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Domino functionalizations of the amino terminus of 6-aminopenicillanates with Ph_3PCCO

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Abstract—6-Aminopenicillanates, or the sulfoxides or the sulfones thereof, were *N*-acylated in a three-component reaction with an aldehyde and Ph_3PCCO to give the corresponding 6-(*E*-2′-alkenoyl)amides. This domino addition–Wittig alkenation sequence was extended by an additional Claisen rearrangement step in the side-chain in the case of **5g**.

A recent trend[1] in the chemistry and medicinal refinement of penicillins, complementing the quest for lactamase resistant 6-acylamino derivatives, are covalent conjugates of penams with other prominent drug targets or biochemical shuttle systems such as peptides,[2] or siderophoric catechols.[3] Hence new methods for the attachment of functionalized side-arms to the 6-amino group under conditions milder and more flexible than the conventional treatment with acyl halides/auxiliary base are still of interest. We have recently demonstrated the domino reaction of ketenylidenetriphenylphosphorane, $Ph_3P{=}C{=}C{=}O$ **1**, with amines and aldehydes to give α,β-unsaturated amides in good yields.[4] In this letter we evaluate the applicability of this one-pot approach to the *N*-acylation of esters[5] of 6-amino-penicillanic acid (6-APA) **2**.[6,7]

When a three-component mixture of the optically pure methyl ester (3*S*,5*R*,6*R*)-**3**[5a] of **2**, ylide **1** and an aldehyde was stirred at room temperature for 12–16 h, the corresponding *E*-α,β-unsaturated 6-acylaminopenicillanates **5** were obtained in yields ranging from 60% to 80% via the intermediate acyl ylides **4**, which are isolable in the absence of an aldehyde (Scheme 1). The sulfoxide **6**[5b] and sulfone **8**[5c] reacted analogously, albeit more slowly, furnishing the corresponding *E*-α,β-unsaturated 6-acylamino-1-oxo-penicillanates **7**/**9**.[8] Epimerization at C-3, C-5 or C-6, leading to new diastereoisomers was not detectable in any case by high resolution ^1H and ^{13}C NMR.

Compound **5** was alternatively prepared in two steps and similar yields from the ammonium salt of **3**[9] and **1** via the phosphonium salt **10**.[10] This was deprotonated with DBU at −30 °C to give the corresponding ylide **4** ($n = 0$), which was immediately treated with the respective aldehyde (Scheme 2). While an analogous phosphonium salt could be obtained from methyl 7-ammoniocephalosporanate, its deprotonation with a range of bases including DBU, $NaHCO_3$ and alumina (Al_2O_3), even in the presence of an aldehyde, led to concomitant partial isomerization[11] of the endocyclic C=C bond and gave mixtures of the corresponding Δ^2 and Δ^3 6-aminoacylcephalosporanates (at best 1:7 in the case of Al_2O_3/THF).

The above domino reactions can be extended by further pericyclic steps. For example, the catecholic penam derivative **5h** can be directly synthesized[12] from **1**, **3** and 2-(2′,4′-hexadienyloxy)-3-methoxy-benzaldehyde[13] by a domino acylylidation–Wittig alkenation–Claisen rearrangement reaction as shown in Scheme 3.

As a rule, antibiotic activity of penam derivatives requires a free 3-carboxylic acid functionality, which is best liberated in the last step by cleavage of esters such as benzhydryl,[14] benzyl[15] or *t*-butyl.[16] For instance, 6-amidopenicillanic acid **13**[17] was available in two steps and 40–50% overall yield by acidolysis of

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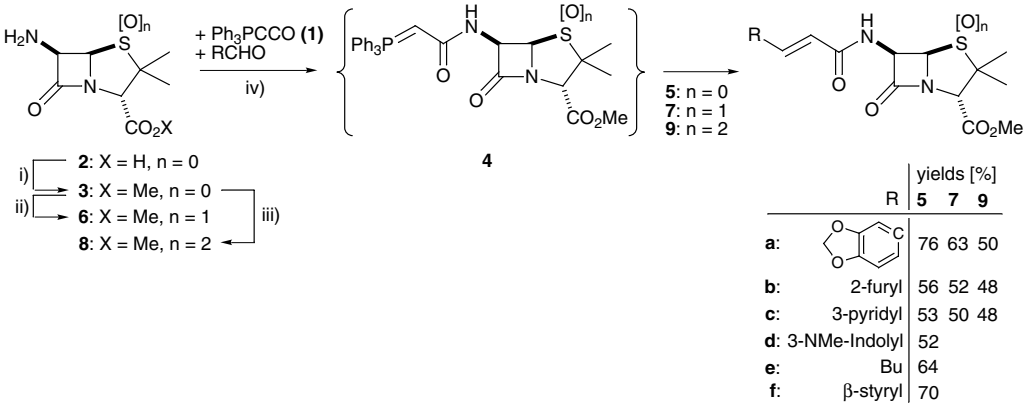
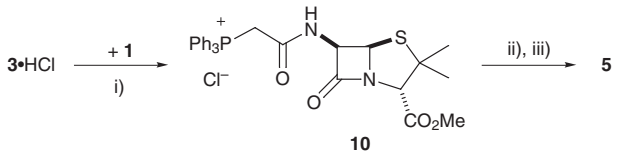


