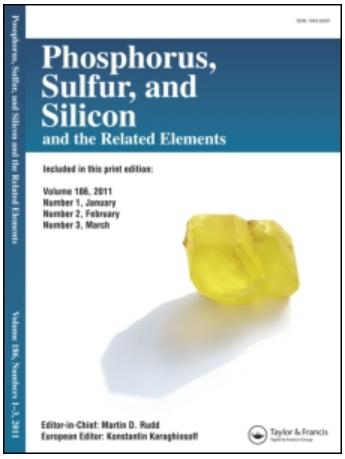

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Synthesis of Phosphonic Acids Possessing Isoindolin-1-one Moiety: Unexpected Acid-Catalyzed C-P-Bond Cleavage

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Synthesis of Phosphonic Acids Possessing Isoindolin-1-one Moiety: Unexpected Acid-Catalyzed C-P-Bond Cleavage

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Phosphonic acids bearing isoindolin-1-one moiety were synthesized by dehydrative aromatization of the corresponding epoxyisoindolyl phosphonates. A mechanism for the unexpected acid catalyzed dephosphorylation was proposed.

Keywords Dehydrative aromatization; dephosphorylation of phosphonic acid; epoxyisoindolyl phosphonates

INTRODUCTION

Isoindolin-1-ones have attracted considerable attention because of their high biological (e.g., antihypertensive,[1] antipsychotic,[2] antivirus,[3] antileukemic,[4] etc.) activity. The isoindolin-1-one fragment is present in synthetic (indoprofen—anti-inflammatory agent[5]) as well as in naturally occuring compounds, in particular in alkaloids (i.e., lennoxamine, nuevamine[6]). One of the most interesting and recent methods for the synthesis of isoindolin-1-ones is the dehydrative aromatization of epoxyisoindolones, which are the products of the reaction between aminomethylfuranes and acylating dienophiles (e.g., maleic anhydride).[7–9]

Continuing our studies on the chemistry of amino- and hydroxyphosphonic acids,[10–12] we have recently synthesized isomeric α-acylaminophosphonates **1** and **2** possessing epoxyisoindolone moiety

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Dedicated to Professor Marian Mikołajczyk, CBMiM PAN, in Łódź, Poland, on the occasion of his 70th birthday.
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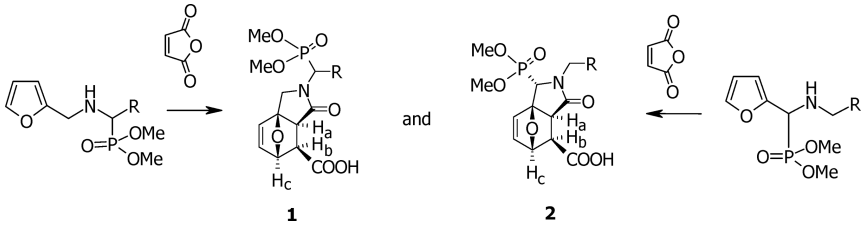


SCHEME 1

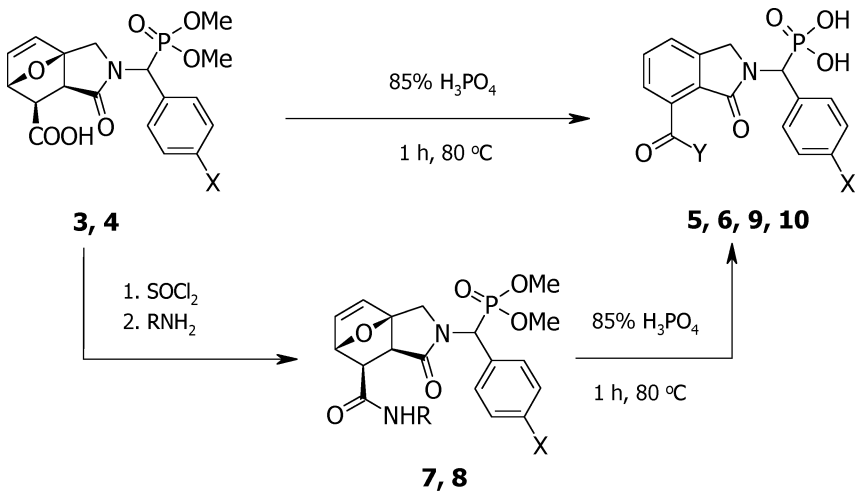
by a tandem acylation/[4+2]-cycloaddition reaction (Scheme 1).[13] *Exo*-epoxyisoindolyl phosphonates **1** were isolated as a mixture of two diastereomeres, formed by two chiral elements: bridge system and carbon atom α to the phosphonate group. Their ratio varied depending on the reaction conditions, but usually was approximately 40:60. The isomeric compounds **2** were formed mainly as one diastereomer with opposite orientation of the epoxy and phosphonate groups.

In this article, we report on the transformation of epoxyisoindolyl phosphonates under the influence of acids, which results in the aromatization of oxabicycloheptene skeleton.

RESULTS AND DISCUSSION

The most convenient method for the dehydrative aromatizations of 2,3,7,7a-tetrahydro-3a,6-epoxyisoindolyl-1-ones was proposed by Zubkov and co-workers—it consists of heating the initial compounds in 85% H_3PO_4.[14,15] With this method, epoxyisoindolyl phosphonates **3** and **4** (types **1**), synthesized earlier by us,[13] were converted into appropriate isoindolin-1-ones by heating for 1 h at 80°C. The reaction was accompanied by simultaneous hydrolysis to give the phosphonic acids **5**, **6** (Scheme 2). Phosphonic acids **5** and **6** were isolated in good yields as solids after dilution of the reaction mixture with water and were purified by crystallization from aqueous alcohol.

