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Selective methylphosphonylation of an echinocandin B analog derived from LY303366

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Abstract—Echinocandin B (ECB) analog **1c** was methylphosphonylated with the new reagent dimethyldiphosphonate **7**. Selective functionalization of the phenol group was achieved in the presence of 11 other reactive alcohol and amide groups. The phosphonylation was best conducted in a mixture of THF and DMF using lithium *t*-butoxide as base. Methylphosphonate diester **1d** was deprotected by hydrogenolysis to afford methylphosphonate monoester **1e**, a potential prodrug for ECB analog **1c**. © 2003 Published by Elsevier Science Ltd.

1. Introduction

Fungal infections are a leading cause of nosocomal blood stream infection. With the increasing resistance of these infections to conventional therapies, the need for new, safe, and effective antifungal agents has never been greater. LY303366 (**1a**) is a cidal antifungal showing activity against Candida and Aspergillus infections.[1] It is a semisynthetic variant of the cyclic peptide echinocandin B (ECB, **2**), a fermentation product of *Aspergillus Nidulans*.[2] Other structural analogs of ECB such as the pneumocandins (L-671,329), mulundocandin, and aculeacins have been widely studied.[3] The low aqueous solubility of LY303366 (<1 mg/mL) has hindered the development of an intravenous formulation. An increase in aqueous solubility could conceivably be engineered through formulation technology or, more attractively, through the advent of a prodrug. Early studies suggested that phosphate and phosphonate derivatives at the homotyrosine phenol residue afforded prodrugs with the best combination of solubility and activity properties. Issues with the stability of the ECB nucleus uncovered in the phosphorylation of **1a** to produce phosphate **1b**,[4] led us to consider dideoxy ECB methylphosphonate monoester **1e** for prodrug development. Methylphosphonate monoester **1e** has been reported to enhance the water solubility of **1c** 200-fold while maintaining comparable antifungal activity.[5] This paper presents the results of our studies on the methylphosphonylation of **1c** to produce methylphosphonate monoester **1e** via dideoxy ECB methylphosphonate diester **1d**. Selective functionalization of the phenol group in high yield has been achieved despite the presence of eleven other reactive alcohol and amide groups.

An important consideration in any chemical manipulation of **1c** is the acid and base lability of the polypeptide. Initial studies employing the classical phosphonylating agent methylphosphonic dichloride[6] gave poor selectivity for the homotyrosine phenol. Moreover, the HCl liberated during hydrolytic work-up caused substantial decomposition. The overall yield of **1e** obtained in one step by treating **1c** with $MeP(O)Cl_2$ in the presence of LiOTMS was 5–10%. Although a number of other reagents have been reported[7] in the literature for the phosphonylation of alcohols, previous success in the selective phosphorylation of **1a**[4] with tetrabenzyl diphosphate led us to consider a prototype dimethyldiphosphonate **7** (Fig. 1).

2. Results and discussions

The synthesis of dimethyldiphosphonate **7** involved self-coupling of methylphosphonate monoester **6**. Two options (path a and path b) were available for the synthesis of monoester **6** (Scheme 1). 1*H*-Tetrazole-catalyzed[8a] reaction of 4-bromobenzyl alcohol with methylphosphonic dichloride **3** led to diester **4** in 89% yield. Treatment of **4** with sodium iodide[10] gave monoester **5** in 89% yield. This reaction also produced benzyl iodide, a strong lachrymator, as the by-product. Acidification of **5** led to methylphosphonate monoester **6** in 99% yield. In the alternative and more desirable procedure (path b), 4-bromobenzyl alcohol was added to a slight excess of the dichloride **3** to