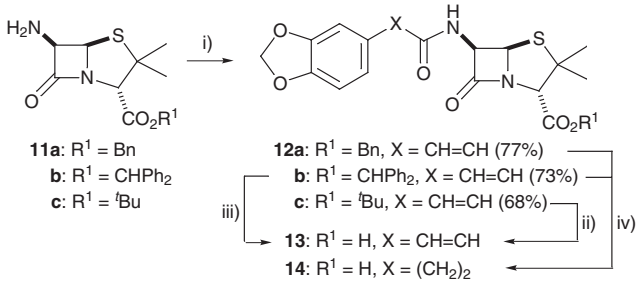
Scheme 1. Reagents and conditions: (i) CH_2N_2, CH_2Cl_2, rt, 95%; (ii) MeCN, *m*-CPBA, 0 °C, 30 min, 85%; (iii) MeCN, $KMnO_4/H_2SO_4$, −10 °C, 75%; (iv) THF, rt, 12–16 h.



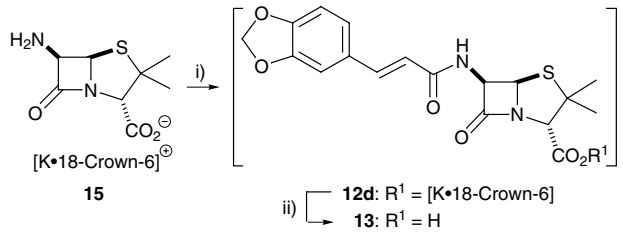
Scheme 2. Reagents and conditions: (i) C_6H_6/THF, rt, 8 h, 85%; (ii) CH_2Cl_2 + DBU, −30 °C; (iii) + RCHO, −30 °C rt, 8 h; 80–85%.

t-butyl ester **12c**[18] with formic acid or of benzhydryl ester **12b**[18] with trifluoroacetic acid/anisole.[19] **12b**, like the benzyl ester **12a**,[18] can alternatively be deprotected with $H_2/PdO(OH_2)$ with concomitant hydrogenation of the olefinic double bond in the newly attached side chain to yield 6-amidopenicillanic acid **14**[20] (Scheme 4).

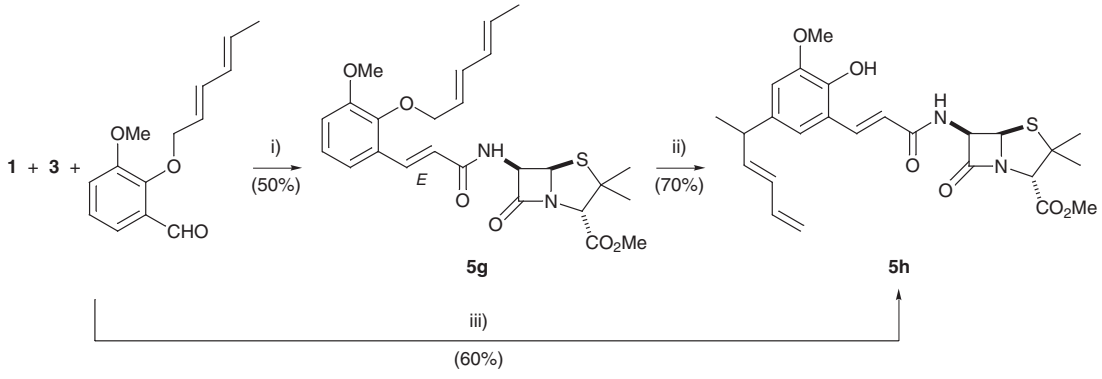
The necessity of protecting groups can be done away with altogether by employing soluble carboxylates of 6-APA **2** in the three-component reaction with **1** and aldehydes. The crown-ether complex **15**[21] of potassium 6-aminopenicillanate for one was reacted with **1** and piperonal in THF/dioxane solution at room temperature to furnish **13** in 50% yield after acidic hydrolysis[22] (Scheme 5).