Functionalization of the COOH group in acids **5** and **6** could be achieved either with preliminary protection of the phosphonic acid or by the dehydrative aromatization of the appropriate epoxyisoindolyl carboxamides **7** and **8**. The epoxyisoindolyl phosphonates **3** and **4** were transformed via the acylchlorides into the carboxamides **7** and **8**, which were isolated as two diastereomers with a ratio of $\sim$ 40:60. Aromatization of compounds **7** and **8** was carried out under reaction conditions elaborated for the acids **3** and **4** (Scheme 2). The carboxamides of phosphonic acids **9** and **10** prepared by this reaction were purified by crystallization.



SCHEME 2

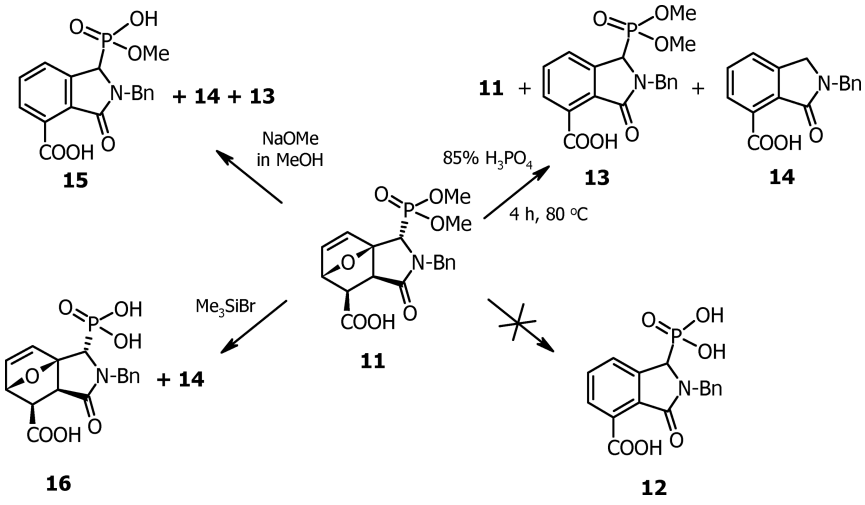
Table I summarizes the results obtained in the preparation of compounds **5–10** using these experimental conditions.

Contrary to our expectations, the treatment of epoxyisoindolyl phosphonate **11** with 85% H_3PO_4 did not result in the formation of phosphonic acid **12**. However, after heating compound **11** for 4 h at 80°C, a mixture of three substances was isolated: the starting epoxyisoindolyl phosphonate **11**, the isoindolyl phosphonate **13**, and the product of dephosphorylation—*N*-benzyl-7-carboxyisoindolin-1-one **14**—in a ratio

TABLE I Epoxyisoindolyl Phosphonates 7 and 8 and Phosphonic Acids 5, 6, 9, and 10

	X	Y	R	Yield %	δ_P, ppm	MS (APCI), m/z
5	H	OH	–	68	14.0	348 [M+1]
6	F	OH	–	70	14.5	366 [M+1]
7a	H	–	4–FC_6H_4	63	22.5/23.5*	487 [M+1]
7b	H	–	4–$FC_6H_4CH_2$	58	23.4/22.5*	501 [M+1]
8a	F	–	Ph	59	22.2/23.1*	487 [M+1]
8b	F	–	CH_2Ph	48	22.3/23.1*	501 [M+1]
9a	H	NH(4-FC_6H_4)	–	46	15.5	441 [M+1]
9b	H	NH(4–$FC_6H_4CH_2$)	–	55	15.4	455 [M+1]
10a	F	NHPh	–	30	14.4	441 [M+1]
10b	F	$NHCH_2Ph$	–	50	15.2	453 [M–1]

*δ_P(major diastereomer)/δ_P(minor diastereomer).



SCHEME 3

of 35:45:20 according to ^{1}H and ^{31}P NMR data and LCMS spectra (Scheme 3, Figure 1).

Dehydrative aromatization of 7-oxabicyclo[2.2.1]heptenes can be carried out also under basic conditions, for example, by action of NaOMe/MeOH or *t*-BuLi.[16] Epoxyisoindolyl phosphonate **11** was

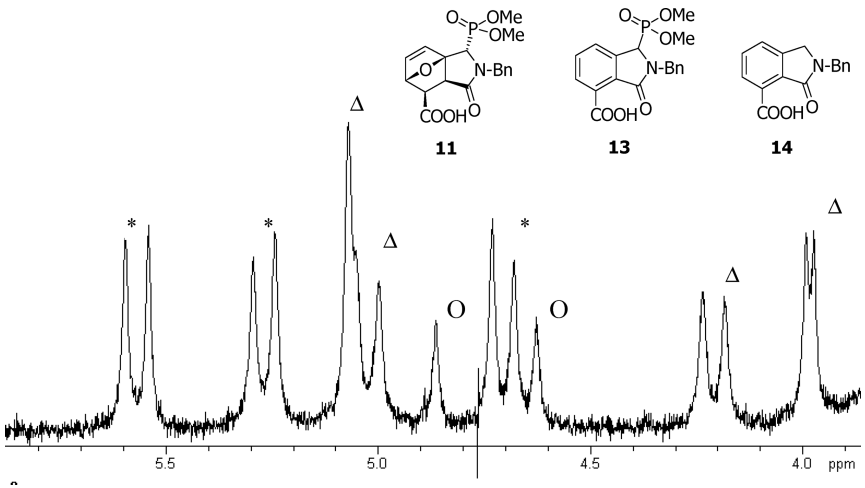
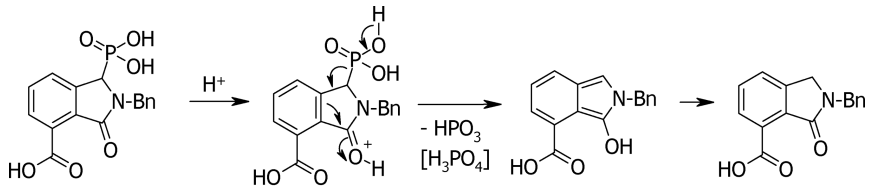


