Synthesis of Geminal Bisphosphonates via Organocatalyzed Enantioselective Michael Additions of Cyclic Ketones and 4-Piperidones

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Supporting Information
# Table of Contents

Experimental Procedures .......................................................... 3  
General procedures ................................................................. 3  
General procedure for the asymmetric Michael addition reaction .......... 3  
General procedure for the Michael addition reaction catalyzed by DBU ...... 4  
Procedures and characterization of compounds ................................ 4  
General procedure for the synthesis of 2,4-dinitrophenylhydrazine adducts .... 10  
References .................................................................................. 11  
NMR spectra .............................................................................. 12  
HPLC traces .............................................................................. 25
Experimental Procedures

General procedures:

The reactions were performed under an argon atmosphere. The reagents were obtained from commercial suppliers and used without further purification. The synthesis and characterization of compounds 3a-c, 6, 9 and 10 has been previously described by us[1]. The solvents used were purified by standard methods and distilled. For column chromatography, Merck silica gel 60 (230–400 mesh) or Mackerey-Nagel GmbH & Co silica gel was used. Thin layer chromatography was performed on silica gel plates Merck 60 F\textsubscript{254}. Optical rotations were measured with an AA-1000 Polarimeter from Optical Activity Ltd, with 1 mL, 0.5 dm cells. NMR spectra were obtained with a Bruker AR X400 NMR spectrometer or a Bruker Avance 400 MHz spectrometer. Chemical shifts are relative to phosphoric acid, used as external standard. The multiplicity of signals in $^{13}$C NMR spectra was determined with DEPT experiments. When necessary, two-dimensional spectra (COSY 45, HMQC, HMBC, NOESY) and decoupling experiments were used to help with structural determinations. Mass spectra were recorded with a Micromass GCT spectrometer, operating in the electron impact mode, and were supplied by the Mass Spectrometry Services of the Chemistry Department/REQUIMTE, FCT, UNL. Elemental analyses were carried on a Thermo Finnigan Elemental Analyser 1112 series, by the Laboratory for External Services of CQFB-Lab Associado / REQUIMTE, of the Department of Chemistry, FCT, UNL. For HPLC analysis, a Merck Hitachi instrument equipped with a Chiralpak AD-H column from Daicel, and a Merck-Hitachi-4250 UV/Vis detector were used.

General procedure for the asymmetric Michael addition reaction: To vinyl gem-bisphosphonate (1.0 mmol) in dry dichloromethane (1.0 mL) was added the ketone (10.0 mmol), (S)-(+)1-(2-pyrrolidinylmethyl)pyrrolidine (0.1 mmol) and benzoic acid (0.1 mmol). The solution was stirred at room temperature, under argon, for the times specified. The reaction was then quenched with a concentrated solution of ammonium chloride, and the products were extracted with dichloromethane. The combined extracts were dried with anhydrous sodium sulfate, and the solvent was evaporated off on a rotary evaporator to give the crude product, which was purified by column chromatography on silica gel. In some cases, as specified for each compound in the supporting information, the presence of benzoic acid in the crude product interfered with product isolation during chromatography. The work-up procedure was then modified to resolve this problem as follows: when the reaction was
complete, water was added, the mixture was treated with a saturated solution of NaHCO₃ and the product was extracted with dichloromethane. The organic phase was then washed successively with a 1 M HCl solution and with water, filtered through anhydrous Na₂SO₄, and the solvent was evaporated off on a rotary evaporator to give the crude product, which was purified by column chromatography on silica gel.

**General procedure for the Michael addition reaction catalyzed by DBU:** This procedure, used for the preparation of racemic standards, is a modification of the method described by Nugent et al.⁵² To vinyl gem-bisphosphonate (1.0 mmol) in dry dichloromethane (1.0 mL) was added the ketone (1.0 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.0 mmol). The solution was stirred at room temperature, under argon, for one hour. Water was then added, and the products were extracted with dichloromethane. The combined organic extracts were dried with anhydrous sodium sulfate, and the solvent was evaporated off on a rotary evaporator to give the crude product, which was purified by column chromatography on silica gel.

