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# 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 phosphates. Their oily nature interfered with a single crystal X-ray structure analysis to determine the stereochemistry at the phosphorus atom.

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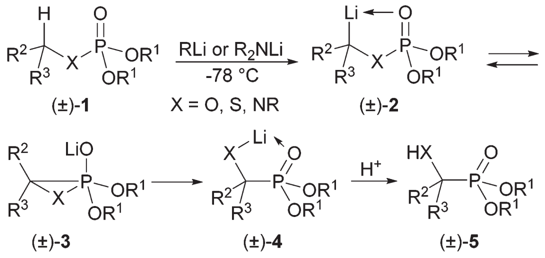
## Introduction

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-stabilised[1] 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 Corbel[2] is called phosphate–phosphonate or more specifically phosphate-α-hydroxyphosphonate rearrangement. This[3–5] and the versions for X = S[6,7] and N[8] have extensively been studied by Hammerschmidt's group. The reverse process with many examples[9–17] for X = O, the α-hydroxyphosphonate-phosphate rearrangement, also termed [1,2]-phospha-Brook rearrangement, has been found by Pudovik and Konovalova[17] 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 $R^2$ = alkyl and $R^3$ = H, the reverse process not. At least one of the substituents, $R^2$ or $R^3$, 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]



**Scheme 1** Phosphate–phosphonate rearrangements and reverse processes.

The phosphate–phosphonate rearrangement for X = O,[3,5] S[7] and N[8] and the reverse process for X = O[11,15,16] follow a retentive 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 diastereomeric α-hydroxyphosphonates $(R,S_\mathrm{P})$- and $(R,R_\mathrm{P})$-**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

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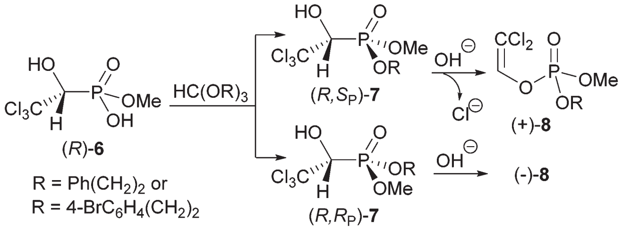


**Scheme 2** α-Hydroxyphosphonate-phosphate rearrangement of diastereomeric α-hydroxyphosphonates **7** to enantiomerically pure enol phosphates **8**.

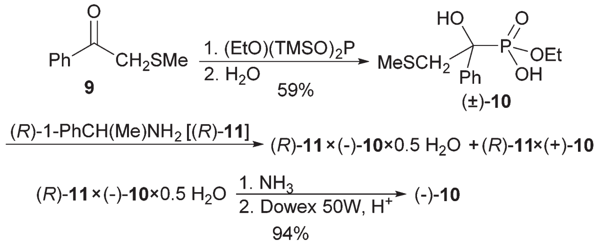
cleavage of the P–C bond eliminated a *β*-chloride, resulting in enantiomerically pure enol phosphates (+)- and (−)-**8**. As they were oils, their absolute configuration could not be determined by X-ray structure analysis and the stereochemistry at the phosphorus atom had to remain unanswered.

## Results and discussion

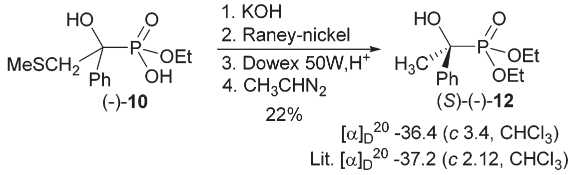
The highly enantioselective synthesis of acyclic phosphate triesters is difficult and challenging.[19,20] While Hall and Inch[19] built their syntheses on 5- and 6-membered cyclic phosphorus compounds derived from (−)-ephedrine and D-glucose, Nakayama and Thompson[20] applied (*S*)-proline derivatives. We reasoned that the α-hydroxyphosphonate-phosphate rearrangement of acyclic substrates with a stereogenic *P*-atom of known configuration would give chiral, nonracemic phosphate triester and alkenyl dialkyl ester. In order to assign the configuration to the *P*-chiral product, the stereochemistry of the rearrangement at the phosphorus atom has to be known. Here we start another approach to unravel it.

At first, an enantiomerically pure alkyl hydrogen α-hydroxyphosphonate was prepared and resolved (Scheme 3).

Ethyl bis(trimethylsilyl) phosphite[3] was added to ketone **9**[21] to give a protected α-hydroxyphosphonate as intermediate, that was hydrolysed to phosphonic acid monoethyl ester (±)-**10** upon aqueous workup and isolated in 59% yield. The phenyl ketone was selected, because the phenyl substituent with its anion-stabilising effect will ascertain that the α-hydroxyphosphonate-phosphate rearrangement at the end of the sequence will be feasible. The methylsulfanyl substituent can be methylated and give the good leaving group dimethyl sulfide. (*R*)-(+)-1-Phenylethylamine [(*R*)-**11**] was found to be a better resolving agent for phosphonic acid (±)-**10** than brucine. The crystals obtained from $Et_2O/CH_2Cl_2$ contained $Et_2O$ (by $^1H$ NMR, salt/$Et_2O$, 2.6 : 1.0) and had a de of already 86% (by $^1H$ NMR, the two methylsulfanyl groups of the two diastereomers resonate as two singlets at $\delta$ 1.77 and 1.79). Two crystallisations from $CHCl_3$ delivered crystals of hemihydrate (*R*)-**11** × (−)-**10** × $0.5H_2O$ of de > 98% in 56% yield. When this salt was dissolved in aqueous ammonia (25%) and extracted with $CH_2Cl_2$, the (*R*)-1-phenylethylamine was recovered. The free acid (−)-**10** was isolated from the aqueous phase by passage through Dowex 50 W, $H^+$ and removal of water under reduced pressure.



