Diastereo- and Enantioselective Synthesis of Bicyclic α-Methylene-δ-valerolactones by Asymmetric Michael Reaction

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Received 4 May 2004

Abstract: A synthesis of optically active α-methylene-δ-valerolactones **7** and **13** with 97% ee was achieved by employing a highly stereoselective Michael reaction between chiral imines **2**, **9** and the acrylate **3**. Reduction of the carbonyl group of the resulting adducts **4** and **10** with KBH_4 followed by lactonization and HWE reaction with formaldehyde yielded the lactones **7** and **13** as mixtures of diastereoisomers. Diastereoselectivity in the reduction of chiral 5-oxoalkanoic acids **4** and **10** was improved by combination of metal salt and hydride reducing agent.

Key words: asymmetric synthesis, Michael reaction, 5-oxoalkanoic acids, α-methylene-δ-valerolactones

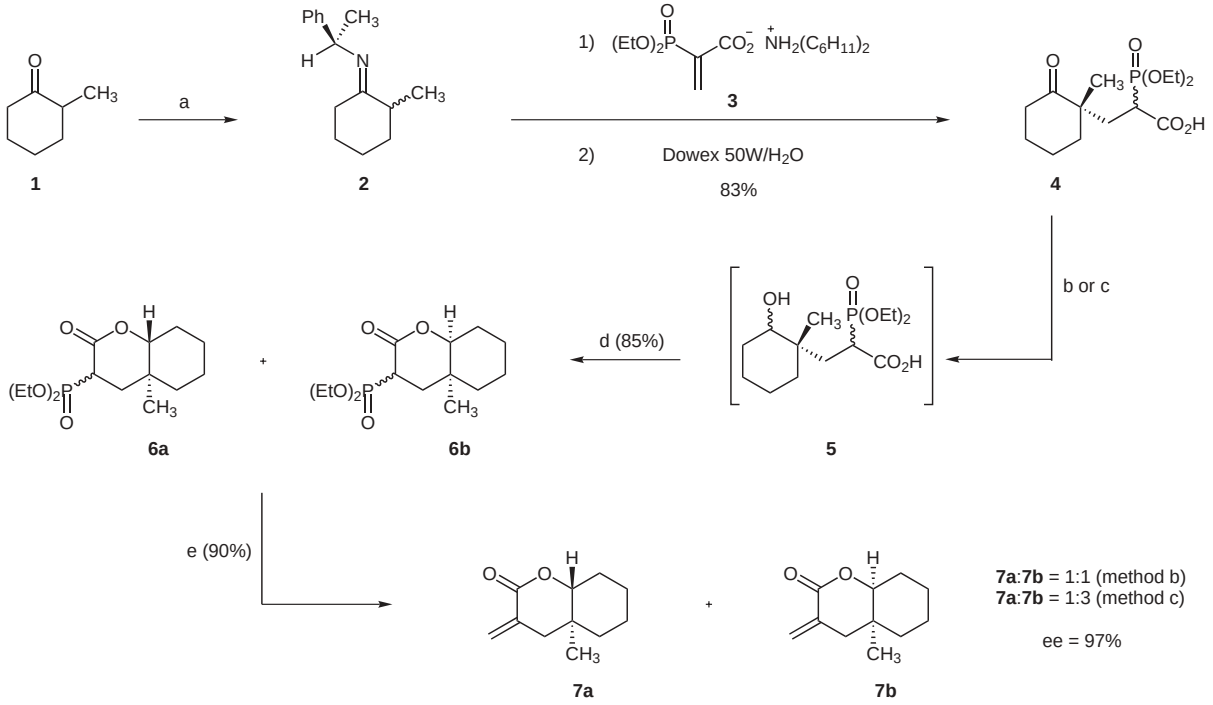
Over the years a number of biologically active natural products containing α-methylene-δ-valerolactone unit such as vernolepin,[1] vernomenin,[1] pentalenolactone E,[2] teucriumlactone,[3] artemisitene,[4] crassin,[5] and crassin acetate[5] have been isolated and characterized. On the other hand, the application of enantiomerically pure α-methylene-δ-valerolactones as chiral building blocks have been restricted by the limited availability of their syntheses. Some use has been made of the methylenation of α-unsubstituted[6] and α-methyl-δ-valerolactones.[4,7] Another strategy reported in the literature is based on a sequential oxidation and methylenation of sugars starting materials.[8] To the best of our knowledge, asymmetric synthesis of enantioenriched α-methylene-δ-valerolactones has not been described yet.