FIGURE 1 Part of the ^{1}H NMR spectrum of a mixture obtained after heating compound **12** for 4 h with 85% H_3PO_4: **11** (Δ) 13(∗), **14** (O).



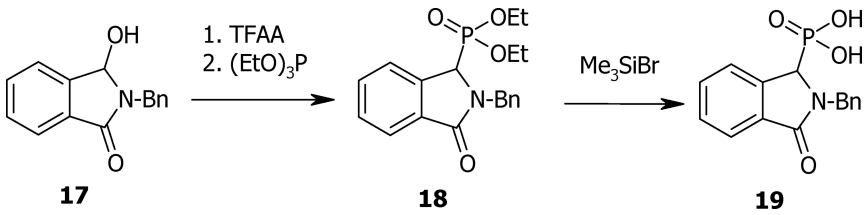
12 **14**

SCHEME 4

aromatized by a reaction with NaOMe in methanol to give a mixture of three products consisting of compounds **13**, **14**, and the monomethyl ester of phosphonic acid **15** in a ratio of 20:55:25 (according to ^{1}H and ^{31}P NMR and LCMS spectra) (Scheme 3). The experimental data allow us to conclude that *N*-benzyl-7-carboxyisoindolin-1-one-3-yl-phosphonic acid **12** is dephosphorylated in the moment of formation. Treatment of compound **11** with an excess of Me_3SiBr gave in addition to the expected epoxyisoindolyl phosphonic acid **16** a small amount of the dephosphorylated product **13**, which was observed and identified by its ^{1}H and ^{31}P NMR spectra (Scheme 3). It is likely that the strong phosphonic acid **16,** the first dissociation constant of which is approximately identical to that of H_3PO_4,[17] causes dehydrative self-aromatization. Therefore the unstable acid **12** is formed and then dephosphorylated to compound **14**.

In summarizing these data, we propose a mechanism of acid catalysis for the dephosphorylation of phosphonic acid **12**, which is shown in Scheme 4. According to this mechanism, the cleavage of the C—P bond occurs as a consequence of electronic density redistribution in the molecule, which is caused by protonation of the amide oxygen atom. The leaving group in this reaction is evidently the metaphosphate (which converts immediately into phosphate); this was proved by aromatization of compound **11** in trifluroacetic acid. The ^{31}P NMR spectrum of the reaction mixture after heating for 14 h at 70°C showed only the signal of H_3PO_4 at 0 ppm. It is probable that dephosphorylation of monomethyl phosphonate **15** also takes place, however much more slowly than the dephosphorylation of acid **12**.

According to the proposed mechanism, the carboxyl group does not influence the dephosphorylation of **12** because it is located in the meta-position of the benzene ring relative to the $(HO)_2P(O)C$-group. Therefore we have anticipated that the model phosphonic acid **19**, which was prepared from **17** as shown in Scheme 5, should be easily dephosphorylated.