Scheme 4. Reagents and conditions: (i) **1**, piperonal, THF, 60 °C, 12 h; (ii) THF/HCO_2H, 0 °C–rt, 30 min, 50%; (iii) CH_2Cl_2, anisole, F_3CCO_2H, 0 °C–rt, 45 min, 61%; (iv) H_2, 1 bar, EtOH/AcOEt, $PdO(H_2O)$, 24–48 h, 72%.



Scheme 5. Reagents and conditions: (i) **1**, piperonal, THF/dioxane 2:1, rt, pH 7–8 ($PhCO_2H$), 30 min; (ii) aq $NaHCO_3$ + HC1, 0 °C (50% overall).



Scheme 3. Reagents and conditions: (i) THF, 35 °C, 12 h; (ii) MeCN, 65 °C, 72 h; (iii) THF, 65 °C, 60 h.

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5. (a) Compound **3** (5.10 g, 95%) from 6-APA **2** (5.0 g, 23.1 mmol) and CH_2N_2 (1.5 equiv) in Et_2O/CH_2Cl_2; mp 48–50 °C; ν_{max} (film)/cm^{-1} 3391, 2965, 1777, 1700; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.45 (3H, s), 1.61 (3H, s), 2.79 (2H, br, NH_2), 3.72 (3H, s), 4.36 (1H, s), 4.59 (1H, d, ^3J 5.7 Hz) 5.44 (1H, d, ^3J 5.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.9, 31.3, 52.3, 62.7, 63.8, 69.6, 69.8, 168.5, 177.7; (b) Micetich, R. G.; Singh, R.; Shaw, C. *J. Org. Chem.* **1986**, *51*, 1811–1815; (c) Bos, J. J.; Cuperus, R.; Wielinga, R. Eur. Patent Appl. 0213685 A1, 1987; CAS 88209-17-0.
6. Compound **5a** from **1**, **3** and piperonal—typical procedure: **1** (610 mg, 2.02 mmol), **3** (460 mg, 2.00 mmol), piperonal (315 mg, 2.10 mmol) and dry THF (30 mL) was stirred at rt for 12 h. The solvent was removed and the residue was purified by column chromatography (silica gel 60; cyclohexane/ethyl acetate, 2:1, v/v; R_f 0.33); yield: 606 mg (76%), mp 76 °C; ν_{max} (KBr)/cm^{-1} 1784, 1741, 1664, 1621; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.39 (3H, s), 1.55 (3H, s), 3.67 (3H, s), 4.34 (1H, s), 5.50 (1H, d, ^3J 4.1 Hz), 5.75 (1H, dd, ^3J 4.1, 7.7 Hz), 5.87 (2H, s), 6.29 (1H, d, ^3J 15.4 Hz), 6.67 (1H, d, ^3J 7.7 Hz), 6.80–7.00 (3H, m), 7.48 (1H, d, ^3J 15.4 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 26.8, 30.6, 52.2, 59.5, 64.2, 67.7, 70.1, 101.5, 106.5, 108.5, 118.8, 123.6, 128.8, 140.2, 148.0, 148.8, 165.1, 168.0, 173.8; *m/z* (EI) 404 (M^+, 1%), 308 (20%), 175 (29%), 174 (100%).
7. Compound **5b**: mp 67 °C; ^{1}H NMR ($CDCl_3$): δ 1.45 (3H, s), 1.61 (3H, s), 3.74 (3H, s), 4.41 (1H, s), 5.56 (1H, d, ^3J 4.3 Hz), 5.82 (1H, dd, ^3J 4.3, 8.8 Hz), 6.35 (1H, d, ^3J 15.2 Hz), 6.40–6.45 (1H, m), 6.55 (1H, d, ^3J 3.2 Hz), 6.62 (1H, d, ^3J 8.8 Hz), 7.40 (1H, d, ^3J 15.2 Hz), 7.43 (1H, d, ^3J 4.3 Hz); ^{13}C NMR (DMSO-d_6): δ 26.6, 30.4, 52.5, 58.7, 64.1, 68.0, 70.1, 112.5, 114.6, 117.8, 133.4, 144.3, 150.8, 164.8, 167.9, 