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α-Acylaminophosphonates possessing epoxyisoindolone moiety

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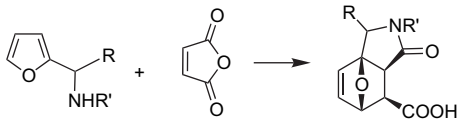
Abstract—α-Acylaminophosphonates possessing an epoxyisoindolone moiety were prepared with good stereoselectivity (de≥80%) by a tandem acylation/[4+2]-cycloaddition reaction between maleic anhydride and α-aminophosphonates derived from a furfurylamine. The cycloaddition products have an opposite orientation of epoxy and phosphonate groups, which was confirmed by NMR spectroscopy and X-ray crystal structure analysis.

1. Introduction

Amino- and hydroxyphosphonates are important biologically active compounds and useful intermediates in organic synthesis.[1,2] Many of these compounds have attracted attention because of their antibacterial, antiviral, antibiotic, pesticidal, anticancer and enzyme inhibitory properties.[3,4]

Several amino- and hydroxyphosphonates are used in clinics for treating different diseases (alaphospholine, phosphomycin, bis-phosphonate derivatives of AZT and others),[1,2b,c] while some functionalized phosphonates are used as intermediates in the synthesis of penicillin.[5] Therefore the synthesis of new types of functionalized phosphonic acids and their derivatives is an interesting problem.

The interest in both natural and synthetic phosphonic acids led us to reconsider the preparation of heterocyclic aminophoshonates through cycloaddition reactions. It is known that *N*-substituted furfurylamines easily react with acylating dienophiles, such as maleic anhydride, through a tandem acylation/[4+2]-cycloaddition reaction. The tricyclic epoxyisoindolone system is formed via an initial N-acylation followed by intramolecular Diels–Alder reaction (Scheme 1).[6]



Scheme 1. Tandem acylation/[4+2]-cycloaddition reaction.

Keywords: α-Aminophosphonates; Epoxyisoindolones; Tandem acylation/[4+2]-cycloaddition reaction.
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These products are used as starting compounds for the synthesis of [1,2]-isoindolo condensed heterocycles,[7] and especially for the synthesis of such important biologically active compounds as isoindolobenzazepine alkaloids.[8]

Continuing with our interest in the chemistry of phosphonic acid derivatives,[9] we report here the synthesis of epoxyisoindolyl phosphonates employing the cycloaddition reaction of maleic anhydride with α-aminophosphonates derived from a furfurylamine. These compounds can be used as intermediates for the synthesis of biomedical compounds. Moreover cyclic α-aminophosphonates possessing the epoxyisoindolone moiety are interesting from a viewpoint of biological activity because the analogous tricyclic nitrogen heterocycles possess high antipsychotic and antidyskinetic activity.[6a]

2. Results and discussion

The initial α-aminophosphonates bearing a furfurylamine fragment could be easily prepared by the Kabachnik–Fields reaction.[10] Addition of dimethyl phosphite to Schiff bases **1** and **2** led to the formation of isomeric α-aminophosphonates **3** and **4**, which were isolated and purified as oxalate salts (Table 1).[11]

Next, these α-aminophosphonates **3** and **4** (in the form of free base) underwent tandem acylation/[4+2]-cycloaddition with maleic anhydride. Reaction was carried out by stirring the reaction mixture in toluene at ambient temperature for 3 days. Products **5** and **6** were isolated in good yields (70–90%) as colourless solids (Scheme 2). Data for compounds **5** and **6** are shown in Table 2.

Tandem acylation/[4+2]-cycloaddition reaction proceeded with exclusive formation of the Diels–Alder *exo*-adducts **5**

Table 1. Oxalates of α-aminophosphonates **3** and **4** (Scheme 2)

Compound	R	Yield (%)	Mp (°C)	δ_H (ppm)/J^b (Hz)				δ_P [c] (ppm)
				OCH	NCH	PCH	Furyl	Ar	
3a	Ph	45	102–104	3.44/10.2; 3.64/10.5	3.46/14.5; 3.70/14.5	4.11/21.0	6.20/3.1; 6.38/3.1, 1.8; 7.57/0.9	7.27–7.43	26.0
3b	4-FC_6H_4	66	122–124	3.47/10.5; 3.64/10.5	3.46/14.0; 3.68/14.0	4.11/20.7	6.19/3.2; 6.36/3.2, 1.9; 7.53	7.18/9.0; 7.45/9.0, 5.5; 2.2	26.0
3c	Piperonyl[a]	79	113–114	3.47/10.6; 3.64/10.6; 6.04	3.46/14.2; 3.69/14.2	4.04/21.0	6.22/3.3; 6.39/3.3, 1.8; 7.58/0.8	6.85/8.0; 6.91/8.0; 7.03/1.0	26.1
3d=4d	2-Furyl	45	102–103	3.53/10.5; 3.67/10.5	3.52/14.5; 3.74/14.5	4.20/22.2	6.23/3.1; 6.38/3.1, 1.8; 6.45–6.50; 7.57/1.8; 7.69/3.1, 1.4	—	23.6
4a	Ph	65	120–122	3.52/10.5; 3.69/10.8	3.53/13.5; 3.78/13.5	4.17/22.5	6.46–6.51; 7.67/3.2, 1.8	7.20–7.37	23.8
4b	4-FC_6H_4	65	104–106	3.53/10.5; 3.69/10.5	3.52/13.8; 3.76/13.8	4.15/22.2	6.45–6.50; 7.66	7.13/8.8; 7.31/8.8, 5.7	23.8
4c	Piperonyl[a]	93	135–137	3.52/10.5; 3.68/10.0 5.98	3.44/14.3; 3.69/14.3	4.15/21.9	6.45–6.50; 7.66	6.70/8.2; 6.83/8.2; 6.86	23.8
4e	H	62	96–98	3.58/10.8; 3.72/10.8	2.32	4.63/20.7	6.52/3.1, 1.8; 6.57/3.1; 7.74	—	21.4

[a] 3,4-(Methylenedioxy)phenyl.
[b] ^{1}H NMR (300 MHz, DMSO-d_6)/J (Hz).
[c] ^{31}P NMR (81 MHz, DMSO-d_6).

and **6** that was confirmed by evaluation of spin–spin coupling constants of hydrogen atoms of oxabicycloheptene moiety. The ^{1}H NMR spectra showed a doublet at δ 2.49–2.61 ppm, J^b_H=9.0–9.3 Hz for the *endo*-H_b proton (*exo*-H_b proton would disclose a double doublet, J^b_H=8.5–10 Hz and J^b_H=1.5–2 Hz). Such stereoselectivity was described for tetrahydroepoxyisoindolones not containing phosphonate group.[6c]

exo-Epoxyisoindolyl phosphonates **5** were isolated as a mixture of two diastereomers derived from the two chiral elements: the bridged system and carbon atom α to the phosphonate (Scheme 3). The diastereomeric ratio varied depending on the reaction conditions, though in general, was ~40:60. Attempts to separate them by crystallization were unsuccessful.