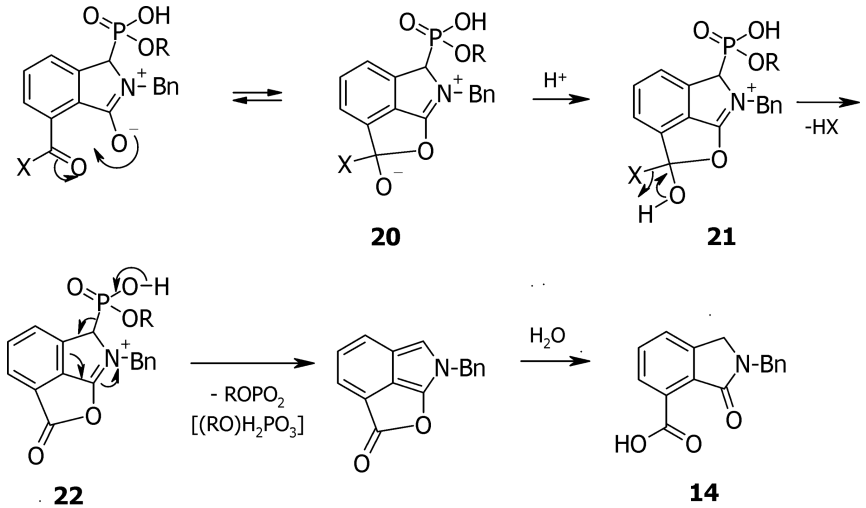


17 **18** **19**

SCHEME 5

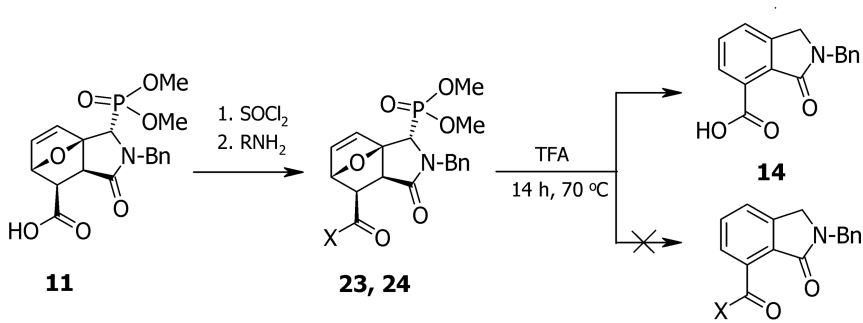
However, phosphonic acid **19** was not dephosphorylated, even after heating for 16 h at 60°C in concentrated H_2SO_4 (according to the ^{31}P NMR spectra). This test proves that the COOH-group must participate in the process of dephosphorylation of **12**, and therefore we propose an alternative mechanism (Scheme 6). We suppose that the protonation of the intermediate compound **20** leads through the elimination of HX from **21** to the formation of lactone **22**, which is dephosphorylated as a result of electronic density redistribution.

In carring out of the dehydrative aromatization of epoxyisoindolyl phosphonates **7** and **8**, we have shown the stability of the amide bond under these reaction conditions (Scheme 2). However, derivatives of epoxyisoindolyl phosphonate **11**—methyl ester **23** and amide (morpholyde) **24**—were converted into the compound **14**, instead of to the appropriate methyl ether **25** or amide **26**, after heating in the



20 **21** **22** **14**

SCHEME 6



X = OMe (23, 25); morpholine-4-yl (24, 26)

SCHEME 7

trifluoroacetic acid solution (Scheme 7). This observation is in agreement with the proposed mechanism and confirms the elimination of HX from the intermediate compound **21** (Scheme 6).

Examples of the acid-catalyzed cleavage of C—P bond by an A-S_E2 mechanism with elimination of H_3PO_4 in heterocyclic aminophosphonic acids were described by Boduszek et al.[18,19]

In conclusion, the chemistry reported here offers a convenient entry to (isoindolin-1-one-2-yl)phosphonic acids, which are of interest as potentially biologically active compounds and can be used as synthetic building blocks for the construction of bioactive compounds. We continue to study the properties of (isoindolin-1-one-2-yl)phosphonic acids including their biological activity.

EXPERIMENTAL

All commercially available reagents were used without further purification. Melting points are uncorrected. IR spectra were obtained in KBr pellets or in CCl_4 solution (for **18**) and with a Vertex 70 IR Fourier spectrophotometer. ^1H, ^{13}C, and ^{31}P NMR spectra were measured at 300, 100, and 80 MHz, respectively, in DMSO-d_6 solution with TMS as internal or H_3PO_4 as external standard with a Varian VXR-300 and a Gemini 2000 (400 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million. Coupling constants (J) are reported in Hertz. H_a, H_b, and H_c hydrogen atoms are shown in Scheme 1. LC and APCI MS data were obtained with an Agilent 1100/DAD/MSD VL G1965a instrument. Elemental analyses were performed in the analytical laboratory of this institute. All solvents were distilled and purified by standard

procedures. Compounds **3**, **4, 11**,[13] and **17**[20] were prepared according to published methods.

Synthesis of Epoxyisoindolyl Phosphonate Carboxamides 7, 8, and 24: General Procedure

To a suspension of the epoxyisoindolyl phosphonate **3**, **4**, or **11** (1 mmol) in anhydrous dichloromethane (10 mL), $SOCl_2$ (0.15 mL, 2 mmol) was added. The reaction mixture was refluxed until the evolution of SO_2 and HCl had stopped (ca. 0.5 h). After this, the amine (4 mmol) was added, and the resulting suspension was stirred and refluxed for additional 0.5 h. After cooling, the reaction mixture was poured into water, and the organic layer was separated and washed with 2% HCl solution, water, 5% $NaHCO_3$ solution, and again with water. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The oil residue was treated with ether and solidified. The precipitate formed was filtered off, washed with ether, and dried. The product is obtained as a pale solid.

Dimethyl 1-[3-Aza-6-((4-fluorophenyl)aminocarbonyl)-10-oxa-exo-tricyclo[5.2.1.0^{1,5}]-4-oxodec-8-en-3-yl]-1-phenylmethylphosphonate (7a)

Yield 63%; pale solid; *dr* = 40:60. IR (KBr, cm^{-1}), ν_{max}: 1697 (NCO), 1664, 1548 (RNHC=O), 1215 (P=O). Anal. Calcd for $C_{24}H_{24}N_2O_6FP$ (486.44): C, 59.26; H, 4.97; P, 6.37. Found: C, 59.12; H, 5.00; P, 6.48%. m/z (M+1) 487.