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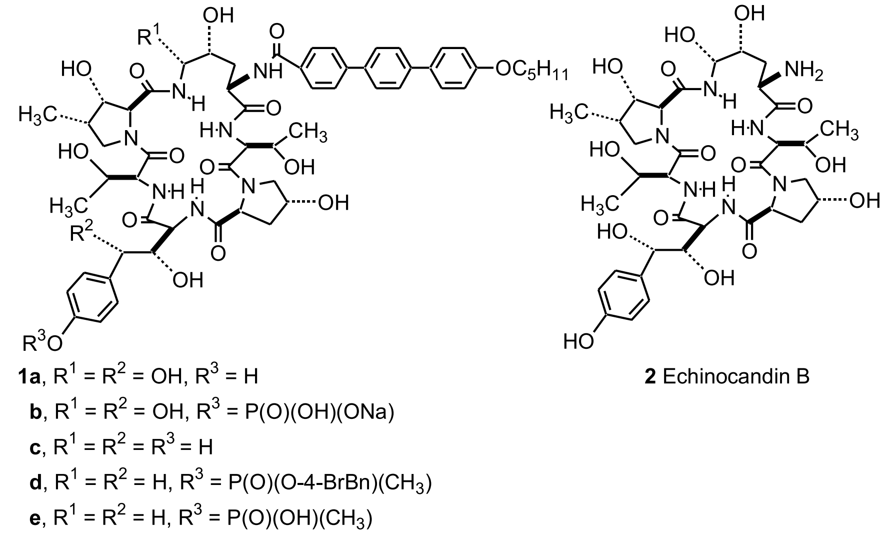
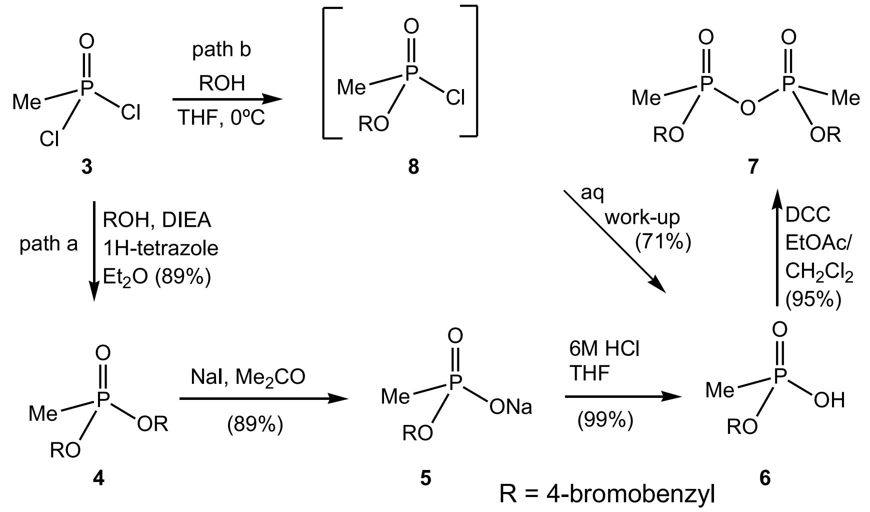


Figure 1.

provide a 1:4 mixture of diester **4** and monoester **8**.[8] Addition of aqueous sodium hydroxide to the reaction mixture initially provided desired monoester **6**, along with dimethyldiphosphonate **7** as the major product. Formation of dimethyldiphosphonate **7** can be explained by rapid reaction of the initially formed anion **5** with unquenched monochlorophosphonate monoester **8**.[9] Diphosphonate **7** could not be obtained cleanly by this procedure; so the quenched reaction mixture, consisting of **4**, **5**, and **7**, was stirred for 12–24 h with aqueous base to hydrolyze **7** to anion **5**. The diester **4** was removed by extraction, and the monoester **6** was isolated in good yield after acidification and extraction. This procedure provides a practical one-step synthesis of methylphosphonate monoester **6** in high yield and purity.[10]

Dicyclohexylcarbodiimide-promoted self-coupling of monoester **6** occurred rapidly at room temperature in tetrahydrofuran, ethyl acetate, toluene, or methylene chloride to afford dimethyldiphosphonate **7** as a 1:1 mixture of diastereomers.[11] THF and methylene chloride would have been the preferred solvents due to good solubility of the diphosphonate. However, at the end of the reaction the dicyclohexylurea (DCU) was removed by filtration, and these solvents retained 3–4% DCU in the evaporated product filtrate. In addition, hydrolysis of the dimethyldiphosphonate during filtration and isolation was more pronounced in THF. In toluene or ethyl acetate, the DCU precipitation was complete (<0.5% DCU in the filtrate) but coprecipitation of the dimethyldiphosphonate (after 1 h in toluene and after 24 h in ethyl acetate) led to lower yields of the product, if the DCU was not removed immediately by filtration. The ideal solvent adopted for a 20 g scale synthesis of **7** was a 10:1 mixture of ethyl acetate and methylene chloride. Similar chemistry was utilized to prepare the dibenzyl analog of **7** as an oil, but the 4-bromobenzyl derivative proved advantageous due to easy purification and the exceptional storage stability of this crystalline derivative.[12]