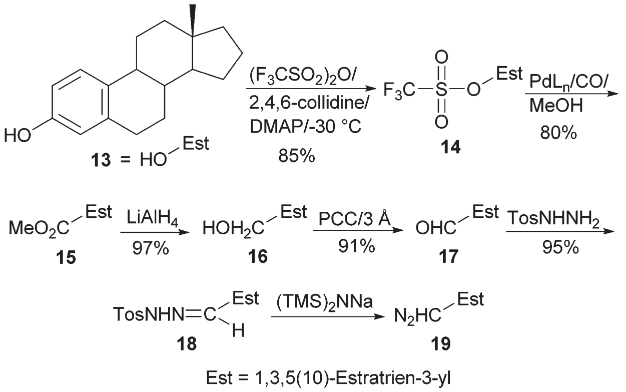
**Scheme 3** Preparation and resolution of ethyl hydrogen phosphonate (±)-**10**.



**Scheme 4** Determination of absolute configuration of (−)-**10**.

To determine the absolute configuration of (−)-**10**, it was transformed into the known α-hydroxyphosphonate (*S*)-(−)-**12** (Scheme 4). This was achieved by desulfurisation of the respective potassium salt with aged RANEY-nickel,[22] followed by passage through Dowex 50 W, $H^+$ to get the free acid. Esterification with diazoethane[23] furnished phosphonic acid diethyl ester (−)-**12** (in 22% overall yield), which has (*S*)-configuration based on the comparison of the specific optical rotation with the literature value.[3] When freshly prepared RANEY-nickel was used, the $CH_3S$ and OH groups were both reductively removed. This experiment proved that phosphonic acid (−)-**10**[3] has (*R*)-configuration. The change of the descriptor is caused by the change in the priority for the substituents according to the CIP rules [for (*S*)-(−)-**12**: P > Ph > $CH_3$; for (*R*)-(−)-**10**: P > $CH_2SCH_3$ > Ph.

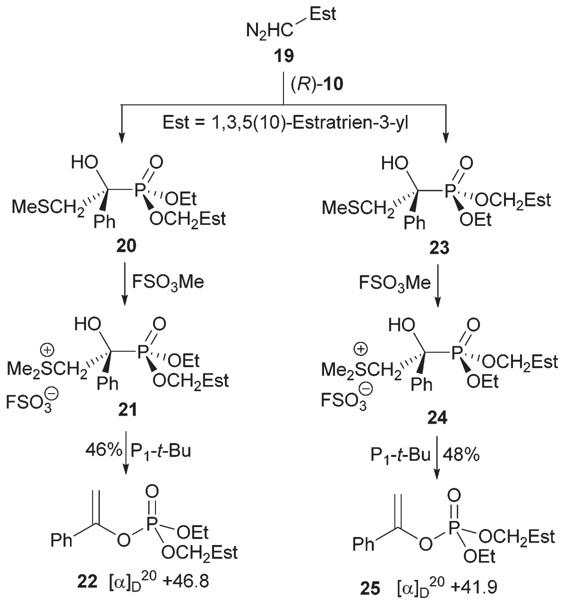
The next step was the esterification of phosphonic acid (*R*)-(−)-**10** with a diazoalkane under mild conditions, which should give (1) separable diastereomeric α-hydroxyphosphonates and (2) at least one crystalline phosphate upon α-hydoxyphosphonate-phosphate rearrangement. Previously, a variety of bromoaryldiazomethanes were tested, but they delivered inseparable mixtures of α-hydroxyphosphonates and oily phosphates unfortunately.[24] We reasoned that a steroid such as the fairly easily available 1,3,5(10)-estratrien-3-yldiazomethane (**19**) could fulfil 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 (**13**) prepared by a literature procedure[25] 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.[26] Alkoxycarbonylation[27] catalysed by $Pd(OAc)_2$-1,3-bis(diphenylphosphino)propane of the phenolic triflate with CO/MeOH/



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

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 molecular sieves,[28] which facilitated a smooth reaction and workup. Heating a mixture of aldehyde **17** with tosyl hydrazine in MeOH[29] at 40 °C, furnished in 95% yield tosyl hydrazone **17**, the starting material for the preparation of the substituted diazomethane. Refluxing a mixture of the hydrazone and sodium bis(trimethylsilyl)amide in dry THF for 90 min gave the substituted diazomethane **19**.[29,30]

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.



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

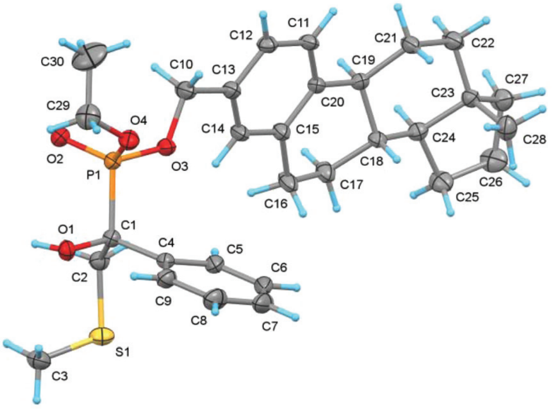
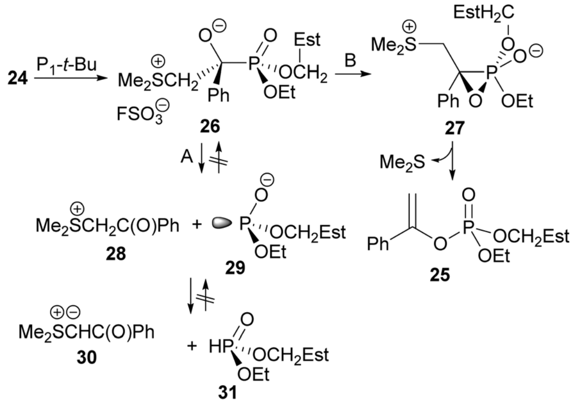


