 0.06 equiv.) and 1,3-bis(diphenylphosphino)propane (0.914 g, 1.75 mmol, 0.32 equiv.) to give triflate 14 (15.1 g, 85%) as colourless crystals; mp 51–52 °C [hexanes; [α]D 19° + 58.7 (c. 1.06, acetone).

IR (Si): ν 2935, 2870, 1490, 1424, 1294, 1211, 1172, 1143 cm⁻¹; ¹H NMR (400.13 MHz, CDCl₃): δ 0.73 (s, 3H), 1.09–1.80 (m, 11H), 1.85–1.97 (m, 2H), 2.18–2.30 (m, 2H), 2.83–2.93 (m, 2H), 6.94 (d, J = 2.6 Hz, 1H), 6.99 (dd, J = 8.6, 2.6 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H); ¹³C NMR (100.61 MHz, CDCl₃): δ 17.4, 20.5, 25.2, 26.5, 27.6, 29.7, 38.5, 38.7, 40.4, 41.0, 44.2, 53.6, 118.0, 118.8 (q, JCF = 321.0 Hz, CF₃), 121.1, 127.2, 139.6, 141.3, 147.4. Anal. calcd for C₁₉H₂₃F₃O₃S: C, 58.75; H, 5.97. Found: C, 58.65; H, 6.03.

Methyl 1,3,5(10)-estratriene-3-carboxylate (15)

A solution of methyl 1,3,5(10)-estratriene-3-carboxylic acid (15) (8.57 g, 28.7 mmol) in dry Et₂O (40 mL) at room temperature was added, followed by H₂SO₄ (120 mL, 2 M). The organic phase was separated and the aqueous one extracted with Et₂O (2 × 120 mL). The combined organic layers were washed with brine (120 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography (CH₂Cl₂, Rf 0.32) to give 1,3,5(10)-estratrien-3-ylmethanol (16) (7.51 g, 97%) as colourless crystals; mp 99–101 °C (methanol); [α]D 19° + 84.7 (c. 1.99, acetone).

IR (Si): ν 3286, 2932, 2868, 1452, 1428, 1377, 1155, 1046, 1014, 1002 cm⁻¹; ¹H NMR (400.13 MHz, CDCl₃): δ 0.73 (s, 3H), 1.09–1.54 (m, 8H), 1.55 (br s, 1H), 1.60–1.81 (m, 3H), 1.84–1.91 (m, 2H), 2.20–2.34 (m, 2H), 2.80–2.95 (m, 2H), 4.61 (s, 2H), 7.08 (s, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H); ¹³C NMR (100.61 MHz, CDCl₃): δ 17.5, 20.5, 25.2, 26.6, 28.0, 29.6, 38.8, 39.0, 40.5, 41.0, 44.4, 53.6, 65.3, 124.3, 125.6, 127.7, 137.1, 138.0, 140.4. Anal. calcd for C₁₉H₂₃O₃: C, 84.39; H, 9.70. Found: C, 83.83; H, 9.80.

1,3,5(10)-Estratriene-3-carbaldehyde (17)

Pyridinium chlorochromate (10.91 g, 50.6 mmol) was portion wise added to a stirred mixture of 1,3,5(10)-estratrien-3-ylmethanol (16) (6.84 g, 25.3 mmol) and molecular sieves (25 g, 3 Å) in dry CH₂Cl₂ (125 mL) under cooling with cold water. The mixture was stirred for 1 h at room temperature. After addition of Et₂O (380 mL), the mixture was filtered through silica 60 (50 g). The reaction flask was washed with Et₂O (3 × 80 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/CH₂Cl₂, 2:1, Rf 0.17) to give aldehyde 17 (6.18 g, 91%) as colourless crystals; mp 95–97 °C (hexanes/CH₂Cl₂; [α]D 19° + 88.4 (c. 2.04, acetone).