The effectiveness of dimethyldiphosphonate **7** as a phosphonylating agent is seen in the highly selective synthesis of



Scheme 1. Synthesis of dimethyldiphosphonate **7**.

Table 1. Methylphosphonylation of ECB **1c**

Entry	Base[a] (mol equiv.)	**7** (mol equiv.)	Solvent	% **1c**[b]	% **1d**[b]	% By-products[c]
1	2.2 LiOH	1.5	DMF	15	74	3.0
2	1.0 LiOH	2.0	2:3 DMF/THF	23	74	0.1
3	1.05 LIOH	2.0	DMF	<1	95	1.5
4	2.2 LiOH	2.0	DMF	<1	80	16.0
5	1.1 LiOTMS	1.1	1:1 DMF/THF	5	89	1.5
6	1.3 LiOTMS	1.2	1:1 DMF/THF	3	90	1.7
7	1.0 ^{t}BuOLi	1.1	2:3 DMF/THF	5	86	1.8
8	1.18 ^{t}BuOLi	1.18	1:1 DMF/THF	<1	94	1.0
9	1.25 ^{t}BuOLi	1.33	1:1 DMF/THF	<1	94	1.5

Reactions were run with 0.5–2.0 g of **1c**.
[a] 3 M LiOH was used.
[b] UV area percent by HPLC.
[c] Percent late-eluting by-products by HPLC.

methylphosphonate diester **1d** and ultimately methylphosphonate monoester **1e** from ECB analog **1c**. The greater acidity of the phenolic hydroxyl in **1c** should allow selective derivatization under basic conditions; however, the presence of eleven other acidic functional groups suggests the potential for reaction at other sites or at multiple sites. Typically, the phenolic hydroxyl of the ECB was first deprotonated with lithium *t*-butoxide by adding a THF solution of the base to a DMF solution of the substrate at 0°C.[13] A solution of the dimethyldiphosphonate **7** in THF or DMF was then added dropwise. The reaction was stirred at 5°C and monitored to completion by HPLC (0.5–3 h). In some cases, additional base and dimethyldiphosphonate were added in small portions to consume remaining starting materials. Other bases such as lithium hydroxide, sodium hydride, tertiary amines, and lithium trimethylsilanolate in a variety of solvents (THF, DMF, DMAc, DME, DMSO) and at different temperatures gave less satisfactory results (Table 1). Aqueous lithium hydroxide required a larger excess of **7** for complete phosphonylation, presumably due to competing hydrolysis of the dimethyldiphosphonate. LiOTMS gave higher levels of by-products, perhaps resulting from multiple methylphosphonylation of the ECB. Entry 4 shows that treatment with excess base and excess dimethyldiphosphonate **7** gave the highest level of by-products (multiple peaks by HPLC), suggesting that these by-products are the result of indiscriminant reaction at other alcohol or secondary amide sites on the molecule. Lithium *t*-butoxide gave the highest yields and the lowest levels of by-products (entry 8).

The crude methylphosphonate diester was purified by silica gel chromatography (CH_2Cl_2/MeOH) to provide **1d**[14] in 71% yield (97% purity, HPLC). Hydrogenolytic debenzylation in 9:1 THF/DMF in the presence of triethylamine furnished methylphosphonate monoester **1e** in 82% yield and 96% purity.[7b] The use of triethylamine was critical to avoid side reactions caused by the liberated HBr.