**Fig. 1** The molecular structure of **23** in solid state showing displacement ellipsoids at 20% probability.

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 phosphonic 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,[31] 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[32]) 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



**Scheme 7** Reaction pathways for alkoxide **26**.

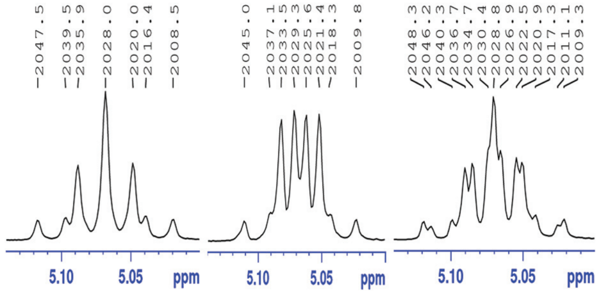


**Fig. 2** Est*CH*$_2$O segments of $^1$H NMR spectra of enol phosphates **22** (left) and **25** (middle) and of 1 : 1 mixture of **22** and **25** (right).

of the phosphite anion, which would lead to epimeric α-hydroxyphosphonates. Additionally, sulfur ylide **30** is not basic enough to deprotonate **31** to give **29**. The *H*-phosphonate **31** was detected in the crude reaction mixture by $^1$H NMR spectroscopy [P(O)H: $\delta_H$ = 6.84, d, $J_{HP}$ = 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.[33] We assume that **27** has a trigonal bipyramidal structure formed by an apical attack of the alkoxide anion on the electrophilc phosphorus atom from the less hindered side opposite to the EstCH$_2$O 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 $[\alpha]_D^{20}$ + 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 ($^1$H, $^{13}$C, $^{31}$P) except for the resonances of Est*CH*$_2$OP group (AB parts of ABP systems) in the $^1$H NMR spectrum (Fig. 2). Inspection of the three segments of the relevant $^1$H 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-hydroxyphosphonate-phosphate rearrangement of a noncyclic α-hydroxyphosphonates 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-hydroxyphosphonate-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

$^1$H, $^{13}$C (*J*-modulated) and $^{31}$P NMR spectra were recorded in CDCl$_3$ on Bruker Avance AV 400 ($^1$H: 400.13 MHz, $^{13}$C: 100.61 MHz, $^{31}$P: 161.97 MHz) and AV III 600 ($^1$H: 600.25 MHz, $^{13}$C: 150.93 MHz, $^{31}$P: 242.94 MHz) spectrometers at 25 °C. Chemical shifts ($\delta$) are reported in parts per million (ppm) relative to CHCl$_3$/CDCl$_3$ ($\delta_H$ 7.24, $\delta_C$ 77.00) and external $H_3PO_4$ (85%; $\delta_P$ 0.00) and coupling constants (*J*) in Hz. Data for $^1$H 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[34] 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), Ø 0.4 cm × 25 cm. Preparative HPLC was performed on a Rainin System (Dynamix Model SD-1 pump, Model UV-1 UV detector, 254 nm) using a Nucleosil 50-7 column, Ø 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 F$_{254}$. Spots were visualised by UV and/or dipping the plate into a solution of $(NH_4)_6Mo_7O_{24} \times 4H_2O$ (23.0 g) and $Ce(SO_4)_2 \times 4H_2O$ (1.0 g) in 10% aqueous $H_2SO_4$ (500 mL), followed by heating with a heat gun.

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

A solution of ethyl bis(trimethylsilyl) phosphite[3] (36.13 g, 142 mmol) and methylsulfanylmethyl 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 Et$_2$O for 2 h and the extract was discarded. The aqueous layer was acidified with diluted $H_2SO_4$ (10 mL conc. $H_2SO_4$ and 30 mL $H_2O$) and again continuously extracted with Et$_2$O 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 Et$_2$O (with cooling at −20 °C) to yield phosphonic acid (±)-**10** (23.0 g, 59%) as colourless crystals. The analytical sample was recrystallised from EtOAc/$Et_2O$; mp 95–98 °C.

IR (nujol): $\nu$ 3409, 3100–2000, 1332, 1162, 1035 $cm^{-1}$; $^1H$ NMR (400.13 MHz, $CDCl_3$): $\delta$ 1.16 (t, $J$ = 7.1 Hz, 3H), 1.80 (s, 3H), 3.33 (AB part of ABP system, $J_{AB}$ = 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 diastereomeric salts formed with the methylsulfanyl groups resonating at 1.77 and 1.79 ppm. The singlet at lower field corresponds to the $CH_3S$ of the salt of the dextrorotary acid. $^{13}C$ NMR (150.93 MHz, $CDCl_3$): $\delta$ 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; $^{31}P$ NMR (242.99 MHz, $CDCl_3$): $\delta$ 23.4. Anal. calcd for $C_{11}H_{17}O_4PS$: C, 47.82; H, 6.20; P, 11.21. Found: C, 47.95; H, 6.00; P, 11.58.