173.6. Compound **5c**: mp 74 °C; ^{1}H NMR ($CDCl_3$): δ 1.42 (3H, s), 1.55 (3H, s), 3.70 (3H, s), 4.35 (1H, s), 5.54 (1H, d, ^3J 4.2 Hz), 5.78 (1H, dd, ^3J 4.2, 8.6 Hz), 6.62 (1H, d, ^3J 15.7 Hz), 7.15–7.25 (1H, m), 7.58 (1H, d, ^3J 15.7 Hz), 7.61 (1H, d, ^3J 8.6 Hz), 7.65–7.70 (1H, m), 8.45–8.50 (1H, m), 8.66 (1H, s, br); ^{13}C NMR (DMSO-d_6): δ 26.9, 31.1, 52.3, 58.8, 64.6, 67.6, 70.5, 121.5, 123.6, 130.3, 134.4, 138.8, 149.1, 150.4, 164.6, 168.0, 173.7. Compound **5d**: mp 82 °C; ^{1}H NMR ($CDCl_3$): δ 1.42 (3H, s), 1.58 (3H, s), 3.76 (3H, s, OMe), 3.79 (3H, s, NMe), 4.43 (1H, s), 5.58 (1H, d, ^3J 4.1 Hz), 5.67 (1H, d, ^3J 12.4 Hz), 5.86 (1H, dd, ^3J 4.1, 9.0 Hz), 6.42 (1H, d, ^3J 9.0 Hz), 7.13 (1H, d, ^3J 12.4 Hz), 7.10–7.35 (3H, m), 7.60–7.70 (1H, m), 8.69 (1H, s); ^{13}C NMR ($CDCl_3$): δ 27.0, 31.3, 33.1, 52.4. 58.7, 64.6, 68.2, 70.5, 109.6, 110.0, 112.6, 117.8, 120.5, 122.2, 128.9, 132.9, 135.1, 136.4, 166.3, 168.2, 174.5. Compound **5e**: mp 59 °C; ^{1}H NMR ($CDCl_3$): δ 0.87 (3H, t, ^3J 8.1 Hz), 1.20–1.45 (4H, m), 1.47 (3H, s), 1.63 (3H, s), 2.10–2.25 (2H, m), 3.75 (3H, s), 4.41 (1H, s), 5.53 (1H, d, ^3J 3.9 Hz), 5.70–5.85 (2H, m), 6.20 (1H, d, ^3J 8.2 Hz), 6.89 (1H, dt, ^3J 15.0, 7.4 Hz); ^{13}C NMR ($CDCl_3$): δ 13.9, 22.3, 27.2, 30.2, 31.5, 31.9, 52.5, 58.6, 64.9, 68.2, 70.6, 122.2, 147.6, 165.2, 168.2, 174.3. Compound **5f**: mp 73 °C; ^{1}H NMR ($CDCl_3$): δ 1.48 (3H, s), 1.65 (3H, s), 3.75 (3H, s), 4.42 (1H, s), 5.57 (1H, d, ^3J 4.3 Hz), 5.63 (1H, dd, ^3J 4.3, 9.1 Hz), 6.01 (1H, d, ^3J 14.7 Hz), 6.44 (1H, d, ^3J 9.1 Hz), 6.80–6.90 (2H, m), 7.20–7.45 (6H, m); ^{13}C NMR ($CDCl_3$): δ 27.2, 31.5, 52.5, 58.8, 64.9, 68.3, 70.7, 122.2, 126.1, 127.2, 128.8, 136.1, 140.5, 143.1, 165.4, 168.3, 174.2. Compound **5g**: mp 66 °C; ^{1}H NMR($CDCl_3$): δ 1.45 (3H, s), 1.61 (3H, s), 1.69 (3H, d, ^3J 6.6 Hz), 3.73 (3H, s), 3.80 (3H, s), 4.41 (1H, s), 4.47 (2H, d, ^3J 6.4 Hz), 5.55 (1H, d, ^3J 4.3 Hz), 5.60–5.75 (2H, m), 5.83 (1H, dd, ^3J 4.3, 9.1 Hz), 5.95–6.10 (1H, m), 6.10–6.25 (1H, m), 6.51 (1H, d, ^3J 15.8 Hz), 6.52 (1H, d, ^3J 9.1 Hz), 6.80–6.90 (1H, m), 6.95–7.15 (2H, m), 7.90 (1H, d, ^3J 15.8 Hz); ^{13}C NMR ($CDCl_3$): δ 18.0, 26.7, 31.2, 52.3, 55.7, 58.6, 64.6, 68.1, 70.4, 73.8, 113.6, 119.1, 120.5, 121.7, 123.9, 125.4, 127.5, 130.6, 134.2, 137.9, 147.0, 153.1, 165.3, 168.1, 174.0. Satisfactory microanalyses (C, 0.2; H, 0.1; N, 0.1) were obtained for **5a**–**g**.