**Tetraethyl [2-(5′-ethyl-2′-oxocyclohexyl)ethylidene]bisphosphonate (3e):** Prepared from ethylidene bisphosphonate 2 and 4-ethylcyclohexanone, according to the General procedure, modified to remove benzoic acid prior to chromatography. The product was obtained as a 70:30 (trans/cis) mixture of diastereoisomers as determined by ³¹P NMR spectroscopy. The crude product was purified by column chromatography on silica gel with 2:3 acetone/CHCl₃ to give product 3e as an inseparable mixture of two diastereoisomers, in the form of a colourless viscous liquid (61 mg, 72%). δH (400 MHz; CDCl₃) 0.75–1.05 (m, 2 × CH₃), 1.14–1.40 (m, 4 × POCCH₃), 1.52–1.94 (m), 1.94–2.02 (m), 2.02–2.39 (m), 2.39–2.61 (tdd, J 5.4, 8.9, 23.8 Hz, PCH, major), 2.61–2.81 (tdd, J 4.5, 8.1, 24.0 Hz, PCH, minor), 2.81–3.00 (m), 4.00–4.25 (m, 4 × POCH₂) ppm; δC (100 MHz; CDCl₃) 11.57 (CH₃, minor), 11.95 (CH₃, major), 16.23 (4 × POCCH₃, major + minor), 25.75 (CH₂ of Et, major), 25.94 (PCCH₂, minor), 26.55 (PCCH₂, major), 28.42 (CH₂ of Et, minor), 31.22 (CH₂, C-4′, major), 33.56 (CH₂, C-4′, minor), 33.66 (CHEt, minor), 33.85 (CH, d, JCP 133.0 Hz, PCH, major + minor), 37.63 (CH₂, C-6′, major), 37.87 (CH₂, C-3′, major), 38.32 (CHEt, major), 40.43 (CH₂, C-6′, minor), 41.42 (CH₂, C-3′, minor), 45.06 (CH, C-1′, major), 47.18 (CH, C-1′, minor), 62.31–62.55 (CH₂, 4 × POCH₂, major + minor), 213.0 (Cq, C=O, minor), 213.6 (Cq, C=O, major); δp (162 MHz; CDCl₃) 23.47 (minor), 23.53 (major), 24.09 (major), 24.17 (minor);
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m/z 427 (M+1, 4), 426 (M⁺, 21), 397 (7), 381 (5), 302 (5), 301 (30), 290 (5), 289 (38), 288 (100), 273 (6), 261 (30), 260 (10), 244 (6), 243 (7), 233 (14), 215 (8), 204 (6), 177 (5), 165 (6), 159 (7), 152 (21), 138 (5), 109 (8), 105 (6), 97 (8), 96 (5), 95 (10), 83 (7), 82 (6), 81 (14), 72 (5), 71 (5), 69 (10), 67 (7), 59 (6), 57 (7), 56 (5), 55 (13), 45 (5) (Found C, 50.45; H, 8.75. Caled for C₁₈H₃₆O₉P₂: C, 50.70; H, 8.51). The enantiomeric excesses were determined by HPLC on a chiral column after conversion of the diastereoisomers into their 2,4-dinitrophenylhydrzones, (Chiralpak AD-H, 25% i-PrOH in hexane, 1.0 ml min⁻¹, 365 nm): tR = 9.00 (cis, major), 12.6 (trans, major), 14.0 (trans, minor), 15.8 (cis, minor) min, relative to the racemic sample prepared with DBU as base.