IR (Si): ν 2946, 1691, 1606, 1568, 1453, 1378, 1281, 1226, 1153 cm⁻¹; ¹H NMR (400.13 MHz, CDCl₃): δ 0.73 (s, 3H), 1.00–1.82 (m, 11H), 1.85–2.00 (m, 2H), 2.24–2.37 (m, 2H), 2.88–2.98 (m, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 1.2 Hz, 1H), 7.63 (dd, J = 8.2, 1.2 Hz, 1H), 9.92 (s, 1H); ¹³C NMR (100.61 MHz, CDCl₃): δ 17.5, 20.5, 25.2, 26.4, 27.8, 29.5, 38.6, 38.7, 40.4, 41.0, 44.8, 51.9, 53.7, 125.4, 126.6, 127.2, 130.1, 137.0, 146.3, 167.4. Anal. calcd for C₁₉H₁₉O: C, 85.03; H, 8.01. Found: C, 85.12; H, 9.07.

1,3,5(10)-Estratriene-3-carbaldehyde tosylhydrazone (18)

A solution of 1,3,5(10)-estratriene-3-carbaldehyde (17) (6.10 g, 22.7 mmol) and tosyl hydrazide (4.95 g, 26.6 mmol, 1.17 equiv.) in dry CH₂Cl₂ (75 mL) was stirred for 1 h at room temperature and 1 h at 40 °C. The solution was concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/CH₂Cl₂, 2:1, Rf 0.29) to give hydrazone 18 (9.40 g, 95%) as crystals; mp 189–192 °C (toluene/EtOH); [α]D 19° + 46.9 (c. 1.92, CHCl₃).

IR (Si): ν 3196, 2925, 2867, 1451, 1364, 1321, 1167, 1052 cm⁻¹; ¹H NMR (400.13 MHz, CDCl₃): δ 0.71 (s, 3H), 1.07–1.80 (m, 11H), 1.82–1.95 (m, 2H), 2.18–2.31 (m, 2H), 2.38 (s, 3H), 2.79–2.87 (m, 2H), 7.24–7.34 (m, 5H), 7.68 (s, 1H), 7.74 (br s, 1H), 7.82–7.87 (m, 2H); ¹³C NMR (100.61 MHz, CDCl₃): δ 17.5, 20.5, 25.2, 26.4, 27.8, 29.5, 38.6, 38.7, 38.8, 40.4, 41.0, 41.1.
Preparation of 1,3,5(10)-estratrien-3-yl-diazomethane (19) from 1,3,5(10)-estratrien-3-carbaldehyde tosyl hydrazide (18): A mixture of tosyl hydrazide 18 (1.51 g, 3.46 mmol) and NaHMDS (0.8 g, 4.15 mmol, 95%, 1.2 equiv.) in dry THF (45 mL) was refluxed for 90 min. After cooling at room temperature the solvent was removed under reduced pressure. Water (60 mL) was added and the mixture was extracted with CH₂Cl₂ (3 × 40 mL). The combined organic layers were washed with water, dried (Na₂SO₄) and concentrated under reduced pressure. The residue was twice dissolved in toluene und concentrated each time under reduced pressure. The dark red residue was dried for 10 min (0.5 mbar/RT) and then immediately used for the next step.

2. Esterification of phosphonic acid: A solution of (R)-(−)-ethyl hydrogen (1-hydroxy-2-methylsulfanyl-1-phenylethyl)-phosphonate [[R]−(−)-10] (0.577 g, 2.1 mmol, prepared from the (R)-1-phenylethylammonium salt by general procedure A) in dry CH₂Cl₂ (20 mL) was dropwise added to a stirred solution of the above prepared crude steroidal diazomethane in dry CH₂Cl₂ (25 mL) within 15 min at room temperature. While the reaction mixture was stirred for 40 min at room temperature, the colour changed from deep red to orange. Excess diazomethane was destroyed by dropwise addition of AcOH (colour changed to yellow). The solvent was removed under reduced pressure. The residue was purified by flash chromatography (CH₂Cl₂/EtOAc, 10 : 1, Rf 0.31) to give phosphate 20 (0.741 g, 90%; ratio 1 : 1, by 1H NMR) as a colourless oil. The epimers were separated by HPLC (analytical HPLC: Nucleosil 50–4 column, 0.46 × 25 cm, 5% i-PrOH in hexanes, 1 mL × min⁻¹, t₀ = 10.7 and 11.4 min; preparative HPLC: Nucleosil 50–7 column, 6.3 × 28.8 cm, 2.5% i-PrOH in hexanes). The less polar epimer 20 had a de of 88% and the more polar 23 of 96%. Crystallisation increased the de of the former to >98% [from hexanes, crystals contained solvent; 20/hexanes, 3.13 : 1, by 1H NMR] and of the latter to also >98% [hexanes/i-PrOH]. Crystals of 23 were unsolvated and used for the determination of the X-ray structure.