8. Compounds **7** or **9** were obtained from **1**, the respective aldehyde and sulfoxide **6**[5b] or sulfone **8**,[5c] respectively, following the protocol described for the synthesis of **5** (Ref. 7). Compound **7a**: mp 98 °C; ^{1}H NMR ($CDCl_3$): δ 1.14 (3H, s), 1.64 (3H, s), 3.74 (3H, s), 4.63 (1H, s), 5.04 (1H, d, ^3J 4.7 Hz), 5.90 (2H, s), 6.12 (1H, dd, ^3J 4.7, 10.1 Hz), 6.21 (1H, d, ^3J 15.4 Hz), 6.70 (1H, d, ^3J 7.9 Hz), 6.85–6.95 (2H, m), 7.23 (1H, d, ^3J 10.1 Hz), 7.47 (1H, d, ^3J 15.4 Hz); ^{13}C NMR (DMSO-d_6): δ 17.9, 18.9, 52.8, 55.3, 65.6, 74.7, 76.3, 101.5, 106.3, 108.5, 118.9, 124.0, 129.1, 140.8, 148.0, 148.9, 165.1, 168.3, 174.3. Compound **7b**: mp 91 °C; ^{1}H NMR ($CDCl_3$): δ 1.19 (3H, s), 1.66 (3H, s), 3.76 (3H, s), 4.64 (1H, s), 5.05 (1H, d, ^3J 4.5 Hz), 6.13 (1H, dd, ^3J 4.5, 10.1 Hz), 6.28 (1H, d, ^3J 15.3 Hz), 6.35–6.43 (1H, m), 6.53 (1H, d, ^3J 3.0 Hz), 7.23 (1H, d, ^3J 10.1 Hz), 7.36 (1H, d, ^3J 15.3 Hz), 7.40 (1H, d, ^3J 1.7 Hz); ^{13}C NMR (DMSO-d_6): δ 18.7, 19.4, 53.0, 56.6, 66.4, 75.3, 76.9, 112.3, 114.7, 117.1, 129.6, 144.6, 151.0, 165.4, 168.4, 173.9. Compound **7c**: mp 96 °C; ^{1}H NMR ($CDCl_3$): δ 1.18 (3H, s), 1.67 (3H, s), 3.76 (3H, s), 4.65 (1H, s), 5.09 (1H, d, ^3J 4.5 Hz), 6.13 (1H, dd, ^3J 4.5, 9.9 Hz), 6.52 (1H, d, ^3J 15.6 Hz), 7.35–7.55 (2H, m), 7.59 (1H, d, ^3J 15.6 Hz), 7.70–7.80 (1H, m), 8.45–8.55 (1H, m), 8.68 (1H, s); ^{13}C NMR ($CDCl_3$): δ 18.7, 19.4, 53.1, 56.6, 60.4, 66.4, 77.0, 121.8, 123.9, 130.4, 134.6, 139.1, 149.4, 150.4, 164.8, 168.3, 173.6. Compound **9a**: mp 95 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 1.39 (3H, s), 1.60 (3H, s), 3.80 (3H, s), 4.55 (1H, s), 4.83 (1H, d, ^3J 4.7 Hz), 5.98 (2H, s), 6.25 (1H, d, ^3J 15.4 Hz), 6.28 (1H, dd, ^3J 4.7, 10.2 Hz), 6.77 (1H, d, ^3J 7.9 Hz), 6.95–7.10 (3H, m), 7.57 (1H, d, ^3J 15.4 Hz); ^{13}C NMR ($CDCl_3$): δ 17.7, 20.2, 53.1, 57.3, 63.8, 64.8, 66.1, 101.5, 106.5, 108.5, 116.7, 124.5, 128.6, 143.4, 148.3, 149.6, 165.5, 167.1, 174.2. Compound **9b**: mp 96 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 1.36 (3H, s), 1.56 (3H, s), 3.78 (3H, s), 4.53 (1H, s), 4.82 (1H, d, ^3J 4.6 Hz), 6.25 (1H, dd, ^3J 4.6,10.2 Hz), 6.32 (1H, d, ^3J 15.3 Hz), 6.41 (1H, dd, ^3J 1.5, 3.2 Hz), 6.56 (1H, d, ^3J 3.2 Hz), 7.11 (1H, d, ^3J 10.2 Hz), 7.41 (1H, d, ^3J 15.3 Hz), 7.42 (1H, d, ^3J 1.5 Hz); ^{13}C NMR ($CDCl_3$): δ 17.6, 20.1, 53.1, 57.1, 63.7, 64.6, 66.0, 112.2, 114.9, 116.3, 129.9, 144.6, 150.7, 165.4, 167.1, 174.1. Compound **9c**: mp 98 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 1.35 (3H, s), 1.55 (3H, s), 3.77 (3H, s), 4.51 (1H, s), 4.84 (1H, d, ^3J 4.6 Hz), 6.23 (1H, dd, ^3J 4.6, 10.2 Hz), 6.55 (1H, d, ^3J 15.7 Hz), 7.25–7.40 (2H, m), 7.55 (1H, d, ^3J 15.7 Hz), 8.00–8.10 (1H, m), 8.45–8.55 (1H, m), 8.65 (1H, s); ^{13}C NMR ($CDCl_3$): δ 17.6, 20.1, 53.0, 57.1, 63.7, 64.7, 65.9, 121.0, 124.0, 130.4, 134.3, 139.7, 149.4, 150.6, 164.7, 167.0, 173.7. Satisfactory microanalyses (C, 0.2; H, 0.1; N, 0.1) were obtained for all compounds.