Tetraethyl [2-(8'-oxo-1',4'-dioxao-spiro[4.5]dec-7'-yl)-ethane-1,1-diyl]bisphosphonate (3f): Prepared from ethyldiene bisphosphonate 2 and 1,4-cyclohexanedione monoethylene acetal, according to the General procedure, but the ratio of ketone to bisphosphonate used was only 4:1. The crude product was purified by chromatography on silica gel with 2:1 EtOAc/hexane, followed by 1:1 acetone/CHCl₃ to give product 3f in the form of a white solid (29 mg, 62%). δH (400 MHz; CDCl₃) 1.17–1.50 (m, 8 H, POCH₂), 1.56–1.77 (m + t, J 13.0 Hz, 2 H, PCCH + H-6'), 1.95 (td, J 5.0, 13.5 Hz, 1 H, H-10'), 2.00–2.06 (m, 1 H, H-10'), 2.11 (ddd, J 3.5, 5.6, 12.9 Hz, 1 H, H-6'), 2.25–2.50 (ddd + m, J 3.0, 5.0, 13.9 Hz, H-9' + PCCH), 2.56–2.85 (m, 2 H, PCH + H-3'), 3.20–3.35 (m, 1 H, C-7'), 3.94–4.10 (m, 4 H, 2 × acetal-CH₂), 4.10–4.36 (m, 8 H, POCH₂); δC (100 MHz; CDCl₃) 16.34 (4 × CH₃), 25.80 (CH₂, PCCH₂), 34.10 (CH, J 130.5 Hz, PCHP), 34.94 (CH₂, C-10'), 38.31 (CH₂, C-9'), 41.41 (CH₂, C-6'), 44.36 (CH, C-7'), 62.70 (CH₂, m, 4 × OCH₂), 64.58 (CH₂, acetal-CH₂), 64.78 (CH₂, acetal-CH₂), 107.2 (Cq, acetal), 211.3 (Cq, C=O); δP (162 MHz; CDCl₃) 23.39, 24.07; m/z 457 (M+1, 5), 456 (M⁺, 23), 412 (5), 411 (26), 410 (8), 399 (5), 319 (8), 301 (19), 288 (22), 281 (11), 273 (7), 264 (7), 261 (16), 233 (11), 220 (6), 205 (5), 192 (5), 178 (5), 169 (8), 167 (6), 166 (5), 165 (7), 164 (5), 159 (5), 154 (6), 152 (12), 151 (6), 150 (8), 149 (13), 140 (6), 138 (7), 137 (9), 136 (18), 135 (5), 128 (10), 126 (15), 125 (7), 124 (9), 105 (5), 101 (5), 100 (13), 99 (21), 98 (20), 97 (27), 96 (16), 95 (19), 94 (7), 93 (7), 91 (7), 86 (16), 85 (7), 84 (13), 83 (30), 82 (14), 81 (24), 80 (6), 79 (12), 77 (5), 73 (11), 72 (13), 71 (13), 70 (15), 69 (40), 68 (11), 67 (26), 60 (11), 59 (100), 57 (28), 56 (17), 55 (61), 54 (15), 53 (8) (Found C, 47.11; H, 7.72. Caled for C₁₈H₃₆O₉P₂: C, 47.37; H, 7.51). The enantiomeric excesses were determined by HPLC on a chiral column after conversion of the diastereoisomers into their 2,4-dinitrophenylhydrzones, (Chiralpak AD-H, 25% i-PrOH in hexane, 1.0 ml min⁻¹, 365
nm): $t_R = 15.2$ (major), 17.2 (minor), relative to the racemic sample prepared with DBU as base.

**Tetraethyl [2′-(2′,3′-dihydro-1′-oxo-indene-2′-yl)ethylidene]bisphosphonate (12):**
Prepared from ethylidene bisphosphonate 2 and 1-indanone, according to the General procedure. However, a concentration of phosphonate of 0.5 mmol / mL was used, and the reaction mixture was refluxed for 46 h. The crude product, which consisted of a 92:8 mixture of 2-mono to 2,2-disubstituted 1-indanone as determined by $^1$H NMR spectroscopy, was purified by column chromatography on silica gel with 2:1 acetone/toluene or on neutral alumina with 1:100 i-PrOH/CHCl$_3$ to give the product 12 in the form of a colourless oil (60 mg, 81%). $\delta_H$ (400 MHz; CDCl$_3$) 1.20–1.35 (m, 2 H, CH$_3$ of POEt), 1.90–2.11 (m, 1 H, PCCH), 2.25–2.50 (m, 1 H, PCCH), 2.72 (dd, 1 H, J 3.8, 17.0 Hz, ring CHH), 2.94 (tt, 1 H, J 6.3, 24.0 Hz, PCH), 3.09–3.20 (m, 1 H, ring CH), 3.35 (dd, 1 H, J 7.8, 17.0 Hz, ring CHH), 4.06–4.23 (m, 8 H, CH$_2$ of POEt), 7.30 (t, 1 H, J 7.4 Hz, H-6′), 7.38 (d, 1 H, J 7.6 Hz, H-4′), 7.52 (t, 1 H, J 7.2 Hz, H-5′), 7.67 (d, J 7.6 Hz, H-7′); $\delta_C$ (100 MHz; CDCl$_3$) 16.36 (4 × CH$_3$ of POEt), 27.62 (CH$_2$, 2 × PCCH$_2$), 33.18 (CH$_2$, ring-CH$_2$), 34.13 (CH, t, $J_{CP}$ 133.1 Hz, PCH), 45.26 (CH, t, $J_{CP}$ 6.4 Hz, ring-CH), 62.61 (CH$_2$, d, $J_{CP}$ 6.2 Hz, 4 × CH$_2$ of POEt), 123.9 (CH, C-6′), 126.5 (CH, C-4′), 127.5 (CH, C-7′), 134.8 (CH, C-5′), 136.5 (Cq, C-7′a), 153.1 (Cq, C-3′a), 207.8 (Cq, C=O); $\delta_P$ (162 MHz; CDCl$_3$) 23.40, 23.83; m/z 433 (M+1, 3), 432 (M$^+$, 14), 301 (40), 295 (67), 288 (100), 261 (44), 248 (19), 233 (27), 221 (26), 205 (14), 202 (16), 159 (19), 152 (43), 145 (25), 124 (19), 115 (44), 109 (19), 57 (10) (Found C, 52.62; H, 6.83. Calcd for C$_{13}$H$_{36}$O$_7$P$_2$: C, 52.77; H, 6.70). The enantiomeric excesses were determined by HPLC on a chiral column (Chiralpak AD-H, 6% i-PrOH in hexane, 1.1 mL min$^{-1}$, 254 nm): $t_R = 43.8$, 47.2. The proton NMR data of this compound corresponds to that described previously in ref. 2.