### 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 $CH_2Cl_2$ (30 mL) and (*R*)-(+)-1-phenylethylamine (7.27 g, 60 mmol, 7.68 mL) was dropwise added with cooling. After the addition of $Et_2O$ (300 mL) and seeding crystals obtained by slow evaporation of solvent from a $CHCl_3$ solution of this salt, the solution was left for 24 h at 4 °C. The formed crystals were collected, washed with $Et_2O/CH_2Cl_2$ (10/1) and dried at 0.5 mm/20 °C for 30 min to give 9.1 g of salt, de 86% (by $^1H$ NMR, salt/$Et_2O$, 2.6 : 1.0). The crystals were dissolved in hot $CHCl_3$ (136.5 mL). The flask with the solution was placed into a Dewar with warm water (50–55 °C). The Dewar topped with a Styropor plate was allowed to slowly cool in the fridge until the water had 4 °C. The colourless crystals not containing $Et_2O$ were collected, washed with cold $CHCl_3$ and dried; 8.03 g, de 98%. The crystals were recrystallised from $CHCl_3$ as before and furnished phosphonic acid salt (*R*)-**11** × (−)-**10** × $0.5H_2O$ (6.8 g, 56%) as colourless crystals; mp 120–123 °C; $[\alpha]_D^{20}$−7.0 (*c*. 1.53, $CH_2Cl_2$).

IR (nujol): $\nu$ = 3410, 3100–2000, 1620, 1550, 1300, 1190, 1170, 1160, 1050 $cm^{-1}$; $^1H$ NMR (600.25 MHz, $CDCl_3$): $\delta$ = 0.99 (t, $J$ = 6.9 Hz, 3H), 1.42 (d, $J$ = 6.6 Hz, 3H), 1.76 (s, 3H), 2.11 (br. s), 3.26 (AB part of ABP system, $J_{AB}$ = 13.7 Hz, $J$ = 3.1, 6.1 Hz, 2H), 3.50–3.70 (m, 2H), 3.98 (q, $J$ = 6.9 Hz, 1H), 7.17–7.37 (m, 4H), 7.57 (d, $J$ = 7.4 Hz, 1H), 8.32 (br. s); $^{13}C$ NMR (150.93 MHz, $CDCl_3$): $\delta$ 16.7 (d, $J$ = 6.4 Hz), 17.1, 20.9, 44.5, 50.7, 62.0 (d, $J$ = 6.6 Hz), 76.2 (d, $J$ = 149.4 Hz), 126.5 (d, $J$ = 3.1 Hz, 3C), 126.9 (2C), 127.6 (d, $J$ = 1.6 Hz, 2C), 128.4, 128.8 (2C), 139.4, 142.1; $^{31}P$ NMR (242.99 MHz, $CDCl_3$): $\delta$ 17.4. Anal. calcd for $C_{19}H_{28}NO_4PS$: C, 57.42; H, 7.10; N, 3.52; calcd for $C_{19}H_{28}NO_4PS \times 0.5H_2O$: C, 56.14; H, 7.19; N, 3.44. Found: C, 56.12; H, 6.80; N, 3.39.

### 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** × $0.5H_2O$ (1.105 g, 2.72 mmol), $CH_2Cl_2$ (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 $CH_2Cl_2$ (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*-$Pr_2O$/few drops of $CH_2Cl_2$); $[\alpha]_D^{18}$−16.9 (*c*. 1.45, dry EtOH). Anal. calcd for $C_{11}H_{17}O_4PS$: 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.

### Desulfurisation of potassium salt of (−)-ethyl hydrogen (1-hydroxy-2-methylsulfanyl-1-phenylethyl)phosphonate (−)-10

RANEY-nickel prepared by a literature procedure[22] 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:[23] To a solution of KOH (15 g) in water (45 mL) and $Et_2O$ (30 mL) cooled at −35 °C (bath temperature) *N*-nitroso-*N*-ethylurea[35] (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** × $0.5H_2O$ (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 $CH_2Cl_2$). 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 ($CH_2Cl_2$/EtOAc, 5 : 1, $R_f$ 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 by $^1H$ NMR: 19 : 81). The more polar product was flash chromatographed a second time ($CH_2Cl_2$/EtOAc, 2 : 1, $R_f$ 0.17) to give diethyl 1-hydroxy-1-phenylethylphosphonate (−)-**12** (0.11 g, 22%) as a colourless oil; $[\alpha]_D^{20}$−36.4 (*c*. 3.4, $CHCl_3$), after distillation (115–120 °C/0.005 mm) $[\alpha]_D^{20}$−35.67 (*c*. 1.8, $CHCl_3$) {lit.[3] $[\alpha]_D^{20}$−37.2 (*c*. 2.12, $CHCl_3$) for known 1-hydroxy-1-phenylethylphosphonate (*S*)-(−)-**12**}.

### 1,3,5(10)-Estratrien-3-yl trifluoromethanesulfonate (14)

1,3,5(10)-Estratrien-3-ol[25] (**13**) (11.7 g, 45.6 mmol, crystalline product, freed from EtOH by dissolution in toluene and concentration under reduced pressure) was dissolved in dry $CH_2Cl_2$ (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, 11.33 mL, 1.5 equiv.).[26] 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 $NaHCO_3$ (each with 100 mL). The organic phase was dried ($MgSO_4$), concentrated under reduced pressure. The residue was flash chromatographed (hexanes, $R_f$ 0.27) to give triflate **14** (15.1 g, 85%) as colourless crystals; mp 51–52 °C (hexanes); $[\alpha]_D^{20}$ + 58.7 (*c.* 1.06, acetone).