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10. Compound **10**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.40 (3H, s), 1.68 (3H, s), 3.70 (3H, s), 4.41 (1H, s), 5.27 (1H, dd, ^2J 15.8, 13.8 Hz), 5.28 (1H, dd, ^3J 4.2, 7.5 Hz), 5.35 (1H, d, ^3J 4.2 Hz), 5.52 (1H, dd, ^2J 15.8, 14.2 Hz), 7.60–7.90 (15H, m); 10.40 (1H, d, ^3J 7.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.8, 31.7, 32.3, 52.2, 60.0, 64.6, 67.1, 70.4, 118.3, 133.2, 134.3, 134.9, 163.4, 168.5, 171.6. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 21.7.
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12. Compound **5h** (583 mg, 60%) from **1** (610 mg, 2.02 mmol), **3** (460 mg, 2.00 mmol) and 2-(2′,4′-hexadienyloxy)-3-methoxy-benzaldehyde[13] (490 mg, 2.10 mmol); mp 79 °C; ν_{max} (KBr)/cm^{-1} 1784, 1751, 1665; ^{1}H NMR ($CDCl_3$): δ 1.32 (3H, d, ^3J 5.1 Hz), 1.47 (3H, s), 1.65 (3H, s), 3.35–3.50 (1H, m), 3.75 (3H, s), 3.85 (3H, s), 4.43 (1H, s), 4.99 (1H, dd, ^3J 10.1, ^2J 1.5 Hz), 5.11 (1H, dd, ^3J 16.9, ^2J 1.5 Hz), 5.56 (1H, d, ^3J 4.2 Hz), 5.90–5.73 (2H, m), 6.10–5.95 (1H, m), 6.35–6.20 (1H, m), 6.42 (1H, d, ^3J 9.1 Hz), 6.66 (1H, d, ^4J 1.6 Hz), 6.67 (1H, d, ^3J 15.8 Hz), 6.83 (1H, d, ^4J 1.6 Hz), 7.79 (1H, d, ^3J 15.8 Hz); ^{13}C NMR ($CDCl_3$): δ 21.0, 27.1, 31.3, 41.7, 52.3, 56.2, 58.7, 64.7, 68.2, 70.6, 111.0, 115.8, 120.1, 120.3, 120.4, 129.6, 136.8, 137.0, 138.6, 139.2, 143.8, 146.7, 165.8, 168.2, 174.5; *m/z* (EI) 486 (M$^+$, 8%), 298 (10%), 229 (8%), 174 (100%).
13. Synthesis of 2-(2′,4′-hexadienyloxy)-3-methoxy-benzaldehyde: a suspension of *o*-vanillin (4.50 g, 29.6 mmol), (*E*-2,*E*-4)-hexadienyl bromide (4.77 g, 29.6) and K_2CO_3 (5.52 g, 40.0 mmol) in DMF (30 mL) was vigorously stirred at rt for 12 h. Toluene (150 mL) and water (50 mL) were added and the pH was adjusted to 11–12 with 0.1 M aqueous NaOH. The organic phase was separated, neutralized with satd $NaHCO_3$ solution and concentrated to leave a yellow oil. Purification (silica gel 60; cyclohexane/ethyl acetate, 10:1, v/v; R_f 0.50) gave 4.55 g (66 %) of a pale yellow solid, mp 42 °C.