20: Less polar epimer; for crystals from hexanes: mp 52–54 °C; [α]D²⁰ + 18.24 (c. 1.03, CHCl₃). Crystallisation from cyclohexane furnished crystals containing cyclohexane (20/cyclohexane, 2 : 1, by 1H NMR), mp 49–52 °C.

IR (Si); ν 3280, 2932, 2867, 1449, 1376, 1220, 1100, 1014, 985, 972 cm⁻¹. NMR spectra are given for cyclohexane-containing crystals. 1H NMR (400.27 MHz, CDCl₃): δ 0.72 (s, 3H), 1.06 (td, J = 7.0, 0.4 Hz, 3H), 1.09–1.80 (m, 11H), 1.41 (s, 6H, cyclohexane), 1.81 (s, 3H), 1.83–1.95 (m, 2H), 2.18–2.33 (m, 2H), 2.77–2.91 (m, 2H), 3.39 (AB part of ABP system, JAB = 14.0 Hz, J = 7.8, 7.4 Hz, 2H), 3.47 (d, J = 17.6 Hz, 1H), 3.67–3.79 (m, 1H), 3.82–3.93 (m, 1H), 5.03 (AB part of ABP system, JAB = 11.6 Hz, J = 7.8, 6.9 Hz, 2H), 7.02 (br. s, 1H), 7.09 (dd, J = 8.0, 1.5 Hz, 1H), 7.25–7.37 (m, 4H), 7.60–7.65 (m, 2H); 13C NMR (100.65 MHz, CDCl₃): δ 16.2 (d, J = 5.8 Hz, 17.1, 17.5, 20.6, 25.2, 26.6, 26.9 (cyclohexane), 28.0, 29.6, 38.8, 38.9, 40.5, 41.0, 43.8 (d, JPC = 6.5 Hz), 44.5, 53.7, 63.9 (d, J = 6.5 Hz), 68.6 (d, J = 7.5 Hz), 75.0 (d, J = 161.7 Hz), 125.3, 125.6, 126.4 (d, J = 4.2 Hz, 2C), 127.8 (d, J = 2.8 Hz), 128.2 (d, J = 2.7 Hz, 2C), 128.7, 133.3 (d, J = 6.7 Hz), 137.1, 138.9, 141.2. 13P NMR (162.03 MHz, CDCl₃): δ 21.37. Anal. calcd for C₃₀H₄₁O₄PS×0.5C₆H₁₂:C, 69.44; H, 8.30. Found: C, 69.06; H, 8.12.