IR (Si): $\nu$ 2935, 2870, 1490, 1424, 1249, 1211, 1172, 1143 $cm^{-1}$; $^1H$ NMR (400.13 MHz, $CDCl_3$): $\delta$ 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); $^{13}C$ NMR (100.61 MHz, $CDCl_3$): $\delta$ 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, $J_{CF}$ = 321.0 Hz, $CF_3$), 121.1, 127.2, 139.6, 141.3, 147.4. Anal. calcd for $C_{19}H_{23}F_3O_3S$: C, 58.75; H, 5.97. Found: C, 58.65; H, 6.03.

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

This reaction was performed in a well vented hood (CO!). 1,3,5(10)-Estratrien-3-yl trifluoromethanesulfonate (**14**) (14.4 g, 37.1 mmol) were dissolved in a stirred mixture of dry methanol (74 mL) and dry DMSO (110 mL). Triethylamine (8.2 g, 81 mmol, 11.3 mL, 2.2 equiv.), $Pd(OAc)_2$ (0.499 g, 2.22 mmol, 0.06 equiv.) and 1,3-bis(diphenylphosphino)propane (0.914 g, 2.22 mmol, 0.06 equiv.) were added.[27] The apparatus was flushed with CO for 15 min and then the mixture was heated at 70 °C (oil bath temperature) under the CO atmosphere for 4 h. After cooling to room temperature water (380 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3 × 120 mL). The combined organic layers were washed with HCl (2 M), water and a saturated aqueous solution of $NaHCO_3$, dried ($Na_2SO_4$) and concentrated under reduced pressure. The residue was flash chromatographed (hexanes/$CH_2Cl_2$, 2 : 1, $R_f$ 0.24) to give methyl ester **15** (8.83 g, 80%) as colourless crystals; mp 92–94 °C (hexanes); $[\alpha]_D^{20}$ + 78.6 (*c.* 1.58, acetone).

IR (Si): $\nu$ 2948, 2868, 1723, 1435, 1291, 1263, 1193 $cm^{-1}$; $^1H$ NMR (400.13 MHz, $CDCl_3$): $\delta$ 0.73 (s, 3H), 1.08–1.82 (m, 11H), 1.84–1.91 (m, 2H), 2.23–2.36 (m, 2H), 2.85–2.95 (m, 2H), 3.87 (s, 3H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 1.6 Hz, 1H), 7.77 (dd, *J* = 8.2, 1.6 Hz, 1H); $^{13}C$ NMR (100.61 MHz, $CDCl_3$): $\delta$ 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 $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.28; H, 8.79.

### 1,3,5(10)-Estratrien-3-ylmethanol (16)

A solution of methyl 1,3,5(10)-estratriene-3-carboxylate (**15**) (8.57 g, 28.7 mmol) in dry $Et_2O$ (40 mL) was dropwise added to a stirred suspension of $LiAlH_4$ (0.82 g, 21.5 mmol, 1.5 equiv.) in dry $Et_2O$ (50 mL) at 0 °C. The mixture was refluxed for 2 h and cooled at 0 °C. Then water (12 mL, 0 °C) was dropwise added, followed by $H_2SO_4$ (120 mL, 2 M). The organic phase was separated and the aqueous one extracted with $Et_2O$ (2 × 120 mL). The combined organic layers were washed with brine (120 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography ($CH_2Cl_2$, $R_f$ 0.32) to give 1,3,5(10)-estratrien-3-ylmethanol (**16**) (7.51 g, 97%) as colourless crystals; mp 99–101 °C (methanol); $[\alpha]_D^{20}$ + 84.7 (*c.* 1.99, acetone).

IR (Si): $\nu$ 3286, 2932, 2868, 1452, 1428, 1377, 1155, 1046, 1014, 1002 $cm^{-1}$; $^1H$ NMR (400.13 MHz, $CDCl_3$): $\delta$ 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); $^{13}C$ NMR (100.61 MHz, $CDCl_3$): $\delta$ 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 $C_{19}H_{26}O$: 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) und molecular sieves (25 g, 3 Å)[28] in dry $CH_2Cl_2$ (125 mL) under cooling with cold water. The mixture was stirred for 1.5 h at room temperature. After addition of $Et_2O$ (380 mL), the mixture was filtered through silica 60 (50 g). The reaction flask was washed with $Et_2O$ (3 × 80 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/$CH_2Cl_2$, 2 : 1, $R_f$ 0.17) to give aldehyde **17** (6.18 g, 91%) as colourless crystals; mp 95–97 °C (hexanes/$CH_2Cl_2$); $[\alpha]_D^{20}$ + 88.4 (*c.* 2.04, acetone).

IR (Si): $\nu$ 2946, 1691, 1606, 1568, 1453, 1378, 1281, 1226, 1153 $cm^{-1}$; $^1H$ NMR (400.13 MHz, $CDCl_3$): $\delta$ 0.73 (s, 3H), 1.10–1.82 (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* = 8.0, 1.2 Hz, 1H), 9.92 (s, 1H); $^{13}C$ NMR (100.61 MHz, $CDCl_3$): $\delta$ 17.5, 20.5, 25.2, 26.4, 27.7, 29.4, 38.5, 38.7, 40.4, 40.9, 45.0, 53.7, 126.1, 127.0, 130.3, 134.0, 137.8, 148.3, 192.4. Anal. calcd for $C_{19}H_{24}O$: C, 85.03; H, 9.01. 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 methanol (75 mL) was stirred for 1 h at room temperature and 1 h at 40 °C.[29] The solution was concentrated under reduced pressure. The residue was purified by flash chromatography ($CH_2Cl_2$, $R_f$ 0.29) to yield hydrazone **18** (9.40 g, 95%) as crystals; mp 189–192 °C (toluene/EtOH); $[\alpha]_D^{20}$ + 46.9 (*c.* 1.92, $CHCl_3$).