Contrary to our expectations, isomeric compounds **6** were formed with the major diastereomer having the opposite orientation of epoxy and phosphonate groups (Fig. 1). The biggest content (11%) of minor diastereomer, in which these groups are unidirectional, was found for compound **6e**. Probably such stereoselectivity is a consequence of a steric effect of the phosphonate group in the transition state geometry of the cycloaddition reaction. The major diastereomer of compounds **6** was isolated in a pure state by crystallization from appropriate solvent.

The relative stereochemistry of the major diastereomer of compounds **6** was confirmed by a single-crystal X-ray analysis of a representative compound **6e** (Fig. 1).

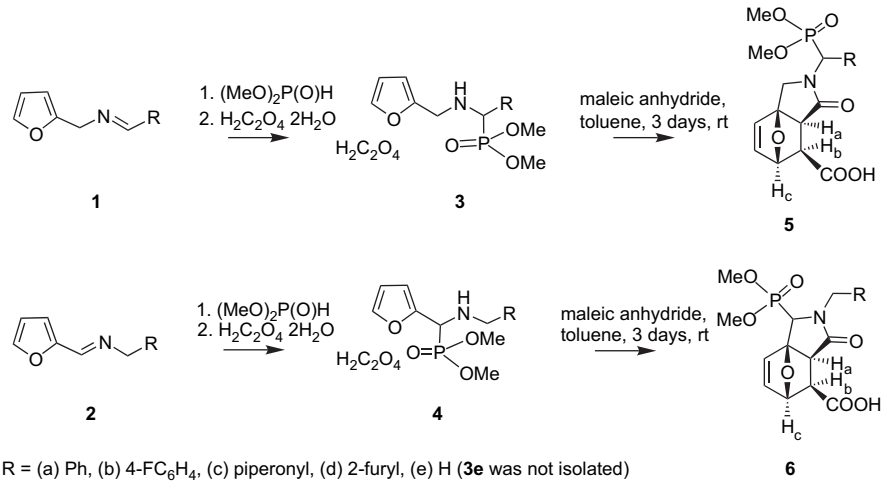
Both epoxyisoindolyl phosphonates **5d** and **6d** were prepared from the same aminophosphonate **3d** (or **4d**) as the initial compound. Compound **3d** (or **4d**) reacted with maleic anhydride to afford the compounds **5d+6d** in a ratio of 55:45. These isomeric epoxyisoindolyl phosphonates appeared as a mixture of minor and major diastereomers (Table 2).

Some interesting features have been found in ^{1}H NMR spectra of phosphonates **5** and **6**. The doublet signal of the hydrogen geminal to the phosphonate group in compounds **5** (except **5e**) arrived at 5.60–5.70 ppm with ^2J 21–22 Hz. In contrast, the signal of the same H-atom of compounds **6** is shifted to 3.95–4.70 ppm with the coupling constant value ^2J 5.3–8.7 Hz, which is unusual for α-aminophosphonates (Fig. 2, Table 2).[12]

These data probably are the consequence of the rigid fixation of the phosphonate group to the bridged tricyclic moiety of compound **6**.

A PH COSY experiment showed remote (through five bounds) spin–spin interaction between H_a and phosphorus in the minor diastereomer of compounds **5** with the coupling constant value of ^5J 2.5–2.7 Hz that is unusual for the $\lambda^5\sigma^4$-phosphorus atom (Fig. 3).[13]

It should be noted that the interaction of α-amino-α-(2-furyl)phosphonates with maleic anhydride was previously described by Borisov et al.[14] However, they characterized isolated products only as Diels–Alder adducts, without aminogroup acylation.

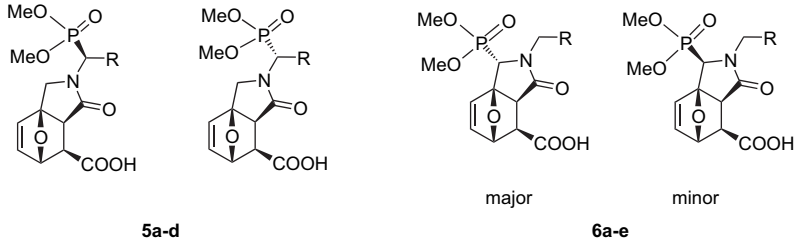


Scheme 2. Synthesis of epoxyisoindolyl phosphonates **5** and **6**.

Table 2. Isomeric epoxyisoindolyl phosphonates **5** and **6** (Scheme 2)

Compound	R	Yield (%)	dr[a]	δ_{CHP} (ppm)		$^2J_{HP}$ (Hz)		δ_P (ppm)	
				Major	Minor	Major	Minor	Major	Minor
5a	Ph	85	60:40	5.60	5.66	21.0	22.3	26.16	26.92
5b	4-FC_6H_4	75	60:40	5.62	5.66	21.4	22.0	25.94	26.70
5c	Piperonyl[b]	82	60:40	5.52	5.56	21.5	22.2	26.09	26.87
5d	2-Furyl	80[c]	66:33	5.67	5.69	22.2	22.2	23.67	24.44
5e	H	29[d]	—	3.71; 3.83		16.6		28.37	
6a	Ph	81	97:3	3.98	4.65[e]	5.7	8.1[e]	25.59	25.16
6b	4-FC_6H_4	89	98:2	4.03	4.65[e]	5.7	8.1[e]	25.58	25.14
6c	Piperonyl[b]	91	98:2	3.95	4.64[e]	5.7	7.8[e]	25.60	25.26
6d	2-Furyl	80[c]	91:9	4.15	4.66[e]	5.3	8.7[e]	25.55	25.12
6e	H	68	89:11	4.44	4.69[e]	5.7	8.1[e]	26.10	25.59

[a] dr Values were obtained by integration of ^1H and ^{31}P NMR spectra.
[b] 3,4-(Methylenedioxy)phenyl.
[c] Yield of mixture **5d**:**6d**.
[d] Yield within two steps.
[e] Data obtained from ^1H NMR spectrum of crude (not crystallized) product.