3. Conclusions

We have developed a practical and reliable method for preparation of dimethyldiphosphonate **7**.[15] ECB analog **1c** was chemoselectively methylphosphonylated with **7** in the presence of lithium *t*-butoxide to afford methylphosphonate diester **1d**, which was further converted to the methylphosphonate monoester **1e**.

4. Experimental

4.1. General

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. DMF and THF were stored over 4 Å molecular sieves. For small-scale reactions (less than 20 g), THF was distilled from sodium benzophenone ketyl. Anhydrous *t*-butyl methyl ether (MTBE), and DME were obtained from Aldrich. Reactions using base or organometallic reagents were run under nitrogen. Reactions were monitored by HPLC using the conditions specified below. Thin layer chromatography (TLC) was done using Merck plates of Silica Gel 60 with a fluorescent indicator (F_{254}). ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded at 300, 75, and 121 MHz respectively, using $CDCl_3$ as solvent unless specified otherwise, except for the ECB compounds which required DMSO-d_6. NMR chemical shifts are reported in ppm with solvent as the internal standard on the δ scale and *J* values are in Hertz. IR, UV, and Mass Spec analyses were done by Eli Lilly Physical Chemistry Laboratory. HPLC conditions: 25 cm Zorbax R_X C18 column, 60:40 CH_3CN/H_2O, with 0.1% TFA in each, 230 nm for **2** and 280 nm for **1**, 1 mL/min flow rate. Preparatory HPLC conditions for **1c** and **1e**: HP20SS column by step gradient elution; solvent A—42:58 MeCN/0.1% HOAc at pH 5; solvent B—60:40 MeCN/0.1% HOAc at pH 5.

4.1.1. Di-[(4-bromophenyl)methyl] methylphosphonate (4). A solution of 4-bromobenzyl alcohol (22 g, 117.6 mmol) and 1*H*-tetrazole (0.34 g, 4.85 mmol) in Et_2O (300 mL) was cooled to 0°C under nitrogen and treated with diisopropylethylamine (24 mL, 137.8 mmol). A solution of methylphosphonic dichloride (8.7 g, 65.45 mmol) in Et_2O was added dropwise over 0.5 h while maintaining the temperature between 0 and 3.5°C with an ice-salt bath. The mixture was stirred at 0°C for 0.5 h and then at room temperature for 4 h until TLC (9:1 CH_2Cl_2/EtOAc) showed complete consumption of the alcohol. The precipitated salt was removed by suction filtration and rinsed with Et_2O. The filtrate was concentrated and redissolved in 10 mL of CH_2Cl_2. This was filtered through a sintered glass funnel of silica gel (68 g, packed with CH_2Cl_2) and eluted with 9.5:0.5 CH_2Cl_2/EtOAc to collect 22.7 g (89% yield) of **4**. R_f 0.43 (9:1 CH_2Cl_2/ EtOAc). IR ($CHCl_3$) 3420, 3005 cm^{-1}. ^{1}H NMR δ 1.47 (d, 3H, J=18 Hz), 4.92 (dd, 2H, J=9, 12 Hz), 4.98 (dd, 2H, J=9, 12 Hz), 7.19 (d, 4H, J=8 Hz), 7.46 (d, 4H, J=8 Hz). ^{1}H NMR (DMSO-d_6) δ 10.6 (d, J=140 Hz), 65.4 (d, J=6 Hz), 121.2, 129.7, 131.3, 136.1 (d, J=6 Hz). MS (FD$^+$) m/z 434. ^{31}P NMR (DMSO-d_6) δ 24.36. Anal. calcd for $C_{15}H_{15}BrO_3P$: C, 41.51; H, 3.48; Br, 36.82. Found: C, 41.31; H, 3.34; Br, 37.21.