Major diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.70$ (d, $J =$ 9.2 Hz, 1H, H_b), 2.80 (d, $J = 9.2$ Hz, 1H, H_a), 3.49 (d, $J = 10.6$ Hz, 3H, OCH_3), 3.75 (d, $J = 10.6$ Hz, 3H, OCH_3), 3.79 (d, $J = 11.5$ Hz, 1H, CH_2N), 4.22 (d, $J = 11.5$ Hz, 1H, CH_2N), 5.08 (d, $J = 1.2$ Hz, 1H, H_c), 5.59 (d, $J = 21.2$ Hz, 1H, PCHN), 6.46 (dd, $J = 5.7$ Hz, 1.2 Hz, 1H, CH=CH), 6.56 (d, $J = 5.7$ Hz, 1H, CH=CH), 7.15 (t, $J = 9.2$ Hz, 2H, 4-FC_6H_4), 7.32–7.62 (m, 7H, 4-FC_6H_4, Ph), 9.93 (s, 1H, CONH). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 46.998$, 47.008, 50.6, 52.2 (d, $J = 157$ Hz), 53.5 (d, $J = 8.1$ Hz), 55.2 (d, $J = 8.1$ Hz), 81.8, 88.7, 115.8 (d, $J =$ 22.1 Hz), 121.8, 129.2, 129.6, 130.2 (d, $J = 8.2$ Hz), 133.4 (d, $J = 3.5$ Hz), 136.4 (d, $J = 2.3$ Hz), 136.4, 137.5, 158.5 (d, $J = 239$ Hz), 169.5, 171.3 (d, $J = 5.3$ Hz). ^{31}P NMR (81 MHz, DMSO-d_6): $\delta = 22.5$.

Minor diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.71$ (d, $J =$ 8.9 Hz, 1H, H_b), 2.93 (dd, $J = 8.9$ Hz, 2.6 Hz, 1H, H_a), 3.56 (d, $J = 12.0$ Hz, 1H, CH_2N), 3.63 (d, $J = 10.8$ Hz, 3H, OCH_3), 3.72 (d, $J = 10.8$ Hz, 3H, OCH_3), 4.21 (d, $J = 12.0$ Hz, 1H, CH_2N), 5.06 (d, $J = 1.4$ Hz, 1H, H_c), 5.65 (d, $J = 21.3$ Hz, 1H, PCHN), 6.50 (dd, $J = 5.6$ Hz, 1.4 Hz, 1H,

CH=CH), 6.69 (d, $J = 5.6$ Hz, 1H, CH=CH), 7.12 (t, $J = 9.2$ Hz, 2H, 4-FC_6H_4), 7.32–7.62 (m, 7H, 4-FC_6H_4, Ph), 9.84 (s, 1H, CONH). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 46.996$, 47.001, 50.8, 51.1 (d, $J = 155$ Hz), 53.8 (d, $J = 6.6$ Hz), 54.1 (d, $J = 6.6$ Hz), 81.9, 88.8, 115.8 (d, $J = 21.9$ Hz), 121.9, 128.8, 129.1 (d, $J = 7.6$ Hz), 129.4, 133.3 (d, $J = 3.7$ Hz), 136.3 (d, $J = 3.0$ Hz), 136.4, 137.6, 158.5 (d, $J = 239$ Hz), 169.3, 171.4 (d, $J = 4.6$ Hz). ^{31}P NMR (81 MHz, DMSO-d_6): $\delta = 23.5$.

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Yield 58%; pale solid; *dr* = 40:60. Anal. Calcd. for $C_{25}H_{26}N_2O_6FP$ (500.47): C, 60.00; H, 5.24; P, 6.19. Found: C, 59.95; H, 5.13; P, 6.18%. m/z (M+1) 501.

Major diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.57$ (d, $J = 9.1$ Hz, 1H, H_b), 2.70 (d, $J = 9.1$ Hz, 1H, H_a), 3.52 (d, $J = 10.6$ Hz, 3H, OCH_3), 3.76 (d, $J = 10.6$ Hz, 3H, OCH_3), 3.77 (d, $J = 11.5$ Hz, 1H, CCH_2N), 4.20 (d, $J = 11.5$ Hz, 1H, CCH_2N), 4.30 (dd, $J = 13.0$ Hz, 6.0 Hz, 2H, 4-$FC_6H_4\underline{CH_2}NH$), 5.00 (d, $J = 1.5$ Hz, 1H, H_c), 5.68 (d, $J = 22.0$ Hz, 1H, PCHN), 6.46 (dd, $J = 5.7$ Hz, 1.5 Hz, 1H, CH=CH), 6.53 (d, $J = 5.7$ Hz, 1H, CH=CH), 7.15 (t, $J = 9.2$ Hz, 2H, 4-FC_6H_4), 7.32–7.50 (m, 5H, 4-FC_6H_4, Ph), 7.55 (d, $J = 7.5$ Hz, 1H, Ph), 8.22 (t, $J = 6.0$ Hz, 1H, CONH). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 41.6$, 45.2, 46.0, 49.2, 51.2 (d, $J = 158$ Hz), 52.5 (d, $J = 7.2$ Hz), 54.1 (d, $J = 7.2$ Hz), 81.2, 87.7, 114.6 (d, $J = 21.1$ Hz), 128.3, 128.7, 129.1 (d, $J = 7.8$ Hz), 129.2 (d, $J = 7.5$ Hz), 132.6 (d, $J = 3.7$ Hz), 135.4 (d, $J = 3.1$ Hz), 135.5, 136.5, 160.9 (d, $J = 242$ Hz), 169.8, 170.5 (d, $J = 5.5$ Hz). ^{31}P NMR (81 MHz, DMSO-d_6): $\delta = 23.4$.