Scheme 3. Diastereomer pairs of isomeric epoxyisoindolyl phosphonates **5** and **6**.

3. Conclusion

In conclusion, new α-acylaminophosphonates, possessing an epoxyisoindolyl moiety, **5** and **6** have been synthesized by a tandem acylation/[4+2]-cycloaddition reaction. Phosphonates **5** were obtained as a mixture of two diastereomers in a typical 40:60 ratio. Isomeric phosphonates α-acylaminophosphonates **6** possessing an epoxyisoindolone moiety were prepared with good stereoselectivity (de≥80%). The epoxy and phosphonate groups in these compounds are oppositely oriented. This was confirmed by ^1H, ^{13}C and ^{31}P NMR spectroscopies as well as X-ray crystal structure analysis. Phosphonates **5** and **6** are interesting as intermediates for the synthesis of [1,2]-isoindolo condensed heterocyclic systems.

4. Experimental

4.1. General

All commercially available reagents were used without further purification, with the exception of 2-furaldehyde, which was distilled prior to use. Melting points are uncorrected. IR spectra were obtained in KBr pellets and recorded on a Specord M80 Carl Zeiss Jena spectrometer. ^1H, ^{13}C and ^{31}P NMR spectra were measured at 300, 100 and 80 MHz (for **3** and **4**) or 200 (for **5** and **6**) MHz, respectively, for DMSO-d_6 solution with TMS as internal or H_3PO_4 as external standard on Varian VXR-300, Bruker Avance 500 and Gemini 2000 (400 MHz) spectrometers. 2D NMR spectra (PH COSY) were measured using standard Bruker software.

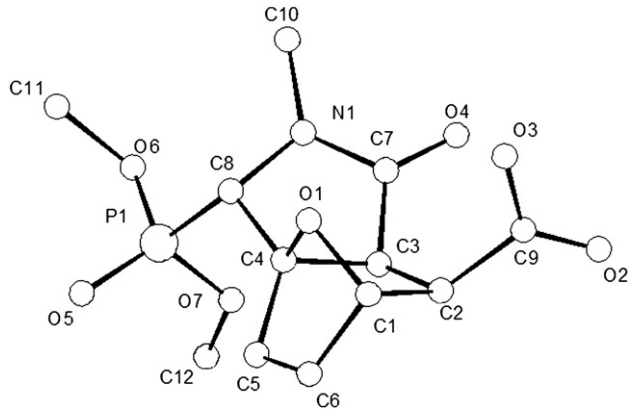


Figure 1. Major diastereomer of compound **6e**: molecular structure showing the numbering used in the crystallographic work.

Chemical shifts (δ) are reported in parts per million. Coupling constants (J) are reported in Hertz. Elemental analyses were performed in the analytical laboratory of our institute. All solvents were distilled and purified by standard procedures.

4.2. X-ray crystallography

Crystallographic data for the structure of major diastereomer of **6e** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-650983 and can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033, or e-mail: deposit@ccdc.cam.ac.uk.

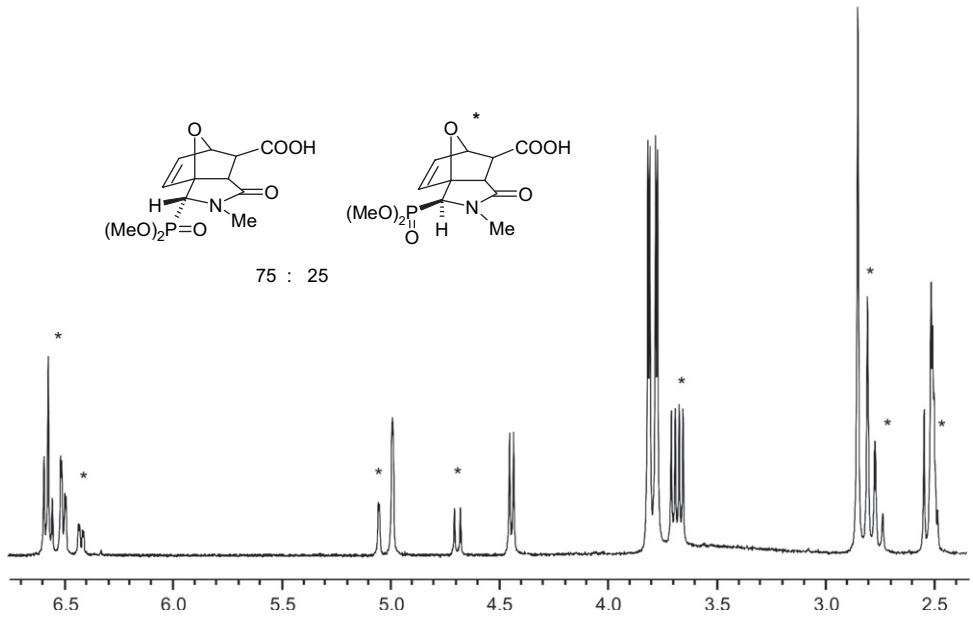


Figure 2. ^{1}H NMR spectrum of diastreomeric mixture of epoxyisoindolyl phosphonate **6e** (enriched with minor diastereomer (*) mixture was obtained by evaporation of mother liquid after recrystallization of major diastereomer).