4.1.2. Mono[(4-bromophenyl)methyl] methylphosphonate (6): from diester 4. *Note*. 4-Bromobenzyl iodide, the by-product of this reaction, is a strong lachrymator. A mixture of **4** (17 g, 39.16 mmol) and NaI (11.7 g, 78.06 mmol) in acetone (20 mL, dried over 4 Å molecular sieves) was heated at reflux for 5 h until TLC (9:1 CH_2Cl_2/EtOAc) showed complete consumption of **4**. The mixture was allowed to cool to room temperature and then suction filtered to collect the precipitated salt. The salt was transferred to a flask and slurried with acetone (20 mL) to break up the lumps and then refiltered. The solid was rinsed with acetone to remove all yellow color. The resulting white solid was dried under vacuum to obtain 10 g (88.9% yield) of sodium mono[(4-bromophenyl)methyl] methylphosphonate (**5**). IR ($CHCl_3$) 1489, 1307 cm^{-1}; ^{1}H NMR (D_2O) δ 1.29 (d, 3H, J=16 Hz), 4.87 (d, 2H, J=7 Hz), 7.36 (d, 2H, J=8 Hz), 7.59 (d, 2H, J=8 Hz). MS (FAB$^+$) m/z 287. Anal. calcd for $C_8H_9BrNaO_3P$: C, 33.48; H, 3.16. Found: C, 33.71; H, 3.11.

A solution of **5** (7 g, 24.38 mmol) in 35 mL of THF was cooled to 0°C and treated dropwise with 6 M HCl (4.2 mL, 25.2 mmol). The cooling bath was removed and the mixture stirred for 10 min. The precipitated NaCl was removed by filtration and the filtrate was concentrated. The resulting solid was taken up in CH_2Cl_2 and dried over Na_2SO_4. The solution was concentrated and dried under vacuum to obtain 6.8 g of a white solid. HPLC showed 96.3% uv purity. The solid was dissolved in warm EtOAc and filtered through a fritted disc to remove insoluble white particles. The filtrate was concentrated to remove half the volume. Hexanes were added to precipitate a white powder. The solid was collected by filtration, washed with 80:20 hexanes/EtOAc, and dried under vacuum to obtain 5.5 g of **6**. HPLC showed 99% uv purity and the spectral data was identical with the material prepared by the one step method below.

4.1.3. Mono[(4-bromophenyl)methyl] methylphosphonate (6): one-step method. Methyl phosphonic dichloride (**3**) (36.96 g, 0.28 mol) was rapidly poured into an oven-dried flask under N_2 and dissolved in 200 mL of CH_2Cl_2. The solution was cooled in an ice/H_2O bath and a solution of 4-bromobenzyl alcohol (49.4 g, 0.26 mol) and Et_3N (stored over KOH, 39 mL, 0.28 mol) in CH_2Cl_2 (150 mL) was added over 90 min using an addition funnel. HPLC 10 min after the addition was complete showed 78% **6**, 19% **4**, and 1.2% unreacted alcohol (little dimethyldiphosphonate formed upon quenching into acidic HPLC eluent). An additional 39 mL of Et_3N was added, followed by 20 mL of H_2O over 1 min. An exotherm up to 27°C occurred and then an additional 30 mL of H_2O was added over 5 min. HPLC showed 55% dimethyldiphosphonate **7**, 4.5% **6** and 20% **4**. The cooling bath was removed and the mixture was transferred to a separatory funnel and washed with 1N HCl (2×). To the organic layer was added 150 mL of 2N NaOH and 50 mL of H_2O and the mixture was stirred overnight to complete hydrolysis of the dimethyldiphosphonate. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (2×) to remove **4**. The aqueous layer was acidified with 22 mL of 12N HCl and extracted with 400 mL of CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to afford 53.74 g (78% crude yield) of a white solid. After EtOAc (110 mL) was added, the large chunks were broken with a spatula and the suspension was stirred vigorously for 3 h. The white solid was collected by filtration and dried overnight in a vacuum oven at 50°C to afford 48.72 g (71% yield) of **6**. IR ($CHCl_3$) 3600–3000, 1597 cm^{-1}; ^{1}H NMR δ 1.50 (d, 3H, J=18 Hz), 4.97 (d, 2H, J=8 Hz), 7.23 (d, 2H, J=8 Hz), 7.48 (d, 2H, J=8 Hz), 12.41 (br s, 1H); ^{1}H NMR (DMSO-d_6) δ 11.8 (d, J=148 Hz), 65.8 (d, J=6 Hz), 122.4, 129.4, 131.7, 135.2 (d, J=7 Hz). ^{31}P NMR δ 34.51. Anal. calcd for $C_8H_{10}BrO_3P$: C, 36.25; H, 3.80. Found: C, 36.55; H, 3.86.