Minor diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.59$ (d, $J = 9.0$ Hz, 1H, H_b), 2.84 (dd, $J = 9.0$ Hz, 2.6 Hz, 1H, H_a), 3.53 (d, $J = 11.6$ Hz, 1H, CCH_2N), 3.65 (d, $J = 10.8$ Hz, 3H, OCH_3), 3.74 (d, $J = 10.8$ Hz, 3H, OCH_3), 4.19 (d, $J = 11.6$ Hz, 1H, CCH_2N), 4.23 (d, $J = 5.7$ Hz, 2H, 4-$FC_6H_4CH_2NH$), 4.98 (d, $J = 1.4$ Hz, 1H, H_c), 5.63 (d, $J = 21.5$ Hz, 1H, PCHN), 6.44 (dd, $J = 5.6$ Hz, 1.4 Hz, 1H, CH=CH), 6.67 (d, $J = 5.6$ Hz, 1H, CH=CH), 7.12 (t, $J = 9.2$ Hz, 2H, 4-FC_6H_4), 7.32–7.50 (m, 7H, 4-FC_6H_4), 8.04 (t, $J = 5.7$ Hz, 1H, CONH). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 41.5$, 45.2, 46.0, 49.4, 50.2 (d, $J = 155$ Hz), 52.8 (d, $J = 7.0$ Hz), 53.1 (d, $J = 7.0$ Hz), 81.2, 87.8, 114.6 (d, $J = 21.1$ Hz), 127.8, 128.1 (d, $J = 7.3$ Hz), 128.4, 129.2 (d, $J = 7.8$ Hz), 132.5 (d, $J = 3.5$ Hz), 135.3 (d, $J = 3.3$ Hz), 135.5, 136.5, 160.9 (d, $J = 242$ Hz), 169.6, 170.6 (d, $J = 5.1$ Hz). ^{31}P NMR (81 MHz, DMSO-d_6): $\delta = 22.5$.

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Yield 59%; pale solid; dr = 40:60. Anal. Calcd. for $C_{24}H_{24}N_2O_6FP$ (486.44): C, 59.26; H, 4.97; P, 6.37. Found: C, 59.19; H, 5.04; P, 6.28%. m/z (M+1) 487.

Major diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.72$ (d, $J =$ 9.2 Hz, 1H, H_b), 2.80 (d, $J = 9.2$ Hz, 1H, H_a), 3.50 (d, $J = 10.9$ Hz, 3H, OCH_3), 3.76 (d, $J = 10.9$ Hz, 3H, OCH_3), 3.78 (d, $J = 11.2$ Hz, 1H, CH_2N), 4.19 (d, $J = 11.2$ Hz, 1H, CH_2N), 5.08 (d, $J = 1.3$ Hz, 1H, H_c), 5.60 (d, $J = 21.5$ Hz, 1H, PCHN), 6.48 (dd, $J = 5.6$ Hz, 1.3 Hz, 1H, CH=CH), 6.55 (d, $J = 5.6$ Hz, 1H, CH=CH), 7.03 (t, $J = 7.2$ Hz, 1H, Ph), 7.20–7.34 (m, 4H, Ph), 7.48–7.62 (m, 4H, 4-FC_6H_4), 9.87 (s, 1H, CONH). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 46.4$, 46.5, 50.0, 50.8 (d, $J = 158$ Hz), 53.1 (d, $J = 7.5$ Hz), 54.9 (d, $J = 7.5$ Hz), 81.5, 88.3, 116.2 (d, $J = 21.8$ Hz), 119.7, 123.3, 128.9, 129.5 (t, $J = 3.6$ Hz), 132.1 (t, $J =$ 8.4 Hz), 136.1, 137.3, 139.8, 162.5 (d, $J = 246$ Hz), 169.4, 171.1 (d, $J =$ 5.1 Hz). ^{31}P NMR (81 MHz, DMSO-d_6): $\delta = 22.2$.

Minor diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6): $\delta =$ 2.74 (d, $J =$ 9.2 Hz, 1H, H_b), 2.92 (dd, $J =$ 9.2 Hz, 2.6 Hz, 1H, H_a), 3.54 (d, $J =$ 11.2 Hz, 1H, CH_2N), 3.63 (d, $J =$ 10.9 Hz, 3H, OCH_3), 3.72 (d, $J =$ 10.9 Hz, 3H, OCH_3), 4.19 (d, $J =$ 11.2 Hz, 1H, CH_2N), 5.07 (d, $J =$ 1.4 Hz, 1H, H_c), 5.66 (d, $J =$ 22.0 Hz, 1H, PCHN), 6.50 (dd, $J = 5.7$ Hz, 1.4 Hz, 1H, CH=CH), 6.69 (d, $J =$ 5.7 Hz, 1H, CH=CH), 7.01 (t, $J = 7.2$ Hz, 1H, Ph), 7.20–7.34 (m, 4H, Ph), 7.48–7.62 (m, 4H, 4-FC_6H_4), 9.78 (s, 1H, CONH). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 46.4$, 46.6, 49.8 (d, $J = 155$ Hz), 50.3, 53.4 (d, $J =$ 6.7 Hz), 54.7 (d, $J = 6.7$ Hz), 81.6, 88.4, 116.0 (d, $J = 21.4$ Hz), 119.7, 123.3, 128.9, 129.2 (t, $J = 3.6$ Hz), 130.9 (t, $J = 8.4$ Hz), 136.1, 137.4, 139.6, 162.2 (d, $J = 246$ Hz), 169.2, 171.3 (d, $J = 5.1$ Hz). ^{31}P NMR (81 MHz, DMSO-d_6): $\delta = 23.1$.

*Dimethyl 1-[3-Aza-6-(benzylaminocarbonyl)-10-oxa-***exo***-tricyclo [5.2.1.0^{1,5}]-4-oxodec-8-en-3-yl]-1-(4-fluorophenyl) methylphosphonate (8b)*

Yield 48%; pale solid; *dr* = 40:60. Anal. Calcd. for $C_{25}H_{26}N_2O_6FP$ (500.47): C, 60.00; H, 5.24; P, 6.19. Found: C, 59.95; H, 5.13; P, 6.18%. m/z (M+1) 501.