IR (Si): $\nu$ 3196, 2925, 2867, 1451, 1364, 1321, 1167, 1052 $cm^{-1}$; $^1H$ NMR (400.13 MHz, $CDCl_3$): $\delta$ 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); $^{13}C$ NMR (100.61 MHz, $CDCl_3$): $\delta$ 17.5, 20.5, 21.5, 25.2, 26.4, 27.8, 29.5, 38.69, 38.74, 40.4, 41.0, 44.7, 53.6, 124.7, 125.7, 127.8, 127.9 (2C), 129.7 (2C), 130.3, 135.3, 137.3, 143.8, 144.1, 148.5. Anal. cald for $C_{26}H_{32}N_2O_2S$: C, 71.52; H, 7.39; N, 6.42. Found: C, 71.43; H, 7.29; N, 6.35.

### (1*R*,$S_\text{p}$)- and (1*R*,$R_\text{p}$)-(1′,3′,5′(10′)-estratrien-3′-ylmethyl) ethyl (1-hydroxy-2-methylsulfanyl-1-phenylethyl)phosphonate (20 and 23)

Preparation of 1,3,5(10)-estratrien-3-yl-diazomethane (**19**) from 1,3,5(10)-estratrien-3-carbaldehyde tosyl hydrazone (**18**): A mixture of tosyl hydrazone **18** (1.51 g, 3.46 mmol) and NaHMDS (0.80 g, 4.15 mmol, 95%, 1.2 equiv.) in dry THF (45 mL) was refluxed for 90 min[30] After cooling at room temperature the solvent was removed under reduced pressure. Water (60 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3 × 40 mL). The combined organic layers were washed with water, dried ($Na_2SO_4$) 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 $CH_2Cl_2$ (20 mL) was dropwise added to a stirred solution of the above prepared crude steroidal diazomethane in dry $CH_2Cl_2$ (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 ($CH_2Cl_2$/EtOAc, 10 : 1, $R_f$ 0.28) to give a mixture of epimers **20** and **23** (0.99 g, 90%; ratio 1 : 1, by $^1$H 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$^{-1}$, $t_R$ = 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 $^1$H 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; $[\alpha]_D^{20}$ + 18.24 (*c.* 1.03, $CHCl_3$). Crystallisation from cyclohexane furnished crystals containing cyclohexane (**20**/cyclohexane, 2 : 1, by $^1$H NMR), mp 49–52 °C.

IR (Si): $\nu$ 3280, 2932, 2867, 1449, 1376, 1220, 1100, 1014, 985, 972 cm$^{-1}$. NMR spectra are given for cyclohexane-containing crystals. $^1$H NMR (400.27 MHz, $CDCl_3$): $\delta$ 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, $J_{AB}$ = 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, $J_{AB}$ = 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); $^{13}$C NMR (100.65 MHz, $CDCl_3$): $\delta$ 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, $J_{PC}$ = 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. $^{31}$P NMR (162.03 MHz, $CDCl_3$): $\delta$ 21.37. Anal. calcd for $C_{30}H_{41}O_4PS\times0.5C_6H_{12}$:C, 69.44; H, 8.30. Found: C, 69.06; H, 8.12.

**23**: More polar epimer; mp 108–112 °C (hexanes/*i*-PrOH); $[\alpha]_D^{20}$ + 31.7 (*c.* 0.99, $CHCl_3$). IR (Si): $\nu$ 3280, 2922, 2866, 1449, 1377, 1222, 1102, 1047, 1037, 999, 985 cm$^{-1}$. $^1$H NMR (400.13 MHz, $CDCl_3$): $\delta$ 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, $J_{AB}$ = 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, $J_{AB}$ = 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); $^{13}$C NMR (100.61 MHz, $CDCl_3$): $\delta$ 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, $J_{PC}$ = 6.5 Hz), 136.9, 138.9, 141.0; $^{31}$P NMR (161.98 MHz, $CDCl_3$): $\delta$ 22.13. Anal. calcd for $C_{30}H_{41}O_4PS$: C, 68.16; H, 7.82. Found: C, 68.36; H, 7.77.

### [1′,3′,5′(10′)-Estratrien-3′-ylmethyl] ethyl 1-phenylethenyl phosphate [22, prepared from 20]

A solution of methyl fluorosulfate (0.32 g, 2.8 mmol, 0.22 mL, 2.0 equiv.) in dry $CH_2Cl_2$ (1.2 mL) was dropwise added to a stirred solution of α-hydroxyphosphonate **20** (0.741 g, 1.4 mmol) in dry $CH_2Cl_2$ (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 $P_1$-*t*-Bu[31] (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 $Et_2O$ (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 ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 3 : 1; $R_f$ 0.31) to give phosphate **22** (0.308 g, 46%) as a colourless oil; $[\alpha]_D^{20}$ + 46.8 (*c.* 2.01, ethanol).