In 1998, we reported the synthesis of dicyclohexylammonium 2-(diethoxyphosphoryl) acrylate (**3**) and demonstrated that it undergoes Michael reaction with 1,3-dicarbonyl and monocarbonyl compounds without participation of any external catalyst.[9] Since then, this type of self-catalytic conjugate addition has been developed as an efficient method for the synthesis of various 2-(diethoxyphosphoryl)alkanoic acids.[10] We have recently demonstrated that 2-(dietoxyphosphoryl)-5-oxoalkanoic acids can be easily transformed into the corresponding α-methylene-δ-valerolactones through the sequence of standard reactions involving reduction of the carbonyl group, lactonization of the resulting 5-hydroxyalkanoic acids and finally Horner–Wadsworth–Emmons (HWE) olefination of the obtained α-phosphono-δ-valerolactones with formaldehyde.[11] Based on this methodology we now report on the synthesis of highly enantioenriched α-methylene-δ-valerolactones.

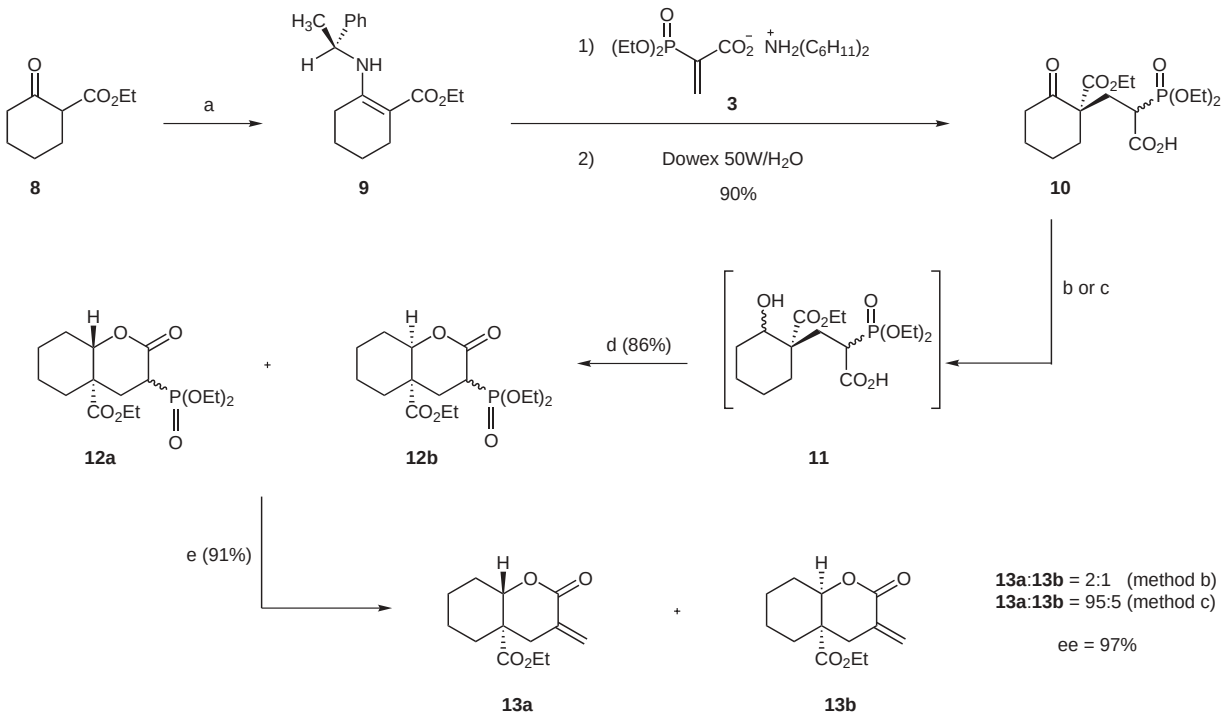
The synthetic strategy depicted on Scheme 1 and Scheme 2 relies on a variant of the asymmetric Michael reaction pioneered by Pfau and d'Angelo.[12] It is widely recognized that imines derived from 2-substituted cycloalkanones and enantiomerically pure 1-phenyl-ethylamines undergo Michael reactions with excellent levels of diastereoselectivity. The use of acrylates as the acceptors leads to highly enantioenriched 3-(2-oxocycloalkyl) propanoates. Despite the synthetic significance of these 5-oxoesters their application for asymmetric synthesis of δ-valerolactones is relatively undeveloped.[13] We reasoned that the use of acrylate **3** as the acceptor holds considerable potential for enantio- and diastereoselective synthesis of α-methylene-δ-valerolactones.