Major diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.58$ (d, $J =$ 9.4 Hz, 1H, H_b), 2.69 (d, $J = 9.4$ Hz, 1H, H_a), 3.53 (d, $J = 10.6$ Hz, 3H, OCH_3), 3.75 (d, $J = 10.6$ Hz, 3H, OCH_3), 3.76 (d, $J = 11.3$ Hz, 1H, CCH_2N), 4.17 (d, $J = 11.3$ Hz, 1H, CCH_2N), 4.30 (d, $J = 5.8$ Hz, 2H,

PhCH$_2$NH), 5.00 (d, $J = 1.3$ Hz, 1H, H$_c$), 5.65 (d, $J = 21.6$ Hz, 1H, PCHN), 6.44 (dd, $J = 5.6$ Hz, 1.3 Hz, 1H, CH=CH), 6.53 (d, $J = 5.6$ Hz, 1H, CH=CH), 7.21–7.42 (m, 7H, 4-FC$_6$H$_4$, Ph), 7.60 (dd, $J = 8.1$ Hz, 5.4 Hz, 2H, 4-FC$_6$H$_4$), 8.20 (t, $J = 5.8$ Hz, 1H, CONH). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 42.8$, 45.6, 46.4, 49.7, 50.8 (d, $J = 158$ Hz), 53.1 (d, $J = 7.1$ Hz), 54.9 (d, $J = 7.1$ Hz), 81.8, 88.2, 116.2 (d, $J = 21.6$ Hz), 127.1, 127.8, 128.6, 129.5 (t, $J = 3.8$ Hz), 132.0 (t, $J = 8.3$ Hz), 136.1, 137.2, 139.8, 162.4 (d, $J = 246$ Hz), 170.4, 171.2 (d, $J = 5.4$ Hz). ^{31}P NMR (81 MHz, DMSO-d_6): $\delta = 22.3$.

Minor diastereomer: ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.60$ (d, $J = 9.3$ Hz, 1H, H$_b$), 2.83 (dd, $J = 9.3$ Hz, 2.6 Hz, 1H, H$_a$), 3.52 (d, $J = 11.9$ Hz, 1H, CCH$_2$N), 3.66 (d, $J = 11.0$ Hz, 3H, OCH$_3$), 3.74 (d, $J = 11.0$ Hz, 3H, OCH$_3$), 4.18 (d, $J = 11.9$ Hz, 1H, CCH$_2$N), 4.25 (d, $J = 5.9$ Hz, 2H, PhCH$_2$NH), 4.99 (d, $J = 1.2$ Hz, 1H, H$_c$), 5.68 (d, $J = 22.2$ Hz, 1H, PCHN), 6.46 (dd, $J = 5.8$ Hz, 1.2 Hz, 1H, CH=CH), 6.67 (d, $J = 5.8$ Hz, 1H, CH=CH), 7.13–7.34 (m, 7H, 4-FC$_6$H$_4$, Ph), 7.50 (dd, $J = 8.2$ Hz, 5.5 Hz, 2H, 4-FC$_6$H$_4$), 7.99 (t, $J = 5.9$ Hz, 1H, CONH). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 42.8$, 45.6, 46.5, 49.8 (d, $J = 158$ Hz), 49.9, 53.4 (d, $J = 6.8$ Hz), 53.8 (d, $J = 6.8$ Hz), 81.8, 88.4, 116.0 (d, $J = 21.7$ Hz), 127.1, 127.9, 128.6, 129.4 (t, $J = 3.0$ Hz), 130.9 (t, $J = 8.0$ Hz), 136.1, 137.2, 139.7, 162.1 (d, $J = 245$ Hz), 170.3, 171.3 (d, $J = 5.3$ Hz). ^{31}P NMR (81 MHz, DMSO-d_6): $\delta = 23.1$.

Dimethyl N-*Benzyl-3-aza-6-[(morpholine-4-yl)carbonyl]-10-oxa*-exo-*tricyclo[5.2.1.0^{1,5}]-4-oxodec-8-en-2-yl*-endo-*phosphonate (24)*

Yield 72%; pale solid; mp 121–123°C. Anal. Calcd. for C$_{22}$H$_{27}$N$_2$O$_7$P (464.44): C, 57.14; H, 5.89; P, 6.70. Found: C, 57.05; H, 5.93; P, 6.78%. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.93$ (d, $J = 9.2$ Hz, 1H, H$_b$), 3.05 (d, $J = 9.1$ Hz, 1H, H$_a$), 3.13–3.25 (m, 2H, CH$_2$N-morpholine), 3.46 (m, 2H, CH$_2$N-morpholine), 3.55–3.70 (m, 4H, CH$_2$O-morpholine), 3.76 (d, $J = 10.7$ Hz, 3H, OCH$_3$), 3.77 (d, $J = 10.7$ Hz, 3H, OCH$_3$), 3.93 (d, $J = 5.5$ Hz, 1H, PCHN), 4.18 (d, $J = 16.2$ Hz, 1H, CH$_2$N), 4.99 (d, $J = 16.2$ Hz, 1H, CH$_2$N), 5.07 (s, 1H, H$_c$), 6.57 (s, 2H, CH=CH), 7.16 (d, $J = 7.2$ Hz, 2H, Ph), 7.22–7.36 (m, 3H, Ph).