IR (Si): $\nu$ 2933, 2868, 1635, 1449, 1377, 1270, 1158, 1103, 1014 cm$^{-1}$. $^1$H NMR (400.13 MHz, $CDCl_3$): $\delta$ 0.72 (s, 3H), 1.09–1.82 (m, 11H), 1.32 (td, *J* = 7.4, 0.8 Hz, 3H), 1.80–1.96 (m, 2H), 2.22–2.32 (m, 2H), 2.76–2.91 (m, 2H), 4.17 (quin, *J* = 7.4 Hz, 2H), 5.07 (AB part of ABP system, $J_{AB}$ = 11.5 Hz, *J* = 8.0, 7.9 Hz, 2H), 5.21 (≈ t, *J* = 2.6 Hz, 1H), 5.26 (≈ t, *J* = 2.5 Hz, 1H), 7.05 (br. s, 1H), 7.11 (br. d, *J* = 8.1 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.29–7.36 (m, 3H), 7.50–7.56 (m, 2H); $^{13}$C NMR

(100.61 MHz, $CDCl_3$): $\delta$ 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), 137.1, 141.3, 152.3 (d, $J$ = 7.9 Hz). Anal. cald for $C_{29}H_{37}O_4P$: C, 72.48; H, 7.76. Found: C, 72.05; H, 7.71.

### [1′,3′,5′(10′)-Estratrien-3′-ylmethyl] ethyl 1-phenylethenyl phosphate [25, prepared from 23]

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**; $[\alpha]_D^{20}$ + 41.9 (*c.* 1.92, ethanol).

The IR spectrum and the $^{13}C$ and $^{31}P$ NMR spectra are identical to those of **22**. The $^1H$ NMR spectrum is identical to that of **22** except for the resonances of the $POCH_2$ group (see Fig. 2): $\delta$ 5.07 (AB part of ABP system, $J_{AB}$ = 11.6 Hz, $J_{AP}$ = $J_{BP}$ = 7.9 Hz, 2H). Anal. calcd for $C_{29}H_{37}O_4P$: 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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## References

1 (*a*) P. Beak and D. B. Reitz, *Chem. Rev.*, 1978, **78**, 275; (*b*) M. C. Whisler, S. McNeil, V. Snieckus and P. Beak, *Angew. Chem., Int. Ed.*, 2004, **43**, 2206.

2 (*a*) G. Sturtz and B. Corbel, *C. R. Acad. Sci., Ser. C*, 1973, **276**, 1807; (*b*) G. Sturtz, J.-J. Yaouanc, F. Krausz and B. Labeeuw, *Synthesis*, 1980, 289.

3 F. Hammerschmidt and H. Völlenkle, *Liebigs Ann. Chem.*, 1986, 2053.

4 F. Benayoud, D. J. deMendonca, C. A. Digits, G. A. Moniz, T. C. Sanders and G. B. Hammond, *J. Org. Chem.*, 1996, **61**, 5159.

5 F. Hammerschmidt and S. Schmidt, *Eur. J. Org. Chem.*, 2000, 2239.

6 S. Masson, M. Saquet and P. Marchand, *Tetrahedron*, 1998, **54**, 1523.

7 V. Philippitsch and F. Hammerschmidt, *Org. Biomol. Chem.*, 2011, **9**, 5220.

8 (*a*) F. Hammerschmidt and M. Hanbauer, *J. Org. Chem.*, 2000, **65**, 6121; (*b*) E. Kuliszewska, M. Hanbauer and F. Hammerschmidt, *Chem. – Eur. J.*, 2008, **14**, 8603.

9 (*a*) W. F. Barthel, B. H. Alexander, P. A. Giang and S. A. Hall, *J. Am. Chem. Soc.*, 1955, **77**, 2424; (*b*) W. Lorenz, A. Henglein and G. Schrader, *J. Am. Chem. Soc.*, 1955, **77**, 2554; (*c*) M. S. Kharasch and I. S. Bengelsdorf, *J. Org. Chem.*, 1955, **20**, 1356; (*d*) I. S. Bengelsdorf, *J. Org. Chem.*, 1956, **21**, 475; (*e*) G. W. Fischer and P. Scheider, *J. Prakt. Chem.*, 1977, **319**, 399.

10 (*a*) M.-J. Brienne and M. J. Jacques, *C. R. Acad. Sci., Ser. C*, 1975, **280**, 291; (*b*) M. J. Brienne, J. Jacques, M. C. Brianso and E. Surcouf, *Nouv. J. Chim.*, 1978, **2**, 19.