As model substrates for our studies we selected the readily available (α*R*)-imine **2** and (*S*)-β-enaminoester **9**. These compounds were prepared by condensation of 2-methylcyclohexanone (**1**) with (*R*)-1-phenylethylamine (97% ee) and 2-ethoxycarbonylcyclohexanone (**8**) with (*S*)-1-phenylethylamine (97% ee), respectively, according to the literature procedures.[12a,14] Preliminary studies were focused on the diastereo- and enantioselective synthesis of 2-(diethoxy-phosphoryl)-5-oxoalkanoic acids **4** and **10**. We found that the addition of (α*R*)-imine **2** to acrylate **3** proceeded effectively in benzene at room temperature and it was completed within two days. Acidic hydrolysis of the crude adduct afforded exclusively the acid **4** in 83% yield as a mixture of diastereoisomers in a 1:1 ratio. The same procedure was next employed in the addition of (*S*)-enaminoester **9** to acrylate **3**. It appeared that this reaction was also completely regioselective giving after acidic work-up a 1:1 mixture of the diastereoisomeric acids **10** in 93% yield. All attempts to separate particular diastereoisomers by column chromatography were in both cases unsuccessful. One can assume that diastereoisomeric products **4** and **10** are mixtures of epimers, which possess the same absolute stereochemistry at the quaternary carbon stereocenter and differ in configuration at the stereogenic center bearing diethoxyphosphoryl and carboxylic acid groups. Given the acidity of the hydrogen at this center it is likely that diastereoisomeric products **4** and **10** undergo rapid epimerization. In this context it is worth to note that a few

SYNLETT 2004, No. 11, pp 1995–1999
Advanced online publication: 06.08.2004
DOI: 10.1055/s-2004-830877; Art ID: G12804ST



Scheme 1 *Reagents and conditions:* a. (*R*)-1-Phenylethylamine, *p*TSA (cat.), toluene, reflux, 12 h; b. EtOH, KOH (1 equiv), KBH_4 (1 equiv), r.t., 24 h; c. MeOH, $BaCl_2 \cdot 2H_2O$ (1 equiv), KBH_4 (1 equiv), –70 °C, 1 h, r.t., 24 h; d. *p*TSA (cat.), benzene, reflux, 4 h; e. *t*-BuOK (1.1 equiv), $(HCHO)_n$ (5 equiv), Et_2O, r.t., 1 h.