23: More polar epimer; mp 108–112 °C (hexanes/i-PrOH); [α]D²⁰ + 31.7 (c. 0.99, CHCl₃). IR (Si): ν 3280, 2922, 2866, 1449, 1377, 1222, 1102, 1047, 1037, 999, 985 cm⁻¹. 1H NMR (400.13 MHz, CDCl₃): δ 0.72 (s, 3H), 1.07–1.81 (m, 11H), 1.25 (t, J = 7.0 Hz, 3H), 1.83 (s, 3H), 1.85–1.96 (m, 2H), 2.16–2.33 (m, 2H), 2.73–2.90 (m, 2H), 3.40 (AB part of ABP system, JAB = 14.1 Hz, J = 7.8, 7.5 Hz, 2H), 3.61 (d, J = 17.4 Hz, 1H), 4.05–4.18 (m, 2H), 4.71 (AB part of ABP system, JAB = 11.5 Hz, J = 7.5, 6.5 Hz, 2H), 6.88 (s, 1H), 6.96 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 7.9 Hz, 1H), 7.26–7.39 (m, 3H), 7.60–7.67 (m, 2H); 13C NMR (100.61 MHz, CDCl₃): δ 16.3 (d, J = 5.8 Hz), 17.1, 17.5, 20.5, 25.2, 26.5, 27.9, 29.6, 38.77, 38.83, 40.4, 41.0, 43.7 (d, J = 6.6 Hz), 44.4, 53.6, 63.5 (d, J = 7.6 Hz), 68.9 (d, J = 7.3 Hz), 75.0 (d, J = 161.3 Hz), 125.1, 125.5, 126.4 (d, J = 4.1 Hz, 2C), 127.8 (d, J = 2.8 Hz), 128.1 (d, J = 2.3 Hz, 2C), 128.5, 133.2 (d, JPC = 6.5 Hz), 136.9, 138.9, 141.0; 13P NMR (161.98 MHz, CDCl₃): δ 22.13. Anal. calcd for C₆₀H₄₁O₄PS×2 C: 68.16; H, 7.82. Found: C, 68.36; H, 7.77.

[1,3,5(10)-Estratrien-3-yl]methyl 1-phenylethenyl phosphate [22, prepared from 20] of solution of methyl fluorosulfate (0.32 g, 2.8 mmol, 0.22 mL, 2.0 equiv.) in dry CH₂Cl₂ (1.2 mL) was dropwise added to a stirred solution of α-hydroxyphosphonate 20 (0.741 g, 1.4 mmol) in dry CH₂Cl₂ (10 mL) at −35 °C. The mixture was stirred for 35 min at −35 °C and 2 h at room temperature. Then, the solvent was removed under reduced pressure. The residue was dried for 45 min and dissolved in dry DMSO (10 mL). Phosphazene base P₃-t-Bu⁻¹ (0.656 g, 2.8 mmol, 0.71 mL, 2.0 equiv) was added. After stirring for 30 min at room temperature, water (75 mL) was added and the mixture was twice extracted with Et₂O (75 mL and 50 mL). To improve phase separation, the aqueous layer was saturated with NaCl. The combined organic layers were washed with water (3 × 50 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 3 : 1; Rf 0.31) to give phosphate 22 (0.308 g, 46%) as a colourless oil; [α]D²⁰ + 46.8 (c. 2.01, ethanol).
(100.61 MHz, CDCl₃): δ 16.1 (d, J = 6.9 Hz), 17.5, 20.5, 25.2, 26.5, 27.9, 29.5, 38.79, 38.83, 40.5, 41.0, 44.4, 53.6, 64.6 (d, J = 6.1 Hz), 69.8 (d, J = 5.7 Hz), 97.3 (d, J = 3.6 Hz), 125.21 (2C), 125.23, 125.6, 128.3 (2C), 128.6, 129.0, 132.6 (d, J = 6.9 Hz), 134.3 (d, J = 6.9 H). Anal. calcd for C₂₉H₃₇O₄P: C, 72.48; H, 7.76. Found: C, 72.05; H, 7.71.

The α-hydroxyphosphonate 23 (0.741 g, 1.4 mmol) was converted to 25 (0.322 g, 48%) as colourless oil by the procedure as used for the preparation of 22; [α]D₂⁰ + 41.9 (c. 1.92, ethanol).

The IR spectrum and the ¹³C and ³¹P NMR spectra are identical to those of 22. The ¹H NMR spectrum is identical to that of 22 except for the resonances of the POCH₂ group (see Fig. 2): 5.507 (AB part of ABP system, J₉ = 11.6 Hz, J₊₋ = 7.9 Hz, 2H). Anal. calcd for C₂₉H₃₇O₄P: C, 72.48; H, 7.76. Found: C, 72.20; H, 7.66.

Conflicts of interest

There are no conflicts to declare.

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