**Octaethyl [(2′,3′-dihydro-1′-oxo-inden-2′,2′-dyl)diethane-2,1,1-triy]tetrakisphosphonate (13):** The title compound was prepared via the reaction of ethylidene bisphosphonate 2 and 1-indanone according to the General procedure using DBU catalysis. The crude product, which consisted of a 1:2 mixture of monosubstituted : disubstituted 2-indanone as determined by $^1$H NMR spectroscopy, was purified by chromatography on silica gel, with 1:1 CHCl$_3$/acetone. Disubstituted 1-indanone 13 (20.3 mg) and monosubstituted 1-indanone 12 (14.0 mg) were obtained from the reaction of 27 mg of 1-
indanone with 61 mg of bisphosphonate. δH (400 MHz; CDCl3) 1.00–1.50 (m, 24 H, 8 × CH3), 2.26–2.50 (m, 6 H, 2 × PCCH2 + 2 × PCH), 3.45 (s, 2 H, ring CH2), 4.00–4.32 (m, 8 H, POCH2), 7.35 (t, J 7.2 Hz, H-6’), 7.44 (d, J 7.3 Hz, H-4’), 7.58 (t, J 7.2 Hz, H-5’), 7.71 (d, J 7.5 Hz, H-7’); δC (100 MHz; CDCl3) 16.27 (m, 8 × CH3), 31.49 (CH2, 4 × PCCH2), 32.57 (CH, JCP 132.4 Hz, 2 × PCH), 35.58 (CH2, ring CH2), 52.08 (CH, ring CH), 62.72 (m, CH2, 4 × OCH2), 124.0 (CH, C-6’), 126.4 (CH, C-4’), 127.4 (CH, C-7’), 135.0 (CH, C-5’), 137.0 (Cq, C-7’a), 153.3 (Cq, C-3’a), 207.4 (Cq, C=O); δp (162 MHz; CDCl3) 23.97, 24.67; m/z 732 (M+, 0.1), 687 (0.2), 595 (0.3), 445 (5), 444 (4), 432 (19), 431 (4), 301 (13), 295 (16), 288 (29), 261 (12), 245 (11), 221 (10), 217 (15), 189 (12), 171 (29), 164 (12), 163 (20), 158 (11), 152 (12), 145 (11), 144 (60), 137 (13), 136 (13), 135 (16), 116 (57), 115 (100), 109 (17), 89 (15), 81 (11), 63 (11), 45 (23) (Found C, 47.50; H, 7.18. Calcd for C29H52O13P4: C, 47.54; H, 7.16).