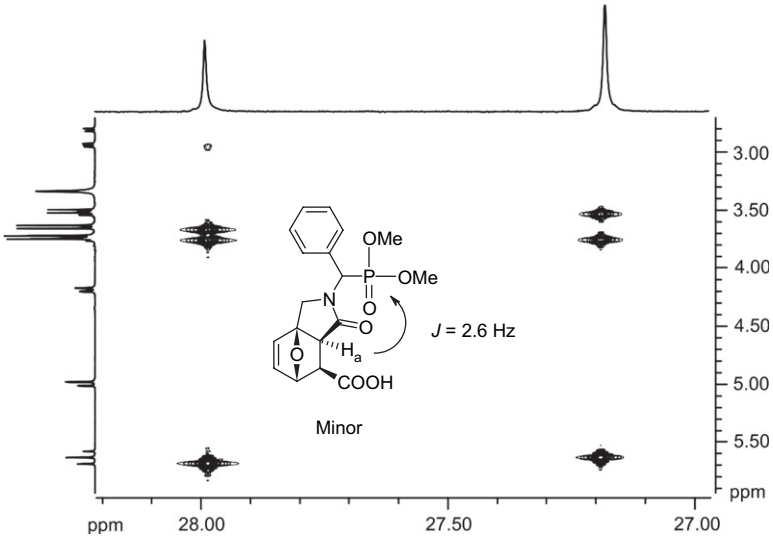


Figure 3. PH COSY spectrum of epoxyisoindolyl phosphonate **5a**.

Table 3. CHP analyses of aminophosphonates **3a–d**, **4a–e**

Compound	Calculated (%)			Formula	Found (%)		
	C	H	P		C	H	P
3a	49.88	5.23	8.04	$C_{16}H_{20}NO_8P$	49.68	5.35	7.95
3b	47.65	4.75	7.68	$C_{16}H_{19}FNO_8P$	47.70	4.73	7.65
3c	47.56	4.70	7.21	$C_{17}H_{20}NO_{10}P$	47.48	4.55	7.09
3d=**4d**	44.81	4.83	8.25	$C_{14}H_{18}NO_9P$	44.59	4.70	8.15
4a	49.88	5.23	8.04	$C_{16}H_{20}NO_8P$	49.71	5.29	8.05
4b	47.65	4.75	7.68	$C_{16}H_{19}FNO_8P$	47.50	4.63	7.90
4c	47.56	4.70	7.21	$C_{17}H_{20}NO_{10}P$	47.60	4.80	7.10
4e	38.84	5.22	10.02	$C_{10}H_{16}NO_8P$	39.01	5.35	9.95

4.3. General procedure for the preparation of the aminophosphonate precursors 3a–d, 4a–e

A solution of aldehyde (50 mmol) and amine (50 mmol) in toluene (100 ml) over anhydrous Na_2SO_4 was stirred at ambient temperature overnight. The mixture was filtered and evaporated to give aldimines **1**, **2** as an oil. Then dimethyl phosphite was added to the prepared aldimine and the reaction mixture was left for 24 h at room temperature. Upon standing the neat reaction mixture was dissolved in 25 ml acetone and a solution of oxalic acid dihydrate (12.6 g, 100 mmol) in acetone (50 ml) was added. The solution was refrigerated and precipitated oxalate of the aminophosphonate was filtered off, washed with acetone and dried. The product appears as colourless or pale solid.

Yields, melting points, NMR spectra and CHP analyses are reported in Tables 1 and 3.

4.4. General procedure for the tandem acylation/[4+2]-cycloaddition reaction

To a stirred solution of the aminophosphonate oxalate (10 mmol) in water (50 ml) was added anhydrous Na_2CO_3 (15 mmol). After evolution of CO_2 had stopped, the reaction mixture was extracted with chloroform, dried over anhydrous Na_2SO_4 and evaporated. The resulting colourless oil was dissolved in toluene (20 ml) and maleic anhydride (10 mmol) was added. The reaction mixture was stirred for 3 days at 25 °C. The crystalline product was collected by filtration, washed with toluene and dried in air to give the desired product as a colourless solid.

4.4.1. Dimethyl 1-[3-aza-6-carboxy-10-oxa-*exo*-tricyclo-[5.2.1.0^{1,5}]-4-oxodec-8-en-3-yl]-1-phenylmethylphosphonate (5a). Yield 85%; white solid; dr=40:60. Found C, 55.02; H, 5.20; P, 7.68; $C_{18}H_{20}NO_7P$ requires C, 54.97; H, 5.13; P, 7.87%. ν_{max} (KBr) 1741 (COO), 1706, 1695 (NCO), 1221 (P=O). *Major diastereomer*: δ_H (300 MHz, DMSO-d_6) 2.50 (1H, d, *J* 9.1 Hz, H_b), 2.81 (1H, d, *J* 9.1 Hz, H_a), 3.50 (3H, d, *J* 10.5 Hz, OCH_3), 3.73 (3H, d, *J* 10.5 Hz, OCH_3), 3.74 (1H, d, *J* 11.7 Hz, CH_2N), 4.18 (1H, d, *J* 11.7 Hz, CH_2N), 5.01 (1H, d, *J* 1.5 Hz, H_c), 5.60 (1H, d, *J* 21.0 Hz, PCHN), 6.41 (1H, dd, *J* 5.7, 1.5 Hz, CH=CH), 6.51 (1H, d, *J* 5.7 Hz, CH=CH), 7.33–7.46 (3H, m, Ph), 7.54 (2H, d, *J* 7.5 Hz, Ph), 12.18 (1H, br s, COOH); δ_C (100.6 MHz, DMSO-d_6) 44.74, 46.01, 49.51, 51.23 (d, *J* 158 Hz), 52.55 (d, *J* 6.8 Hz), 54.18 (d, *J* 6.8 Hz), 81.09, 87.95, 128.44, 128.83, 129.37 (d, *J* 8.0 Hz), 132.52 (d, *J* 3.5 Hz), 135.37, 136.57, 170.34 (d, *J* 5.0 Hz), 172.63; δ_P (202 MHz, DMSO-d_6) 26.12. *Minor diastereomer*: δ_H (300 MHz, DMSO-d_6) 2.53 (1H, d, *J* 9.1 Hz, H_b), 2.95 (1H, dd, *J* 9.1, 2.6 Hz, H_a), 3.52 (1H, d, *J* 11.7 Hz, CH_2N), 3.64 (3H, d, *J* 10.7 Hz, OCH_3), 3.73 (3H, d, *J* 10.7 Hz, OCH_3), 4.18 (1H, d, *J* 11.7 Hz, CH_2N), 4.98 (1H, d, *J* 1.5 Hz, H_c), 5.66 (1H, d, *J* 22.3 Hz, PCHN), 6.43 (1H, dd, *J* 5.8, 1.5 Hz, CH=CH), 6.65 (1H, d, *J* 5.8 Hz, CH=CH), 7.30–7.43 (3H, m, Ph), 7.47 (2H, d, *J* 7.5 Hz, Ph), 12.18 (1H, br s, COOH); δ_C (100.6 MHz, DMSO-d_6) 44.74, 46.06, 49.61, 50.28 (d, *J* 155 Hz), 52.92 (d, *J* 6.8 Hz), 53.25 (d, *J* 6.8 Hz), 81.00, 88.06, 127.98, 128.27 (d, *J* 7.5 Hz), 128.58, 132.54 (d, *J* 4.0 Hz), 135.29, 136.67, 170.59 (d, *J* 5.5 Hz), 172.40; δ_P (202 MHz, DMSO-d_6) 26.92.