4.1.4. Di-[(4-bromophenyl)methyl] dimethyldiphosphonate (7). Acid **6** (70 g, 261.1 mmol) and dicyclohexylcarbodiimide (DCC, 24.7 g, 132.8 mmol) were weighed into a flask and EtOAc (700 mL) and CH_2Cl_2 (140 mL) were added. The mixture was stirred for 1 h then the DCU was removed by filtration. The cake was rinsed with 135 mL of EtOAc and the filtrate was evaporated to a solid. Heptane (340 mL) was added and the mixture was stirred for 20 min to break up the large chunks. The solid was collected by filtration and rinsed with heptane. After drying in a vacuum oven, 64.2 g (95% yield) of **7** was isolated as a white solid (1:1 mixture of diastereomers, NMR data complicated). IR ($CHCl_3$) 3012, 1596 cm^{-1}. ^{1}H NMR δ 1.55–1.80 (m, 6H); 5.21–5.01 (m, 4H), 7.23 and 7.26 (d, 4H, J=8 Hz), 7.48 and 7.49 (d, 4H, J=8 Hz). ^{1}H NMR δ 12.00, 12.05, 12.09, 13.99, 14.04, 14.09, 67.05, 67.10, 67.15, 67.19, 122.80, 129.72, 129.80, 131.86, 134.61. ^{31}P NMR δ 24.20, 24.12. MS (FD$^+$) m/z=508, 509, 510, 511, 512, 513, 514, 515 for ^{79}Br and ^{81}Br combinations. Anal. calcd for $C_{16}H_{18}Br_2O_5P_2$: C, 37.53; H, 3.54. Found: C, 37.74; H, 3.59.

4.1.5. Preparation of dideoxy ECB 1c. A suspension of CH_2Cl_2 (0.77 L), **1a**[1] (0.235 kg, 0.207 mol, 1.0 equiv.), and triethylsilane (0.78 kg, 6.70 mol, 30 equiv.) was cooled to 16°C. Trifluoroacetic acid (0.978 kg, 8.56 mol, 35 equiv.) was added over 3 min via an addition funnel while maintaining the temperature at 20°C. After 1.5 h, the mixture was cooled to −5°C and diluted with THF (4.0 L). The mixture was poured into a solution of K_2CO_3 (0.862 kg, 8.62 mol, 38.5 equiv.) in 4.0 L of H_2O. The aqueous phase was discarded and the organic phase was stripped to dryness to afford 0.308 kg of crude **1c**. After correction for HPLC potency (61.7%), the yield from **1a** was 83.1%. An analytical sample was purified by HPLC chromatography. IR ($CHCl_3$) 1636, 1517 cm^{-1}. HRMS (FAB$^+$) m/z calcd for $C_{58}H_{74}N_7O_{15}$: 1108.5243, Found: 1108.5265. Anal. calcd for $C_{58}H_{73}N_7O_{15}$: C, 62.85; H, 6.63; N, 8.85. Found: C, 62.90; H, 6.49; N, 8.96.

4.1.6. Preparation of dideoxy ECB methylphosphonate diester 1d. A solution of **1c** (91% pure by HPLC, 5.3 g, 4.35 mmol) in DMF (13 mL) was added dropwise to a solution of *t*-BuOLi (95% pure, 0.43 g, 5.13 mmol) in DMF (13 mL). The mixture was stirred at room temperature for 20–30 min or until a homogeneous solution (dark brown) resulted. Upon cooling to 0°C, the dimethyldiphosphonate **7** (97.7% pure, 2.69 g, 5.13 mmol) in THF (26 mL) was added dropwise (0.4 mL/min). After the addition, the reaction was stirred at 0°C and monitored by HPLC until most of **1c** was consumed (1–2% remained). The mixture was quenched with 2 equiv. of acetic acid (based on amount of base used) and stirred at 0°C for 10–15 min. The mixture was poured into CH_3CN (133 mL) with stirring at room temperature. The reaction flask was rinsed with another 100 mL of CH_3CN. The precipitate was collected by filtration and dried under vacuum. The crude product was dissolved in methanol (10.5 mL) and the solution poured into water (133 mL) to re-precipitate the product. The precipitate was stirred vigorously for 10 min and filtered to obtain 4.6 g (84% yield, corrected for 87.7% HPLC potency) of **1d**. An analytical sample was purified by silica gel chromatography (85:15 CH_2Cl_2/MeOH). R_f 0.43 (90:10 CH_2Cl_2/MeOH). IR ($CHCl_3$) 1639, 1609, 1529 cm^{-1}. MS (FAB^+) *m/z* 1356. ^{31}P NMR (DMSO-d_6) δ 25.68.