Scheme 2 *Reagents and conditions:* a. (*S*)-1-Phenylethylamine, *p*TSA (cat.), toluene, reflux, 8 h; b. EtOH, KOH (1 equiv), KBH_4 (1 equiv), r.t., 24 h; c. MeOH, $CeCl_3 \cdot 7H_2O$ (1 equiv), KBH_4 (1 equiv), –70 °C, 1 h, r.t., 24 h; d. *p*TSA (cat.), benzene, reflux, 4 h; e. *t*-BuOK (1.1 equiv), $(HCHO)_n$ (5 equiv), Et_2O, r.t., 1 h.

precedents of such isomerization involving different α-phosphonoalkanoic acids derivatives are known.[15]

Transformation of the acids **4** and **10** into the corresponding α-methylene-δ-valerolactones enabled to determine enantiomeric excesses at the quaternary stereogenic centers. The phosphonolactones **6** and **12** were obtained from the oxoacids **4** and **10**, respectively, by using the previously reported protocol.[11] Reduction of the acids **4** and **10** with KBH_4 followed by lactonization of the obtained hydroxyacids **5** and **11** provided the phosphonolactones **6** and **12,** each as a mixture of diastereoisomers. At this stage, we were not able to establish diastereoselectivity of the reduction. Finally, the HWE reaction of phosphonolactones **6** and **12** with an excess of paraformaldehyde performed in diethyl ether in the presence of potassium *t*-butoxide afforded the corresponding α-methylenelactones **7a**,**b** and **13a**,**b** in high yields. We found that this procedure gave better results in terms of yield and purity of the products than the previously reported.[11] The lactones **7a**,**b** and **13a**,**b** were formed as mixtures of *trans*- and *cis*-diastereoisomers in a ratio 1:1 and 2:1, respectively. These ratios represent roughly the degree of diastereoselection that one can attain in the reduction of the oxoacids **4** and **10**. Improvement of these stereoselectivities was attained as the advantage of the reductions, which were performed in the presence of metal salts.[16] Model studies revealed that the treatment of the oxoacid **4** with KBH_4 and barium chloride ($BaCl_2 \cdot 2H_2O$, 1 equiv) followed by the sequence of standard reactions afforded the lactone **7** as mixture of *trans*- (**7a**) and *cis*-isomers (**7b**) in a ratio 1:3. Similarly, the reduction of oxoacid **10** with KBH_4 performed in the presence of cerium chloride ($CeCl_3 \cdot 7H_2O$, 1 equiv) led to the formation of the lactone **13** as a mixture *trans*- (**13a**) and *cis*-isomers (**13b**) in a ratio 95:5. The mixtures of diastereoisomeric lactones **7a**,**b** and **13a**,**b** were separated by column chromatography. Pure diastereoisomers **7b** and **13a** were isolated as crystalline solids.[17] Gas chromatography analysis in chiral stationary phase showed that the corresponding lactones **7a**,**b** and **13a**,**b** were formed with ee of 97%.[18] Additionally, ^1H NMR shifts experiments using (*R*)-(–)-9-(anthryl)-2,2,2-trifluoroethanol as the chiral solvating agent[19] indicated an ee of ≥95%. A slight divergence of the found ee values is in line with accuracy of the latter measurements.

The optical purity of the acid **4** was further enhanced by a single recrystallization of its dicyclohexylammonium salt **14** from ethyl acetate[20] (Scheme 3). The salt was converted by standard means into the lactones **7a** and **7b** with an ee better then 99%. Assignment of the absolute configuration to the acids **4**, **10**, and the lactones **7a**,**b** and **13a**,**b** was based on X-ray crystallographic analysis. The X-ray analysis conducted on the salt **14**[21] (Figure 1) unequivocally confirmed that there are two independent molecules of epimers in the asymmetric unit of the crystal and both of them have *S* absolute configuration at quaternary stereogenic centers. This result indicates that *trans*- and *cis*-lactones **7a**,**b** must be 4a(*S*),8a(*R*)- and 4a(*S*),8a(*S*)-isomers, respectively. The absolute configuration of the *cis*-lactone **7b** was confirmed by X-ray analysis.[22] An attempt to determine the absolute configuration of *trans*-lactone **13a** failed due to internal disorder of its ethoxycarbonyl substituent[23] (Figure 2). One should note that absolute configuration induced at the quaternary stereocenter in the adduct **4** is in agreement with the transition state model proposed for this type Michael additions.[24] According to this model absolute configuration at the quaternary stereocenter in the adduct **10** was assigned to be *S*. As a consequence the absolute configuration of the *trans*-lactone **13a** must be 4a(*S*),8a(*S*) and therefore that of *cis*-**13b** which differs for the configuration around C-8a is 4a(*S*),8a(*R*).