Tetraethyl [2-(2,3-dihydro-2-oxo-inden-1-yl)ethylidenedibisphosphonate (15): Prepared from ethylidene bisphosphonate 2 (0.533 mmol) and 2-indanone (1.52 mmol), according to the General procedure modified to remove benzoic acid prior to chromatography. The crude product, which consisted of a 70:30 monosubstituted to disubstituted 2-indanone mixture as determined by 1H NMR spectroscopy, was purified by column chromatography on silica gel with 3:2 acetone/CHCl3, to give the product 15 (102 mg, 44%) as a colourless oil, approx. 90% pure. δH (400 MHz; CDCl3) 1.20–1.40 (m, 12 H, 4 × OCCH3), 2.13–2.40 (m, 2 H, PCCH2), 3.26 (tdd, J 3.2, 8.8, 27.2 Hz, 1 H, PCH), 3.54 (s, 2 H, ring-CH2), 3.82–3.95 (m, 4 H, POCH2), 4.13–4.28 (m, 8 H, 4 × OCH2), 7.20–7.40 (m, 4 H, 4 × Ar-H); δp (162 MHz; CDCl3) 23.30, 23.91.

Octaethyl [(2,3-dihydro-2-oxo-inden-1,1-diyl)diethane-2,1,1-triylditetraakisphosphonate (16): To vinyl gem-bisphosphonate 2 (0.13 mmol) in dry dichloromethane (0.6 mL) was added 2-indanone (0.13 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.13 mmol). The solution was stirred for 2 h in an ice bath, under argon. Water was then added, and the products were extracted with dichloromethane. The combined organic extracts were dried with anhydrous sodium sulfate, and the solvent was evaporated off on a rotary evaporator. The crude product, which consisted of a 12:82 monosubstituted to disubstituted 2-indanone mixture as determined by 1H NMR spectroscopy, was purified by column chromatography on silica gel with 2:1 acetone/CHCl3, to give the product 16 as an oil (11 mg, 22%). δH (400 MHz; CDCl3)
MHz; CDCl₃) 0.93–1.47 (m, 24 H, 8 × CH₃), 2.32–2.65 (m, 6 H, 2 × PCH + 2 × PCCH₂), 3.59 (s, 2 H, ring CH₂), 3.93–4.29 (m, 16 H, 8 × OCH₂), 7.26–7.32 (m, 4 H, Ar-H); δC (100 MHz; CDCl₃) 16.29 (8 × CH₃), 32.38 (t, J_Cp 133.2 Hz, 2 × PCHP), 33.09 (CH₂, 2 × PCCH₂), 42.85 (CH₂, ring CH₂), 56.17 (Cq), 62.54–62.69 (m, 8 × OCH₂), 125.1 (2 × CH, C-5 and C-6), 127.1 (CH, C-7), 127.8 (CH, C-4), 137.9 (Cq, C-3a), 142.7 (Cq, C-7a), 215.5 (Cq, C=O); δP (162 MHz; CDCl₃) 23.51, 24.56; m/z 734 (M+2, 1), 733 (M+1, 9), 732 (M⁺, 28), 432 (43), 386 (11), 301 (28), 288 (37), 273 (18), 261 (25), 260 (12), 249 (12), 245 (22), 233 (24), 221 (17), 220 (13), 217 (27), 205 (19), 199 (14), 192 (15), 189 (21), 177 (15), 171 (51), 165 (12), 164 (26), 163 (43), 159 (18), 153 (12), 152 (28), 145 (11), 144 (53), 137 (23), 136 (26), 135 (33), 129 (15), 128 (13), 127 (10), 125 (14), 116 (56), 115 (100), 109 (30), 107 (13), 102 (16), 99 (15), 91 (11), 89 (14), 82 (10), 81 (20), 65 (17), 63 (12), 45 (15).