4.1.7. Preparation of dideoxy ECB methylphosphonate monoester 1e. A solution of **1d** (97% pure, 100 mg, 0.08 mmol) in 90:10 THF/DMF (1.5 mL) was treated with triethylamine (0.03 mL, 0.22 mmol). The solution was hydrogenated for 3 h over 10% Pd–C (50 mg) at 1 atm of hydrogen. The catalyst was removed by filtration through a bed of celite and rinsed with THF (10 mL). The filtrate was concentrated at reduced pressure to remove THF. The residue was triturated with MeCN (10 mL) to give a white precipitate. The solid was filtered and rinsed twice with Et_2O (3 mL) to obtain 65 mg (74%) of **1e**. An analytical sample was purified by HPLC chromatography. IR (KBr) 1634, 1507, 1436 cm^{-1}. HRMS (FAB^+) *m/z* calcd for $C_{59}H_{77}N_7O_{17}P$: 1186.5114. Found: 1186.5139. ^{31}P NMR (DMSO-d_6) δ 20.93.

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8. Compound **8** is only observed by HPLC as monoester **6** following an aqueous quench. Selective formation of the desired phosphonate monoester has been reported using phenylphosphonic dichloride. With alkyl phosphonic dichlorides, variable success has been reported. See: (a) Zhao, K.; Landry, D. W. *Tetrahedron* **1993**, *49*, 363. Entries 8 and 9 in Table 1. (b) Yang, G.; Zhao, K.; Landy, D. W. *Tetrahedron Lett.* **1998**, *39*, 2449. Entries 3 and 4 in Table 1. (c) Mlodnosky, K. L.; Holmes, H. M.; Lam, V. Q.; Berkman, C. E. *Tetrahedron Lett.* **1997**, *38*, 8803.
9. Conversion of phosphonic chlorides to the diphosphonate with water is known. In our process, this results in a mixture of diphosphonate **7**, diester **4** and phosphonate monoester **6**. Due to instability of **7**, this mixture cannot be purified. See: Ohms, G.; Grossmann, G.; Schwab, B.; Schiefer, H. *Phosphorus Sulfur Silicon Relat. Elem.* **1992**, *68*, 77.
10. The process in path b is a significant improvement over path a and avoids the formation of 4-bromobenzyl iodide, a strong lachrymator. See: Zervas, L.; Kilaris, I. *J. Am. Chem. Soc.* **1955**, *77*, 5354.
11. Khorana, H. G.; Todd, A. R. *J. Am. Chem. Soc.* **1953**, 2257.
12. Diphosphonate **7** is stable to storage in a freezer for at least four months.
13. Initial studies of the phosphorylation of **1a** showed that lithium bases gave the fastest reaction, the order of reactivity being $Li^+ > Na^+ > K^+$. See Ref. 4.
14. Compound **1d** is a mixture of diastereomers, but the isomers are so similar that only one set of peaks is observed by ^1H, ^{13}C and ^{31}P NMR spectroscopy.
15. Although toxicity data for the phosphorus compounds

described here is not available, the toxicity of related esters have been recognized. Hence, all phosphorus esters should be handled with caution. O'Brien, R. D. *Toxic Phosphorus Esters. Chemistry, Metabolism, and Biological Effects*; Academic: London, 1960; See, for example, tetraethyl diphosphate in *The Merck Index*; 11th ed., 1989, p 1450.