In summary, the asymmetric Michael addition of chiral imines to the acrylate **3** opens a new, simple and efficient entry to essentially enantiomerically pure bicyclic α-methylene-δ-valerolactones. Since the used chiral auxiliary is commercially available in both optically pure forms and a variety of α-substituted cycloalkanones can be used it is possible to synthesize both enantiomers of a range of α-methylene-δ-valerolactones.

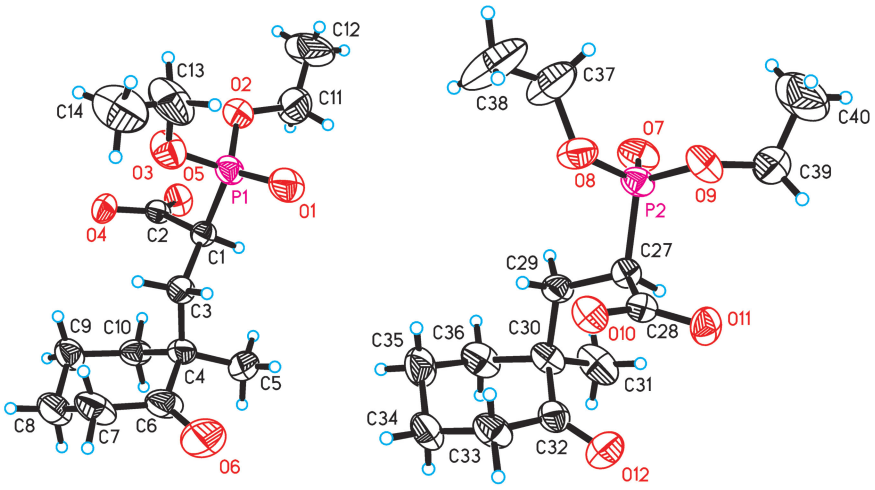
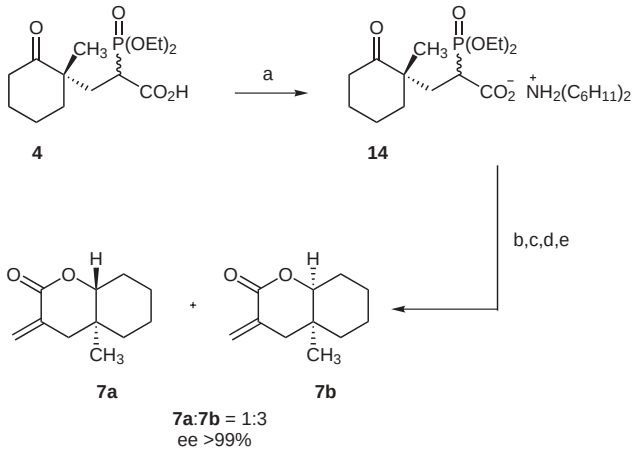


Figure 1 Both epimers of the salt **14** which are present in the asymmetric unit of the crystal. Dicyclohexylammonium cations have been omitted for clarity. Displacement ellipsoids are drawn at the 50% probability level.