4.4.2. Dimethyl 1-[3-aza-6-carboxy-10-oxa-*exo*-tricyclo-[5.2.1.0^{1,5}]-4-oxodec-8-en-3-yl]-1-(4-fluorophenyl)-methylphosphonate (5b). Yield 75%; pale solid; dr=40:60. Found C, 55.67; H, 4.70; P, 7.50. $C_{18}H_{19}FNO_7P$ requires C, 52.56; H, 4.66; P, 7.53%. ν_{max} (KBr): 1740 (COO), 1700 (NCO), 1221 (P=O). *Major diastereomer*: δ_H (300 MHz, DMSO-d_6) 2.50 (1H, d, *J* 9.1 Hz, H_b), 2.81 (1H, d, *J* 9.1 Hz, H_a), 3.52 (3H, d, *J* 10.7 Hz, OCH_3), 3.73 (3H, d, *J* 10.7 Hz, OCH_3), 3.74 (1H, d, *J* 11.5 Hz, CH_2N), 4.15 (1H, d, *J* 11.5 Hz, CH_2N), 5.01 (1H, d, *J* 1.6 Hz, H_c), 5.62 (1H, d, *J* 21.4 Hz, PCHN), 6.41 (1H, dd, *J* 5.8, 1.6 Hz, CH=CH), 6.51 (1H, d, *J* 5.8 Hz, CH=CH), 7.28 (2H, t, *J* 8.9 Hz, Ar), 7.59 (2H, dd, *J* 8.9, 5.7 Hz, Ar), 12.23 (1H, br s, COOH); δ_C (100.6 MHz, DMSO-d_6) 45.10, 46.31, 49.94, 50.79 (d, *J* 159 Hz), 53.02 (d, *J* 7.0 Hz), 54.75 (d, *J* 7.0 Hz), 81.53, 88.39, 116.23 (d, *J* 21.5 Hz), 129.28 (t, *J* 3.4 Hz), 132.14 (t, *J* 8.2 Hz), 135.85, 137.10, 162.46 (d, *J* 246 Hz), 170.91 (d, *J* 5.0 Hz), 173.27; δ_P (202 MHz, DMSO-d_6) 25.94. *Minor diastereomer*: δ_H (300 MHz, DMSO-d_6) 2.53 (1H, d, *J* 9.1 Hz, H_b), 2.94 (1H, dd, *J* 9.1, 2.6 Hz, H_a), 3.52 (1H, d, *J* 11.5 Hz, CH_2N), 3.65 (3H, d, *J* 10.7 Hz, OCH_3), 3.74 (3H, d, *J* 10.7 Hz, OCH_3), 4.18 (1H, d, *J* 11.5 Hz, CH_2N), 4.98 (1H, d, *J* 1.6 Hz, H_c), 5.66 (1H, d, *J* 22.0 Hz, PCHN), 6.43 (1H, dd, *J* 5.8, 1.5 Hz, CH=CH), 6.65 (1H, d, *J* 5.8 Hz, CH=CH), 7.23 (2H, t, *J* 8.8 Hz, Ar), 7.50 (2H, dd, *J* 8.8, 5.5 Hz, Ar), 12.23 (1H, br s, COOH); δ_C (100.6 MHz, DMSO-d_6) 45.13, 46.46, 49.95 (d, *J* 157 Hz), 50.00, 53.43 (d, *J* 7.0 Hz), 53.79 (d, *J* 7.0 Hz), 81.44, 88.54, 115.99 (d, *J* 21.5 Hz), 129.31 (t, *J* 2.8 Hz), 130.89 (t, *J* 8.0 Hz), 135.77, 137.17, 162.17 (d, *J* 246 Hz), 171.22 (d, *J* 5.5 Hz), 173.04; δ_P (202 MHz, DMSO-d_6) 26.70.

4.4.3. Dimethyl 1-[3-aza-6-carboxy-10-oxa-*exo*-tricyclo-[5.2.1.0^{1,5}]-4-oxodec-8-en-3-yl]-1-piperonylmethylphosphonate (5c). Yield 82%; pale solid; dr=40:60. Found C, 52.30; H, 4.71; P, 7.00. $C_{19}H_{20}NO_9P$ requires C, 52.18; H, 4.60; P, 7.08%. *Major diastereomer*: δ_H (300 MHz, DMSO-d_6) 2.49 (1H, d, *J* 9.2 Hz, H_b), 2.80 (1H, d, *J* 9.2 Hz, H_a), 3.52 (3H, d, *J* 10.7 Hz, OCH_3), 3.71 (3H, d, *J* 10.7 Hz, OCH_3), 3.76 (1H, d, *J* 11.4 Hz, CH_2N), 4.14 (1H, d, *J* 11.4 Hz, CH_2N), 5.01 (1H, d, *J* 1.5 Hz, H_c), 5.52 (1H, d, *J* 21.5 Hz, PCHN), 6.06 (2H, s, OCH_2O), 6.41 (1H, dd, *J* 5.6, 1.5 Hz, CH=CH), 6.52 (1H, d, *J* 5.6 Hz, CH=CH), 6.89–7.10 (3H, m, Ar), 12.25 (1H, br s, COOH); δ_C (100.6 MHz, DMSO-d_6) 45.09, 46.32, 49.99, 51.19 (d, *J* 160 Hz), 53.00 (d, *J* 6.8 Hz), 54.70 (d, *J* 6.8 Hz), 81.53, 88.37, 101.65, 108.68, 110.00 (d, *J* 8.5 Hz), 122.58 (d, *J* 7.7 Hz), 126.37 (d, *J* 3.7 Hz), 135.88, 137.05, 147.85,