14. (a) Petrusson, S.; Walley, S. G. *Tetrahedron* **1983**, *39*, 2465–2468; (b) Micetich, R.; Singh, R. *Synthesis* **1985**, 693–695; (c) Smyth, T. P.; O'Donnel, M. E.; O'Connor, M. J.; St Ledger, J. O. *J. Org. Chem.* **1998**, *63*, 7600–7618.
15. Hamilton, C. S.; Yasuhara, A.; Baldwin, J. E.; Lloyd, M. D.; Rutledge, P. *J. Bioorg. Med. Chem. Lett.* **2001**, 2511–2514.
16. Veinberg, G.; Vorona, M.; Musel, D.; Grigan, N.; Lukevics, E. *J. Chem. Res.* **1999**, 270–271.
17. Compound **13**: colourless solid of mp 149–150 °C; ν_{max}/cm^{-1} 3336, 2959, 1734, 1664, 1616; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.35 (3H, s), 1.62 (3H, s), 4.10 (1H, s, 3-H), 5.08 (1H, d, ^3J 4.3 Hz, 5-H), 5.42 (1H, dd, ^3J 4.3, 8.8 Hz, 6-H), 5.95 (2H, s), 6.41 (1H, d, ^3J 15.6 Hz), 6.50 (1H, d, ^3J 8.8 Hz), 6.72 (1H, d, ^3J 8.1 Hz), 6.90 (1H, d, ^3J 8.1 Hz), 6.96 (1H, s), 7.54 (1H, d, ^3J 15.6 Hz), 8.12 (1H, br, OH); ^{13}C NMR (68 MHz, $CDCl_3$): δ 26.3, 26.5, 55.8, 56.1, 63.6, 73.1, 101.5, 106.4, 108.5, 117.7, 124.2, 129.0, 142.2, 148.2, 149.3, 166.9, 170.4, 170.7.
18. Compound **12a** (1.59 g, 3.40 mmol, 77%) from **11a** (1.32 g, 4.30 mmol), **1** (1.33 g, 4.40 mmol) and piperonal (0.68 g, 4.50 mmol); R_f 0.50 (cyclohexane/ethyl acetate, 1:1); pale yellow solid of mp 91 °C; ν_{max}/cm^{-1} 1782, 1746, 1675, 1624, 1491, 1250; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (3H, s), 1.61 (3H, s), 4.50 (1H, s), 5.15 (2H, s, CH_2Ph), 5.56 (1H, d, ^3J 4.2 Hz), 5.81 (1H, dd, ^3J 4.2, 9.1 Hz), 5.96 (2H, s), 6.24 (1H, d, ^3J 15.8 Hz), 6.37 (1H, d, ^3J 9.1 Hz), 6.73 (1H, d, ^3J 7.5 Hz), 6.96 (1H, d, ^3J 7.5 Hz), 6.98 (1H, s), 7.20–7.35 (5H, m), 7.54 (1H, d, ^3J 15.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.0, 31.6, 58.7, 64.9, 67.5, 69.1, 70.5, 101.5, 106.4, 108.5, 116.9, 124.4, 128.7, 128.7, 128.8, 130.0, 134.7, 142.8, 148.3, 149.4, 165.3, 167.5, 174.1; *m/z* (EI) 480 (M$^+$, 18%), 250 (50%), 175 (88%), 91 (100%). Compound **12b** (2.14 g, 3.83 mmol, 73%) from **11b** (2.00 g, 5.25 mmol), **1** (1.68 g, 5.51 mmol) and piperonal (0.87 g, 5.78 mmol); R_f 0.65 (cyclohexane/ethyl acetate, 1:1); pale yellow solid of mp 133–135 °C; ν_{max}/cm^{-1} 1781, 1741, 1658, 1616, 1489, 1245; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (3H, s), 1.62 (3H, s), 4.53 (1H, s), 5.60 (1H, d, ^3J 4.3 Hz), 5.85 (1H, dd, ^3J 4.3, 9.0 Hz), 5.95 (2H, s), 6.26 (1H, d, ^3J 15.5 Hz), 6.45 (1H, d, ^3J 9.0 Hz), 6.76 (1H, d, ^3J 7.7 Hz), 6.93 (1H, s, $CHPh_2$), 6.95 (1H, d, ^3J 7.7 Hz), 6.98 (1H, s), 7.25–7.45 (10H, m), 7.57 (1H, d, ^3J 15.