Tetraethyl [2-(1’-methyl-4’-oxopiperidin-3’-yl)ethane-1,1-diy]bisphosphonate (18a): Prepared from ethyldiene bisphosphonate 2 and 1-methyl-4-piperidone 17a, according to the General procedure, but the reaction was quenched with water only. The crude product was then purified by preparative chromatography on silica gel with 3:1 MeOH/EtOAc to give product 18a in the form of a colourless viscous liquid (84 mg, 58%). δH (400 MHz; CDCl₃) 1.22–1.47 (m, 12 H, 4 × CH₃, POCHCH₂), 1.60–1.78 (m, 1 H, PCCH), 2.10 (t, 1 H, J 10.8 Hz, H-2’), 2.27–2.50 (m + s, 6 H, PCCH + H-5’ + H-6’ + N-CH₃), 2.62–2.79 (m, 2 H, H-5’ + PCH), 2.98–3.22 (m, 3 H, H-2’ + H-3’ + H-6’), 4.08–4.33 (m, 8 H, POCH₂); δC (100 MHz; CDCl₃) 16.34 (CH₃, 4 × CH₃, POCHCH₂), 23.72 (CH₂, POCH₂), 34.08 (CH, t, J_Cp 133.9 Hz, PCH), 41.06 (CH₂, C-5’), 45.10 (CH₃, N-CH₃), 47.47 (CH₂, PCCH), 56.19 (CH₂, C-6’), 61.68 (CH₂, C-2’), 62.49–62.73 (m, 4 × CH₂, POCH₂), 210.0 (Cq, C=O); δP (162 MHz; CDCl₃) 23.31, 23.80; m/z 414 (M⁺ + 1, 1), 413 (M⁺, 4), 395 (17), 325 (7), 302 (15), 301 (10), 288 (5), 276 (7), 275 (5), 274 (6), 273 (5), 261 (8), 259 (8), 258 (64), 245 (10), 233 (9), 217 (7), 215 (5), 205 (6), 188 (5), 177 (6), 171 (8), 166 (12), 165 (74), 163 (6), 161 (9), 159 (9), 153 (5), 152 (7), 138 (11), 137 (15), 136 (7), 135 (7), 127 (7), 126 (100), 125 (6), 124 (19), 113 (10), 112 (41), 111 (8), 110 (12), 109 (14), 99 (5), 96 (5), 95 (5), 94 (14), 83 (6), 82 (7), 70 (7), 55 (9), 45 (6) (Found C, 44.92; H, 8.02; N, 3.17. Caled for C₁₆H₃₅NO₄P₂: C, 46.49; H, 8.05; N, 3.39). The enantiomeric excesses were determined by HPLC on a chiral column (Chiralpak AD-H, i-PrOH : hexane : DEA 100/100/0.1, 1.0 mL min⁻¹, 254 nm): tᵣ = 18.8 (minor), 20.6 (major) min, relative to the racemic sample prepared with DBU as base.
Tetraethyl [(2-[(1′-benzyl-4′-oxopiperidin-3′-yl)ethane-1,1-diyl]bisphosphonate (18b): Prepared from ethyldiene bisphosphonate 2 and 1-benzyl-4-piperidone 17b, according to the General procedure. The crude product was then purified by chromatography on silica gel with 1:1 CHCl3/acetone to give the product 18b in the form of a colourless viscous liquid (46 mg, 61%). δH (400 MHz; CDCl3) 1.23–1.33 (m, 12 H, 4 × CH3), 1.53–1.75 (m, 1 H, PCCH), 2.12 (t, 1 H, J 10.4 Hz, H-2′), 2.19–2.50 (m, 3 H, PCCH + H-5′ + H-6′), 2.50–2.72 (m, 2 H, PCHP + H-5′), 2.94–3.19 (m, 3 H, H-3′ + H-6′ + H-2′), 3.57 (d, AB system, 1 H, J 13.2 Hz, CH2Ph), 3.61 (d, AB system, 1 H, J 13.2 Hz, CH2Ph), 4.00–4.25 (m, 8 H, 4 × OCH2), 7.14–7.41 (m, 5 H, Ph-H); δC (100 MHz; CDCl3) 16.31 (4 × CH3), 23.77 (CH2, PCCH2), 34.01 (CH, t, JCP 132.8 Hz, PCHP), 41.09 (CH2, C-5′), 47.65 (CH, C-3′), 53.58 (CH2, C-6′), 59.61 (CH2, C-2′), 61.49 (CH2, CH2Ph), 62.43–62.65 (CH2, m, 4 × OCH2), 127.3 (CH, pCHAr), 128.3 (CH, 2 × CH-Ar), 128.8 (CH, 2 × CH-Ar), 138.0 (Cq, Ar), 210.4 (Cq, C=O); δp (162 MHz; CDCl3) 23.35, 23.91; m/z 489 (M+ 1, 1), 399 (9), 398 (66), 353 (6), 352 (43), 334 (16), 325 (5), 302 (6), 261 (6), 245 (10), 233 (9), 215 (5), 205 (5), 202 (14), 189 (13), 188 (32), 177 (7), 171 (8), 165 (16), 159 (9), 137 (5), 119 (5), 109 (8), 107 (10), 106 (18), 104 (7), 92 (11), 91 (100), 79 (6), 77 (8), 65 (8) (Found C, 53.73; H, 7.80; N, 2.84. Caled for C22H37NO7P2: C, 53.98; H, 7.62; N, 2.87). The enantiomeric excesses were determined by HPLC on a chiral column (Chiralpak AD-H, 18% i-PrOH in hexane, 1.0 ml min−1, 254 nm): tR = 8.0 (minor), 8.6 (major) min, relative to the racemic sample prepared with DBU as base.