147.88, 170.83 (d, *J* 5.5 Hz), 173.30; δ_P (202 MHz, DMSO-d_6) 26.09. *Minor diastereomer*: δ_H (300 MHz, DMSO-d_6) 2.52 (1H, d, *J* 9.2 Hz, H_b), 2.93 (1H, dd, *J* 9.2, 2.5 Hz, H_a), 3.52 (1H, d, *J* 11.5 Hz, CH_2N), 3.64 (3H, d, *J* 10.7 Hz, OCH_3), 3.73 (3H, d, *J* 10.7 Hz, OCH_3), 4.16 (1H, d, *J* 11.5 Hz, CH_2N), 4.97 (1H, d, *J* 1.5 Hz, H_c), 5.56 (1H, d, *J* 22.2 Hz, PCHN), 6.03 (2H, d, *J* 1.8 Hz, OCH_2O), 6.43 (1H, dd, *J* 5.6, 1.5 Hz, CH=CH), 6.64 (1H, d, *J* 5.6 Hz, CH=CH), 6.89–7.10 (3H, m, Ar), 12.25 (1H, br s, COOH); δ_C (100.6 MHz, DMSO-d_6) 45.09, 46.32, 50.08, 50.26 (d, *J* 158 Hz), 53.38 (d, *J* 6.8 Hz), 53.70 (d, *J* 6.8 Hz), 81.42, 88.51, 101.78, 108.98, 109.21 (d, *J* 8.5 Hz), 123.83 (d, *J* 9.0 Hz), 126.33 (d, *J* 3.7 Hz), 135.77, 137.17, 147.52, 147.90, 171.06 (d, *J* 5.5 Hz), 173.07; δ_P (202 MHz, DMSO-d_6) 26.87.

4.4.4. Dimethyl 1-[3-aza-6-carboxy-10-oxa-*exo*-tricyclo-[5.2.1.0^{1,5}]-4-oxodec-8-en-3-yl]-1-(2-furyl)methylphosphonate (5d) and dimethyl *N*-((2-furyl)methyl)-3-aza-6-carboxy-10-oxa-*exo*-tricyclo[5.2.1.0^{1,5}]-4-oxodec-8-en-2-yl-*endo*-phosphonate (6d). Yellow solid; yield 80%—mixture of four diastereomers; **5d/6d**=55:45. Found C, 50.29; H, 4.83; P, 8.03. $C_{16}H_{18}NO_8P$ requires C, 50.14; H, 4.73; P, 8.08%.

Compound **5d**: dr=33:66. *Major diastereomer*: δ_H (300 MHz, DMSO-d_6) 2.51 (1H, d, *J* 9.3 Hz, H_b), 2.86 (1H, d, *J* 9.3 Hz, H_a), 3.57 (3H, d, *J* 10.8 Hz, OCH_3), 3.66 (1H, d, *J* 11.5 Hz, CH_2N), 3.72 (3H, d, *J* 10.8 Hz, OCH_3), 4.10 (1H, d, *J* 11.5 Hz, CH_2N), 5.01 (1H, d, *J* 1.5 Hz, H_c), 5.67 (1H, d, *J* 22.2 Hz, PCHN), 6.43 (1H, dd, *J* 5.6, 1.6 Hz, CH=CH), 6.53 (2H, br s, Furyl), 6.54 (1H, d, *J* 5.6 Hz, CH=CH), 7.75 (1H, d, *J* 1.1 Hz, Furyl), 12.27 (1H, br s, COOH); δ_C (100.6 MHz, DMSO-d_6) 45.10, 45.77 (d, *J* 160 Hz), 46.55, 49.95, 53.43 (d, *J* 6.8 Hz), 54.78 (d, *J* 6.8 Hz), 81.52, 88.38, 111.30 (d, *J* 2.0 Hz), 111.47 (d, *J* 4.2 Hz), 135.83, 137.14, 144.29 (d, *J* 1.5 Hz), 146.07 (d, *J* 8.0 Hz), 170.78 (d, *J* 4.2 Hz), 173.23; δ_P (202 MHz, DMSO-d_6) 23.67. *Minor diastereomer*: δ_H (300 MHz, DMSO-d_6) 2.52 (1H, d, *J* 9.2 Hz, H_b), 2.91 (1H, dd, *J* 9.2, 2.6 Hz, H_a), 3.59 (1H, d, *J* 11.5 Hz, CH_2N), 3.64 (3H, d, *J* 10.8 Hz, OCH_3), 3.74 (3H, d, *J* 10.8 Hz, OCH_3), 4.21 (1H, d, *J* 11.5 Hz, CH_2N), 4.95 (1H, d, *J* 1.5 Hz, H_c), 5.69 (1H, d, *J* 22.2 Hz, PCHN), 6.44 (1H, dd, *J* 5.6, 1.6 Hz, CH=CH), 6.64 (1H, d, *J* 5.6 Hz, CH=CH), 6.67 (2H, m, Furyl), 7.72 (1H, br s, Furyl), 12.27 (1H, br s, COOH); δ_C (100.6 MHz, DMSO-d_6) 45.17, 45.68 (d, *J* 160 Hz), 46.57, 49.92, 53.70 (d, *J* 6.8 Hz), 53.88 (d, *J* 6.8 Hz), 81.42, 88.45, 111.23 (d, *J* 5.1 Hz), 111.27 (d, *J* 2.0 Hz), 135.61, 137.36, 144.24 (d, *J* 1.5 Hz), 145.97 (d, *J* 5.3 Hz), 170.65 (d, *J* 4.2 Hz), 172.96; δ_P (202 MHz, DMSO-d_6) 24.44.