Scheme 3 *Reagents and conditions:* a. $(C_6H_{11})_2NH$ (1 equiv), crystallization from EtOAc; b. Dowex 50 W, H_2O; c. MeOH, $BaCl_2 \cdot 2H_2O$ (1 equiv), KBH_4 (1 equiv), –70 °C, 1 h, r.t., 24 h; d. *p*TSA (cat.), benzene, reflux, 4 h; e. *t*-BuOK (1.1 equiv), $(HCHO)_n$ (5 equiv), Et_2O, r.t., 1 h.

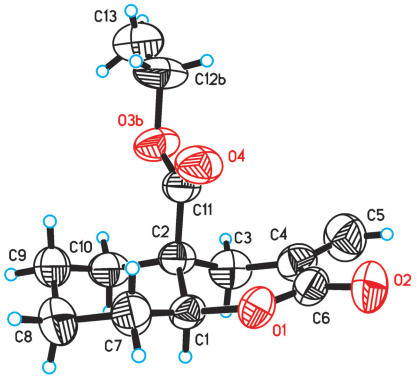


Figure 2 The crystal structure of lactone **13a**. The exocyclic O3 and C12 atoms are disordered. Each of both atoms was refined in two partially occupied positions. The picture shows sites for which the occupation factor was 0.62(1). For clarity, the less occupied positions are not shown. Displacement ellipsoids are drawn at the 50% probability level.

Acknowledgment

This work has been supported by the Polish State Committee for Scientific Research (KBN, Project No T09B 054 24) and Institute of General and Ecological Chemistry (WMW).

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(17) Analytical data for **7a**: colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (3 H, s, C*H*$_3$), 1.07–1.31 (2 H, m, C*H*$_2$), 1.36–1.61 (4 H, m, 2 × C*H*$_2$), 1.75–1.86 (2 H, m, C*H*$_2$), 2.28 (1 H, dt, ^4J = 2.5 Hz, ^2J = 14.0 Hz, C*H*), 2.36 (1 H, dt, ^4J = 1.5 Hz, ^2J = 14.0 Hz, C*H*), 3.98 (1 H, dd, ^3J = 5.0 Hz, ^3J = 16.5 Hz, C*H*O), 5.49 (1 H, dt, $^4J = {}^2J$ = 1.5 Hz, ^4J = 2.5 Hz, C*H*), 6.42 (1 H, dt, $^4J = {}^2J$ = 1.5 Hz, ^4J = 2.5 Hz, C*H*). ^{13}C NMR (62 MH z, $CDCl_3$): δ = 15.3 (*C*H$_2$), 20.8 (*C*H$_2$), 24.2 (*C*H$_3$), 27.1 (*C*H$_2$), 34.0 (*C*), 37.5 (*C*H$_2$), 44.2 (*C*H$_2$), 84.2 (*C*HO), 129.3 (*C*H$_2$), 133.8 (*C*), 165.9 (*C*OO).
Compound **7b**: white solid; mp 71–73 °C; $[\alpha]_D$ –18.00 (*c* 0.5, MeOH). IR (KBr): 3079, 1748, 1625, 1234 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.07 (3 H, s, C*H*$_3$), 1.15–1.30 (2 H, m, C*H*$_2$), 1.38–1.67 (4 H, m, 2 × C*H*$_2$), 1.70–1.90 (m, 2 H, C*H*$_2$), 2.33 (1 H, dt, ^4J = 1.5 Hz, ^2J = 16.0 Hz, C*H*), 2.58 (1 H, dt, ^4J = 2.0 Hz, ^2J = 16.0 Hz, C*H*), 4.20 (1 H, dd, ^3J = 3.0 Hz, ^3J = 6.0 Hz, C*H*O), 5.53 (1 H, dt, $^4J = {}^2J$ = 1.5 Hz, ^4J = 2.0 Hz, C*H*), 6.45 (1 H, dt, $^4J = {}^2J$ = 1.5 Hz, ^4J = 2.0 Hz, C*H*). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 20.7 (*C*H$_2$), 20.8 (*C*H$_2$), 24.6 (*C*H$_3$), 28.1 (*C*H$_2$), 32.3 (*C*H$_2$), 32.5 (*C*), 39.9

(CH_2), 84.4 (*C*HO), 128.6 (CH_2), 133.0 (*C*), 165.6 (*C*OO). Analytical data for racemic **13a** and **13b** have been previously reported (ref.[11]). Compound **13a** $[\alpha]_D$ –99.09 (*c* 1.0, MeOH). Compound **13b** $[\alpha]_D$ –6.00 (*c* 1.20, MeOH).