Tetraethyl [(2-[(4′-oxotetrahydro-2H-pyran-3′-yl)ethane-1,1-diyl]bisphosphonate (20): Prepared from ethyldiene bisphosphonate 2 and tetrahydropyran-4-one 19, according to the General procedure modified to remove benzoic acid prior to chromatography. The crude product was purified by column chromatography on silica gel with 2:1 CHCl3/acetone to give the product 20 in the form of a colourless liquid (104 mg, 88%). δH (400 MHz; CDCl3) 1.26–1.40 (m, 12 H, 4 × CH3), 1.55–1.62 (m, 1 H, PCCH), 2.23–2.43 (m, 2 H, H-5′ + PCCH), 2.56–2.78 (m, 2 H, PCH + H-5′), 3.10–3.25 (m, 1 H, H-3′), 3.33 (t, 1 H, J 10.6 Hz, H-2′), 3.69 (td, 1 H, J 2.8, 11.3 Hz, H-6′), 4.08–4.28 (m, 10 H, 4 × OCH2CH3 + H-2′ + H-6′); δC (100 MHz; CDCl3) 16.27 (4 × CH3), 21.89 (CH2, PCCH2), 33.97 (t, CH, JCP 134.1 Hz, PCP), 42.66 (CH2, C-5′), 49.53 (CH, d, JCP 5.6 Hz, C-3′), 62.62 (m, 4 × OCH2CH3), 68.78 (CH2, C-6′), 72.84 (CH2, C-2′), 208.0 (Cq, C=O); δp (162 MHz; CDCl3) 23.13, 23.61; m/z 401 (M+ 1, 2), 400 (M+′, 14), 355 (5), 344 (11), 302 (25), 301 (64), 289 (10), 288 (100), 273 (19), 263 (37), 261 (53), 260 (14), 245 (45), 235 (23), 233 (38), 217 (18), 214 (12), 207 (13),
205 (18), 199 (10), 191 (15), 189 (10), 177 (12), 171 (10), 165 (37), 163 (10), 161 (24), 159 (20), 152 (41), 137 (10), 135 (24), 133 (10), 125 (12), 109 (26), 99 (19), 91 (12), 81 (14), 65 (11) (Found C, 44.77; H, 7.76. Calcd for C_{13}H_{30}O_2P_2: C, 45.00; H, 7.55). The enantiomeric excess was determined by $^{13}$C NMR analysis of the diastereoisomers obtained after reaction with optically pure (S,S)-2,3-butanediol in the presence of p-TsOH$^{[3]}$. Hence, for tetraethyl [2-(2',3'-dimethyl-1',4',8'-trioxaspiro[4',5']dec-6'-yl)-ethane-1,1-diylo]bisphosphonate (21), major diastereoisomer: $\delta_c$ (100 MHz; CDCl$_3$) 16.40 (POCCH$_3$), 17.57 (C$_4$OCCH$_3$), 21.58 (PCCH$_2$), 35.03 (PCH), 36.77 (C-10'), 42.78 (C-6'), 62.45–62.53 (4 x POCH$_2$), 65.87 (C-9'), 69.08 (C-7'), 77.69 (C-2' or C-3'), 79.00 (C-2' or C-3'), 107.20 (Cq); minor diastereoisomer: 16.20 (POCCH$_3$), 17.73 (C$_4$OCCH$_3$), 21.41 (PCCH$_2$), 33.70 (PCH), 36.41 (C-10'), 43.50 (C-6'), 62.45–62.53 (4 x POCH$_2$), 65.97 (C-9'), 69.02 (C-7'), 78.09 (C-2' or C-3'), 78.87 (C-2' or C-3'), 107.22 (Cq).

**General procedure for the synthesis of 2,4-dinitrophenylhydrazine adducts$^{[4]}$:** The bisphosphonate (0.20 mmol) was dissolved in ethanol (1.0 mL) and 2,4-dinitrophenylhydrazine (0.20 mmol) was added, followed by a catalytic amount of para-toluenesulfonic acid. The mixture was stirred at room temperature for 17 h. An aqueous saturated solution of sodium bicarbonate was added, and the compound was extracted with dichloromethane. The combined organic extracts were washed with water, filtered through anhydrous sodium sulfate, and the solvent was then removed in a rotary evaporator, to give a yellow-orange solid.