Compound **6d**: dr=91:9. *Major diastereomer*: δ_H (300 MHz, DMSO-d_6) 2.59 (d, *J* 9.1 Hz, 1H, H_b), 2.91 (1H, d, *J* 9.1 Hz, H_a), 3.80 (6H, d, *J* 10.8 Hz, OCH_3), 4.16 (1H, d, *J* 5.3 Hz, PCHN), 4.26 (1H, d, *J* 16.1 Hz, CH_2N), 4.90 (1H, d, *J* 16.1 Hz, CH_2N), 5.03 (1H, br s, H_c), 6.30 (1H, d, *J* 3.0 Hz, Furyl), 6.40 (1H, dd, *J* 3.0, 1.4 Hz, Furyl), 6.51 (1H, dd, *J* 5.7, 1.6 Hz, CH=CH), 6.58 (1H, d, *J* 5.7 Hz, CH=CH), 7.58 (1H, d, *J* 1.4 Hz, Furyl), 12.27 (1H, br s, COOH); δ_C (100.6 MHz, DMSO-d_6) 45.44, 46.53, 49.61, 53.75 (d, *J* 6.8 Hz), 53.83 (d, *J* 6.8 Hz), 54.74 (d, *J* 161 Hz), 80.90, 89.03 (d, *J* 6.6 Hz), 107.92, 111.00, 134.32, 137.90, 142.92, 149.45 (d, *J* 1.2 Hz), 171.12 (d, *J* 1.8 Hz), 172.89; δ_P (202 MHz, DMSO-d_6) 25.55. *Minor diastereomer*: δ_P (202 MHz, DMSO-d_6) 25.12.

4.4.5. Dimethyl *N*-benzyl-3-aza-6-carboxy-10-oxa-*exo*-tricyclo[5.2.1.0^{1,5}]-4-oxodec-8-en-2-yl-*endo*-phosphonate (6a). Yield 81%; dr=97:3. Found C, 54.56; H, 5.20; P, 7.84. $C_{18}H_{20}NO_7P$ requires C, 54.97; H, 5.13; P, 7.87%. ν_{max} (KBr): 1725 (COO), 1700 (NCO), 1224 (P=O). *Major diastereomer*: white solid; mp 206–207 °C (MeOH); δ_H (300 MHz, DMSO-d_6) 2.61 (1H, d, *J* 9.1 Hz, H_b), 2.94 (1H, d, *J* 9.1 Hz, H_a), 3.77 (3H, d, *J* 10.6 Hz, OCH_3), 3.78 (3H, d, *J* 10.6 Hz, OCH_3), 3.98 (1H, d, *J* 5.7 Hz, PCHN), 4.21 (1H, d, *J* 16.2 Hz, CH_2N), 5.02 (1H, d, *J* 16.2 Hz, CH_2N), 5.07 (1H, br s, H_c), 6.51 (1H, dd, *J* 5.7, 1.6 Hz, CH=CH), 6.58 (1H, d, *J* 5.7 Hz, CH=CH), 7.21–7.35 (5H, m, Ph), 12.28 (1H, br s, COOH); δ_C (100.6 MHz, DMSO-d_6) 45.21, 45.64, 50.24, 53.90 (d, *J* 7.0 Hz), 54.11 (d, *J* 7.0 Hz), 54.73 (d, *J* 147 Hz), 81.26, 89.30 (d, *J* 6.0 Hz), 127.85, 127.98, 129.07, 134.87, 136.21, 137.99, 171.74, 173.30; δ_P (202 MHz, DMSO-d_6) 25.59. *Minor diastereomer*: δ_P (202 MHz, DMSO-d_6) 25.16.

4.4.6. Dimethyl *N*-(4-fluorophenylmethyl)-3-aza-6-carboxy-10-oxa-*exo*-tricyclo[5.2.1.0^{1,5}]-4-oxodec-8-en-2-yl-*endo*-phosphonate (6b). Yield 89%; dr=98:2. Found C, 52.58; H, 4.63; P, 7.45. $C_{18}H_{19}FNO_7P$ requires C, 52.56; H, 4.66; P, 7.53%. *Major diastereomer*: white solid; mp 169–170 °C (*i*-PrOH); δ_H (300 MHz, DMSO-d_6) 2.61 (1H, d, *J* 9.1 Hz, H_b), 2.93 (1H, d, *J* 9.1 Hz, H_a), 3.77 (3H, d, *J* 10.7 Hz, OCH_3), 3.78 (3H, d, *J* 10.7 Hz, OCH_3), 4.03 (1H, d, *J* 5.7 Hz, PCHN), 4.22 (1H, d, *J* 16.0 Hz, CH_2N), 4.97 (1H, d, *J* 16.0 Hz, CH_2N), 5.06 (1H, br s, H_c), 6.51 (1H, dd, *J* 5.7, 1.5 Hz, CH=CH), 6.59 (1H, d, *J* 5.7 Hz, CH=CH), 7.12 (2H, t, *J* 8.8 Hz, Ar), 7.30 (2H, dd, *J* 8.8, 5.7 Hz, Ar), 12.30 (1H, br s, COOH); δ_C (100.6 MHz, DMSO-d_6) 44.33, 45.32, 49.97, 53.69 (d, *J* 6.3 Hz), 53.82 (d, *J* 6.3 Hz), 54.40 (d, *J* 159 Hz), 80.99, 89.04 (d, *J* 7.1 Hz), 115.49 (d, *J* 21.2 Hz), 129.66 (d, *J* 8.2 Hz), 132.15 (d, *J* 2.1 Hz), 134.58, 137.68, 161.81 (d, *J* 241 Hz), 171.52 (d, *J* 1.0 Hz), 173.09; δ_P (202 MHz, DMSO-d_6) 25.58. *Minor diastereomer*: δ_P (202 MHz, DMSO-d_6) 25.14.

4.4.7. Dimethyl *N*-(piperonylmethyl)-3-aza-6-carboxy-10-oxa-*exo*-tricyclo[5.2.1.0^{1,5}]-4-oxodec-8-en-2-yl-*endo*-phosphonate (6c). Yield 91%; dr=98:2. Found C, 52.20; H, 4.57; P, 7.11. $C_{19}H_{20}NO_9P$ requires C, 52.18; H, 4.60; P, 7.08%. *Major diastereomer*: white solid; mp 189–190 °C (CH_3CN); δ_H (300 MHz, DMSO-d_6) 2.60 (1H, d, *J* 9.3 Hz, H_b), 2.92 (1H, d, *J* 9.3 Hz, H_a), 3.78 (6H, d, *J* 10.7 Hz, OCH_3), 3.95 (1H, d, *J* 5.7 Hz, PCHN), 4.08 (1H, d, *J* 15.7 Hz, CH_2N), 4.95 (1H, d, *J* 15.7 Hz, CH_2N), 5.06 (1H, br s, H_c), 5.98 (2H, d, *J* 2.6 Hz, OCH_2O), 6.51 (1H, dd, *J* 5.7, 1.5 Hz, CH=CH), 6.59 (1H, d, *J* 5.7 Hz, CH=CH), 6.72 (1H, d, *J* 8.0 Hz, Ar), 6.77 (1H, s, Ar), 6.84 (1H, d, *J* 8.0 Hz, Ar), 12.31 (1H, br s, COOH); δ_C (100.6 MHz, DMSO-d_6) 44.60, 45.28, 50.06, 53.69 (d, *J* 6.7 Hz), 53.83 (d, *J* 6.7 Hz), 54.03 (d, *J* 160 Hz), 80.97, 88.95 (d, *J* 6.6 Hz), 101.25, 108.14, 108.38, 121.25, 129.52, 134.58, 137.68, 146.85, 147.92, 171.41 (d, *J* 1.3 Hz), 173.11; δ_P (202 MHz, DMSO-d_6) 25.60. *Minor diastereomer*: δ_P (202 MHz, DMSO-d_6) 25.26.