(18) The ee values were determined by GC analysis by comparison with racemates using a Lipodex E (50m × 0.25mm i.d.) column for **7a**,**b** and a Gamma-dex (30m × 0.25mm i.d.) column for **13a**,**b** after purification by column chromatography.

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(20) Analytical data for **14**: white solid, mp 149–151 °C. IR (KBr): 2965, 1721, 1633, 1242 cm^{-1}. ^{31}P NMR (101 MHz, $CDCl_3$): δ = 29.1, 29.00. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.06 (3 H, s, CH_3), 1.02–1.27 (6 H, m, 3 × CH_2), 1.22 (3 H, t, ^3J = 6.5 Hz, CH_3CH$_2$OP), 1.23 (3 H, t, ^3J = 6.5 Hz, CH_3CH$_2$OP), 1.40–1.65 (8 H, m, 4 × CH_2), 1.70–2.10 (12 H, m, 6 × CH_2), 2.15–2.40 (2 H, m, CH_2), 2.45–2.62 (2 H, m, CH_2), 2.61 (1 H, ddd, ^3J = 3.7 Hz, ^3J = 6.9 Hz, $^2J_{HP}$ = 25.7 Hz, C*H*P, diaA), 2.64 (1 H, ddd, ^3J = 1.0 Hz, ^3J = 10.3 Hz, $^2J_{HP}$ = 25.7 Hz, C*H*P, diaB), 2.91–2.99 (2 H, m, 2 × C*H*N), 3.95–4.11 (4 H, m, 2 × CH_2OP). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 16.2 (*C*H_3CH$_2$OP), 16.3 (*C*H_3CH$_2$OP), 20.7 (CH_2, diaA), 20.9 (CH_2, diaB), 21.3 (CH_3, diaA), 22.3 (CH_3, diaB), 24.7 (4 × CH_2), 25.0 (2 × CH_2), 27.3 (CH_2, diaA), 27.5 (CH_2, diaB), 28.7 (2 × CH_2), 28.8 (2 × CH_2), 34.3 (CH_2, diaA), 34.4 (CH_2, diaB), 34.5 (CH_2, diaA), 34.6 (CH_2, diaB), 38.5 (d, ^2J = 13.1 Hz, *C*H$_2$CHP, diaA), 39.5 (d, ^2J = 28.6 Hz, *C*H$_2$CHP, diaB), 43.8 (d, ^1J = 123.8 Hz, *C*HP, diaA), 44.1 (d, ^1J = 123.6 Hz, *C*HP, diaB), 48.5 (d, ^3J = 14.5 Hz, *C*, diaA), 49.2 (d, ^3J = 14.0 Hz, *C*, diaB), 52.1 (2 × *C*HN), 61.5 (d, ^2J = 5.8 Hz, *C*H$_2$OP), 61.7 (d, ^2J = 5.8 Hz, *C*H$_2$OP), 171.7 (d, ^2J = 4.4 Hz, *C*OO, diaA), 172.3 (d, ^2J = 4.4 Hz, *C*OO, diaB), 214.8 (*C*O, diaA), 215.7 (*C*O, diaB).

(21) Absolute configuration was determined by refinement of Flack parameter. Final value was 0.02 (4). Crystallographic data for the salt **14** have been deposited at the Cambridge Crystallographic Data Centre under number CCDC 241581.

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(23) Crystallographic data for the lactone **13a** have been deposited at the Cambridge Crystallographic Data Centre under number CCDC 241582.

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