**Dinitrophenylhydrazine adduct of tetraethyl [2-(8'-oxo-1',4'-dioxaspiro[4.5]dec-7'-yl)-ethane-1,1-diylo]bisphosphonate (7b):** Prepared from 3f and dinitrophenylhydrazine according to the general procedure. The crude product was purified by preparative TLC on silica gel with EtOAc/acetone 1:1 as eluent to give 7b as a yellow hygroscopic solid (18 mg, 67%). $\delta_h$ (400 MHz; CDCl$_3$) 1.35 (t, 12 H, J 6.0 Hz, 4 x POCCH$_3$), 1.64 (t, 12 J 12.3 Hz, 1 H, H-6'), 1.81 (td, 1 J 4.9, 12.9 Hz, 1 H, H-10'), 1.88–2.17 (m, 3 H, PCCCH, H-10', H-6'), 2.41 (ddd, 1 J 5.2, 11.6, 14.7 Hz, 1 H, H-9'), 2.60–2.96 (superimp. dt + m, 1 J 4.7, 14.6 Hz, H-9', PCHP, PCCCH), 3.21–3.38 (m, 1 H, PCCCH), 4.00–4.01 (m, 4 H, 4 x acetal-H), 4.12–4.33 (m, 8 H, 4 x POCH$_2$), 8.18 (d, 1 H, J = 9.6 Hz, H-6''), Ar), 8.31 (d, 1 H, J = 9.62 Hz, H-5''), Ar), 9.13 (d, 1 H, J = 2 Hz, H-3''), Ar), 11.27 (s, 1 H, N-NH); $\delta_c$ (100 MHz; CDCl$_3$) 16.45 (CH$_3$, 4 x POCCH$_3$), 23.72 (CH$_2$, C-9'), 27.21 (CH$_2$, PCCCH$_2$), 33.82 (CH$_2$, C-10'), 34.51 (d, CH, J$_{CP}$ 133.9 Hz, PCH), 39.76 (CH, PCCCH), 42.01 (CH$_2$, C-6'), 62.43–62.75 (CH$_2$, 4 x POCH$_2$),
64.58 (CH$_2$, acetal CH$_2$), 64.78 (CH$_2$, acetal CH$_2$), 107.4 (C$_q$, O-C-O), 116.8 (CH, C-6′′, Ar), 123.5 (CH, C-3′′, Ar), 129.1 (C$_q$, C-2′′, Ar), 130.1 (CH, C-5′′, Ar), 137.9 (C$_q$, C-4′′, Ar), 145.5 (C$_q$, C-1′′, Ar), 159.8 (C=N); δ$_p$ (162 MHz; CDCl$_3$) 24.26, 24.40; m/z 636 (M$^+$, 20), 601 (66), 454 (33), 437 (53), 409 (35), 408 (38), 363 (35), 301 (67), 299 (79), 288 (59), 273 (34), 261 (57), 245 (35), 233 (44), 217 (36), 205 (39), 202 (50), 189 (37), 177 (34), 170 (66), 166 (34), 165 (82), 164 (40), 163 (52), 159 (31), 153 (44), 152 (66), 137 (54), 136 (32), 135 (53), 134 (37), 125 (31), 123 (44), 122 (46), 119 (37), 110 (30), 109 (79), 108 (41), 107 (50), 106 (32), 105 (49), 100 (41), 99 (87), 98 (30), 97 (54), 96 (41), 95 (63), 94 (41), 93 (35), 92 (31), 91 (65), 86 (53), 83 (69), 82 (66), 81 (61), 80 (45), 79 (65), 78 (30), 77 (50), 76 (34), 72 (37), 71 (31), 70 (30), 69 (75), 68 (30), 67 (63), 65 (32), 59 (54), 57 (69), 56 (40), 55 (100), 54 (46), 53 (37), 45 (60).

References:

NMR Spectra

Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry
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$^{31}$P NMR spectrum of the crude product mixture from the Michael addition with the enone chromophore.
HPLC chromatograms

Determination of the % ee of 3d
HPLC traces of the DNPH adducts
Determination of the % ee of 3e
HPLC traces of the DNPH adducts

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Determination of the % ee of 3f
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Determination of the % ee of 18a
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Determination of the % ee of 18b
HPLC traces