4.4.8. Dimethyl *N*-methyl-3-aza-6-carboxy-10-oxa-*exo*-tricyclo[5.2.1.0^{1,5}]-4-oxodec-8-en-2-yl-*endo*-phosphonate (6e). Yield 68%; dr=89:11. Found C, 45.40; H, 5.11; P, 9.81. $C_{12}H_{16}NO_7P$ requires C, 45.43; H, 5.08; P, 9.76%. *Major diastereomer*: white solid; mp 189–190 °C (*i*-PrOH); δ_H (300 MHz, DMSO-d_6) 2.52 (1H, d, *J* 9.5 Hz, H_b), 2.78 (1H, d, *J* 9.5 Hz, H_a), 2.85 (3H, s, NCH_3), 3.78 (3H, d, *J* 10.7 Hz, OCH_3), 3.79 (3H, d, *J* 10.7 Hz, OCH_3), 4.44 (1H, d, *J* 5.7 Hz, PCHN), 4.99 (1H, br s, H_c), 6.50 (1H, dd, *J* 5.8, 1.7 Hz, CH=CH), 6.58 (1H, d, *J* 5.8 Hz, CH=CH), 12.20 (1H, br s, COOH); δ_C (100.6 MHz, DMSO-d_6) 29.69, 44.85, 49.06, 53.07 (d, *J* 7.0 Hz), 53.18 (d, *J* 7.0 Hz), 56.67 (d, *J* 159 Hz), 80.48, 88.71 (d, *J* 6.8 Hz), 133.97, 137.17, 170.48 (d, *J* 1.6 Hz), 172.40; δ_P (202 MHz, DMSO-d_6) 26.09. *Minor diastereomer*: δ_H (300 MHz, DMSO-d_6) 2.50 (1H, d, *J* 9.0 Hz, H_b), 2.75 (1H, d, *J* 9.0 Hz, H_a), 2.80 (3H, s, NCH_3), 3.67 (3H, d, *J* 10.9 Hz, OCH_3), 3.69 (3H, d, *J* 10.9 Hz, OCH_3), 4.69 (1H, d, *J* 8.1 Hz, PCHN), 5.05 (1H, d, *J* 1.6 Hz, H_c), 6.42 (1H, dd, *J* 5.7, 1.6 Hz, CH=CH), 6.56 (1H, d, *J* 5.7 Hz, CH=CH), 12.20 (1H, br s, COOH); δ_C (100.6 MHz, DMSO-d_6) 28.96, 44.47, 49.92 (d, *J* 6.5 Hz), 52.59 (d, *J* 6.5 Hz), 52.89 (d, *J* 6.5 Hz), 55.67 (d, *J* 160 Hz), 81.45, 88.35 (d, *J* 8.1 Hz), 135.15, 135.64, 170.91 (d, *J* 8.3 Hz), 172.35; δ_P (202 MHz, DMSO-d_6) 25.59.

4.5. Synthesis of epoxyisoindolyl phosphonate 5e

4.5.1. Dimethyl 3-aza-6-carboxy-10-oxa-*exo*-tricyclo-[5.2.1.0^{1,5}]-4-oxodec-8-en-3-yl-methylphosphonate (5e). Mixture of furfurylamine (1.94 g, 20 mmol), dimethyl phosphite (2.20 g, 20 mmol) and paraformaldehyde (0.90 g, 30 mmol) in benzene (25 ml) was refluxed in Dean–Stark apparatus for 5 h. The reaction mixture was filtered off and maleic anhydride (1.96 g, 20 mmol) was added to the filtrate. The resulting solution was stirred at 25 °C for 3 days. The layer of dark oil was collected and dissolved in methanol. The product was crystallized from the refrigerated solution to give 1.83 g (29%) of pale solid; mp 175–176 °C. Found C, 45.38; H, 5.01; P, 9.67. $C_{12}H_{16}NO_7P$ requires C, 45.43; H, 5.08; P, 9.76%. δ_H (300 MHz, DMSO-d_6) 2.48 (1H, d, *J* 9.3 Hz, H_b), 2.81 (1H, dd, *J* 9.3, 2.7 Hz, H_a), 3.660 (3H, d, *J* 10.8 Hz, OCH_3), 3.66 (3H, d, *J* 10.8 Hz, OCH_3), 3.71 (1H, dd, *J* 16.6, 11.1 Hz, NCH_2P), 3.77 (1H, d, *J* 11.8 Hz, CCH_2N), 3.83 (1H, dd, *J* 16.6, 11.1 Hz, NCH_2P), 4.11 (1H, d, *J* 11.8 Hz, CCH_2N), 4.98 (1H, d, *J* 1.6 Hz, H_c), 6.43 (1H, dd, *J* 5.8, 1.6 Hz, CH=CH), 6.61 (1H, d, *J* 5.8 Hz, CH=CH), 12.20 (1H, br s, COOH); δ_C (100.6 MHz, DMSO-d_6) 36.99 (d, *J* 152 Hz), 44.53, 48.80, 49.42, 52.57 (d, *J* 6.2 Hz), 52.74 (d, *J* 6.2 Hz), 81.04, 88.25, 135.31, 136.68, 170.24 (d, *J* 3.2 Hz), 172.57; δ_P (202 MHz, DMSO-d_6) 28.37.

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References and notes

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