11 K. Pallitsch, A. Roller and F. Hammerschmidt, *Chem. – Eur. J.*, 2015, **21**, 10200.

12 F. Hammerschmidt and E. Zbiral, *Monatsh. Chem.*, 1980, **111**, 1015.

13 A. E. Wroblewski and W. Karolczak, *Pol. J. Chem.*, 1999, **73**, 1191.

14 A selection: (*a*) L. A. R. Hall, C. W. Stephens and J. J. Drydale, *J. Am. Chem. Soc.*, 1957, **79**, 1768; (*b*) H. Timmler and J. Kurz, *Chem. Ber.*, 1971, **104**, 3740; (*c*) F. Hammerschmidt, E. Schneyder and E. Zbiral, *Chem. Ber.*, 1980, **113**, 3891; (*d*) M. Kuroboshi, T. Ishihara and T. Ando, *J. Fluorine Chem.*, 1988, **39**, 293; (*e*) C. Meier, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1704; (*f*) C. Meier, L. W. Halbel, J. Balzarini and E. De Clercq, *Liebigs Ann. Chem.*, 1995, 2195; (*g*) R. Gancarz, I. Gancarz and A. Deron, *Phosphorus, Sulfur Silicon*, 2000, **161**, 61; (*h*) K. Pachamuthu and R. R. Schmidt, *Chem. Commun.*, 2004, 1078; (*i*) C. C. Bausch and J. S. Johnson, *Adv. Synth. Catal.*, 2005, **347**, 1207; (*j*) A. S. Demir, Ö. Reis, A. Òª. İğdir, İ. Esiringü and S. Eymur, *J. Org. Chem.*, 2005, **70**, 10584; (*k*) L. E. Kaim, L. Gaultier, L. Grimaud and A. D. Santos, *Synlett*, 2005, 2335; (*l*) A. S. Demir, B. Reis, Ö. Reis, S. Eymür, M. Göllü, S. Tural and G. Saglam, *J. Org. Chem.*, 2007, **72**, 7439; (*m*) R. Ruel, J.-P. Bouvier and R. N. Young, *J. Org. Chem.*, 1995, **60**, 5209; (*n*) D. Coffinier, L. E. Kaim and L. Grimaud, *Synlett*, 2008, 1133; (*o*) M. Hayashi and S. Nakamura, *Angew. Chem., Int. Ed.*, 2011, **50**, 2249; (*p*) M. T. Corbett, D. Uraguchi, T. Ooi and J. S. Johnson, *Angew. Chem., Int. Ed.*, 2012, **51**, 4685; (*q*) A. Kondoh and M. Terada, *Org. Lett.*, 2013, **15**, 4568; (*r*) A. Kondoh, T. Aoki and M. Terada, *Org. Lett.*, 2014, **16**, 3528; (*s*) A. Kondoh and M. Terada, *Org. Chem. Front.*, 2015, **2**, 801; (*t*) A. Kondoh, T. Aoki and M. Terada, *Chem. – Eur. J.*, 2015, **21**, 12577; (*u*) M. A. Horwitz, N. Tanaka, T. Yokosaka, D. Uraguchi, J. S. Johnson and T. Ooi, *J. Chem. Sci.*, 2015, **6**, 6086; (*v*) A. Kondo, A. Takai and M. Terada, *Synlett*, 2016, 1848; (*w*) H. Yoneyama, K. Uemura, Y. Usami and S. Hurusawa, *Tetrahedron*, 2017, **73**, 6109; (*x*) for the rearrangement of a β-oxophosphonate to a phosphate see: M. Anitha, G. Gangadhararao and K. C. Kumara Swamy, *Org. Biomol. Chem.*, 2016, **14**, 3591.

15 F. Hammerschmidt, *Monatsh. Chem.*, 1993, **124**, 1063.

16 S. Jankowski, J. Marczak, A. Olczak and M. L. Główka, *Tetrahedron Lett.*, 2006, **47**, 3341.

17 (*a*) A. N. Pudovik and I. V. Konovalova, *Zh. Obshch. Khim.*, 1962, **32**, 467; (*b*) A. N. Pudovik and M. G. Zimin, *Pure Appl. Chem.*, 1980, **52**, 989.

18 (*a*) C. M. Rojas, in *From Name Reactions for Homologations-2*, ed. J. J. Li, John Wiley & Sons, Inc., Hoboken, New Jersey, 2009, Pt. 2, p. 406; (*b*) A. G. Brook, *Acc. Chem. Res.*, 1974, **7**, 77.

19 C. R. Hall and T. D. Inch, *Tetrahedron*, 1980, **36**, 2059.

20 K. Nakayama and W. J. Thompson, *J. Am. Chem. Soc.*, 1990, **112**, 6936.

21 V. Prelog, V. Hahn, H. Brauchl and H. C. Beyerman, *Helv. Chim. Acta*, 1944, **47**, 1209.

22 L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, John Wiley and Sons, Inc., 1967, p. 729.

23 (*a*) H. G. O. Becker, *et al.*, *Organikum (Organisch-chemisches Grundpraktikum), 21. Auflage*, Wiley-VCH, Weinheim, New York, Chichester, Brisbane, Singapore, Toronto, 2001, p. 633; (*b*) B. Eistert, M. Regitz, G. Heck and H. Schwall, *Methoden der Organischen Chemie (Houben-Weyl, Hsg. E. Müller), 4. Auflage, Band X/4*, Georg Thieme Verlag, Stuttgart, 1968, p. 539.

24 F. Hammerschmidt, unpublished results.

25 Huang-Minlon, *J. Am. Chem. Soc.*, 1949, **71**, 3301.

26 P. J. Stang, M. Hanack and L. R. Subramanian, *Synthesis*, 1982, 85.

27 R. E. Dolle, S. J. Schmidt and L. I. Kruse, *J. Chem. Soc., Chem. Commun.*, 1987, 904.

28 J. Herscovici, M. J. Egron and K. Antonakis, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1967.

29 X. Creary, *J. Org. Synth., Coll.*, 1990, **7**, 438.

30 D. G. Farnum, *J. Org. Chem.*, 1963, **28**, 870.

31 R. Schwesinger, C. Hasenfratz, H. Schlemper, L. Walz, E.-M. Peters, K. Peters and H. G. von Schnering, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1361.

32 (*a*) V. S. Abramov, *Zh. Obshch. Khim*, 1952, **22**, 647; (*b*) A. N. Pudovik and I. V. Konovalova, *Synthesis*, 1979, 81.

33 (*a*) G.-V. Roeschenthaler, *Organophosphorus Chem.*, 2008, **37**, 247; (*b*) C. D. Hall, *Organophosphorus Chem.*, 1986, **16**, 51; (*c*) O. I. Kolodiazhnyi and A. Kolodiazhna, *Tetrahedron: Asymmetry*, 2017, **28**, 1651.

34 W. Mikenda, *Vib. Spectrosc.*, 1992, **3**, 327–334.

35 (*a*) H. G. O. Becker *et al.*, *Organikum (Organisch-chemisches Grundpraktikum), 21. Auflage*, Wiley-VCH, Weinheim, New York, Chichester, Brisbane, Singapore, Toronto, 2001, p. 627.