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.7, 31.9, 58.0, 65.0, 68.4, 70.5, 78.4, 101.4, 106.4, 108.5, 116.9, 124.3, 126.9, 127.5, 128.1, 128.4, 128.5, 128.6, 128.7, 138.9, 139.0, 165.2, 166.7, 173.9; *m/z* (EI) 556 (M$^+$, 13%), 382 (10%), 230 (20%), 175 (98%), 168 (50%), 167 (100%). Compound **12c** (1.13 g, 2.50 mmol, 68%) from **11c** (1.00 g, 3.68 mmol), **1** (1.12 g, 3.70 mmol) and piperonal (0.57 g, 3.80 mmol); R_f 0.55 (cyclohexane/ethyl acetate, 2:1); pale yellow solid of mp 65 °C; ν_{max}/cm^{-1} 1783, 1737, 1671, 1624, 1490, 1248; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (9H, s, CMe_3), 1.55 (3H, s), 1.62 (3H, s), 4.30 (1H, s), 5.56 (1H, d, ^3J 4.4 Hz), 5.83 (1H, dd, ^3J 4.4, 9.2 Hz), 5.95 (2H, s), 6.23 (1H, d, ^3J 15.5 Hz), 6.25 (1H, d,^3J 9.2 Hz), 6.76 (1H, d, ^3J 7.7 Hz), 6.95 (1H, d, ^3J 7.7 Hz), 6.98 (1H, s), 7.58 (1H, d, ^3J 15.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.9, 28.0, 32.1, 58.6, 64.7, 68.2, 70.9, 83.1, 101.5, 106.4, 108.5, 117.0, 124.3, 128.4, 142.8, 148.3, 149.5, 165.2, 166.7, 174.0; *m/z* (EI) 446 (M$^+$, 10%), 316 (30%), 175 (78%), 160 (100%).
19. Hakimelahi, G. H.; Shia, K.-S.; Xue, C.; Hakimelahi, S.; Moosavi-Movahedi, A. A.; Saboury, A. A.; Soltani-Rad, M. M.; Osyetrov, V.; Wang, K.-P.; Liao, J. H.; Luo, F.-T. *Bioorg. Med. Chem.* **2002**, *10*, 3489–3498.
20. Compound **14**: colourless solid of mp 152–154 °C; ν_{max}/cm^{-1} 3330, 2955, 1728, 1650, 1615, 1499; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.32 (3H, s), 1.59 (3H, s), 2.45–2.55 (2H, m, $COCH_2$), 2.80–2.90 (2H, m), 4.08 (1H, s, 3-H), 5.10 (1H, d, ^3J 4.3 Hz, 5-H), 5.44 (1H, dd, ^3J 4.3, 9.0 Hz, 6-H), 5.96 (2H, s), 6.45 (1H, d, ^3J 9.0 Hz), 6.72 (1H, d, ^3J 7.9 Hz), 6.90 (1H, d, ^3J 7.9 Hz), 6.94 (1H, s), 8.10 (1H, br, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0, 26.4, 33.1, 37.8, 56.1, 56.5, 63.3, 73.2, 101.7, 106.2, 108.4, 124.0, 129.2, 148.2, 149.4, 166.8, 170.0, 170.5.
21. Compound **15**: colourless solid of mp 138 °C; ν_{max}/cm^{-1} 3454, 2896, 1758, 1630, 1614, 1473, 1350; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63 (6H, s, 2Me), 2.25 (2H, br, NH_2), 3,62 (24H, s, crown ether), 4.23 (1H, s, 3-H), 4.38 (1H, d, ^3J 6.1 Hz, 5-H), 5.59 (1H, d, ^3J 6.1 Hz, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.9, 33.2, 62.0, 64.3, 69.3, 70.2, 73.5, 172.2, 177.9.
22. Crude **12d** was pre-purified by column chromatography (silica gel 60; chloroform/ethyl acetate/methanol 3:1:1.5, v/v/v, R_f 0.45) and dissolved in sat. aqueous $NaHCO_3$. The free acid **13** was precipitated by addition of diluted aqueous HCl at 0 °C and extracted with ethyl acetate.