Dimethyl *N*-benzyl-3-aza-6-methoxycarbonyl-10-oxa-*exo*-tricyclo [5.2.1.0^{1,5}]-4-oxodec-8-en-2-yl-*endo*-phosphonate (23)

To a suspension of epoxyisoindolyl phosphonate **11** (0.39 g, 1 mmol) in anhydrous dichloromethane (10 mL), $SOCl_2$ (0.15 mL, 2 mmol) was

added. The reaction mixture was refluxed until the evolution of SO_2 and HCl had stopped (ca. 0.5 h). After this, anhydrous methanol (10 mL) was carefully added, and the resulting solution was refluxed for an additional 10 min. After cooling, the solvent was evaporated from the reaction mixture. The residue was dissolved in methanol, and the solvent was evaporated again. Treatment of the residue with ether and filtration gave 0.37 g of **23** as a white solid. Yield 92%; mp 97–98°C. Anal. Calcd. for $C_{19}H_{22}NO_7P$ (407.36): C, 56.02; H, 5.44; P, 7.60. Found: C, 56.11; H, 5.53; P, 7.58%. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.75$ (d, $J = 9.2$ Hz, 1H, H_b), 3.02 (d, $J = 9.2$ Hz, 1H, H_a), 3.58 (m, 3H, OCH_3), 3.77 (d, $J = 10.6$ Hz, 3H, OCH_3), 3.78 (d, $J = 10.6$ Hz, 3H, OCH_3), 4.00 (d, $J = 5.5$ Hz, 1H, PCHN), 4.21 (d, $J = 16.2$ Hz, 1H, CH_2N), 5.01 (d, $J = 16.2$ Hz, 1H, CH_2N), 5.12 (d, $J = 1.2$ Hz, 1H, H_c), 6.52 (dd, $J = 5.8$ Hz, 1.6 Hz, 1H, CH=CH), 6.60 (d, $J = 5.7$ Hz, 1H, CH=CH), 7.18–7.38 (m, 5H, Ph).

Dehydrative Aromatization of the Epoxyisoindolyl Phosphonates: General Procedure

A suspension of the epoxyisoindolyl phosphonate **3**, **4**, **7**, and **8** (1 mmol) in 85% H_3PO_4 (5 mL) was stirred at 80°C for 1 h, cooled, and diluted with water (50 mL). The precipitate formed was filtered off, washed with water, and dried. After crystallization from the appropriate solvent, the product is obtained as a white or pale yellow solid.

1-(7-Carboxyisoindolin-1-one-2-yl)-1-phenylmethylphosphonic Acid (5)

Yield 68%; white solid; mp > 250°C (EtOH/H_2O = 10/1). Anal. Calcd. for $C_{16}H_{14}NO_6P$ (347.27): C, 55.34; H, 4.06; P, 8.92. Found: C, 55.35; H, 4.03; P, 8.97%. m/z (M+1) 348. IR (KBr, cm^{-1}) ν_{max}: 1683 (COO), 1603, 1559 (NCO), 1223 (P=O). ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 4.61$ (d, $J = 19.2$ Hz, 1H, CH_2), 5.14 (d, $J = 19.2$ Hz, 1H, CH_2), 5.64 (d, $J =$ 21.0 Hz, 1H, NCHP), 7.33–7.46 (m, 3H, Ph), 7.65 (d, $J = 7.2$ Hz, 2H, Ph), 7.83 (t, $J = 7.6$ Hz, 1H, H_5), 7.94 (d, $J = 7.6$ Hz, 1H, H_4), 8.13 (d, $J = 7.6$ Hz, 1H, H_6). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 50.0$, 54.8 (d, $J = 149$ Hz), 128.3, 128.5, 128.6, 128.8, 129.1, 129.8 (d, $J = 7.5$ Hz), 132.0, 132.9, 134.8 (d, $J = 7.5$ Hz), 143.7, 165.3, 169.1 (d, $J = 5.5$ Hz). ^{31}P NMR (81 MHz, DMSO-d_6): $\delta = 14.0$.

1-(7-Carboxyisoindolin-1-on-2-yl)-1-(4-fluorophenyl) methylphosphonic Acid (6)

Yield 70%; white solid; mp > 250°C (EtOH/H_2O = 10/1). Anal. Calcd. for $C_{16}H_{13}NO_6FP$ (365.26): C, 52.61; H, 3.59; P, 8.48. Found: C, 52.63;

H, 3.64; P, 8.56%. m/z (M+1) 366. IR (KBr, cm^{-1}) ν_{max}: 1679 (COO), 1597, 1566 (NCO), 1221 (P=O). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.60 (d, J = 19.3 Hz, 1H, CH_2), 5.12 (d, J = 19.3 Hz, 1H, CH_2), 5.65 (d, J = 20.7 Hz, 1H, NCHP), 7.25 (t, J = 8.7 Hz, 2H, 4-FC_6H_4), 7.70 (dd, J = 8.7 Hz, 5.6 Hz, 2H, 4-FC_6H_4), 7.83 (t, J = 7.8 Hz, 1H, H_5), 7.94 (d, J = 7.8 Hz, 1H, H_4), 8.13 (d, J = 7.8 Hz, 1H, H_6). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 49.8, 54.0 (d, J = 149 Hz), 115.9 (d, J = 21.4 Hz), 128.2, 128.5, 128.9, 131.1 (dd, J = 3.4 Hz, 1.4 Hz), 131.9, 132.0 (dd, J = 8.0 Hz, 8.0 Hz), 132.9, 143.8, 162.3 (d, J = 244 Hz), 165.3, 169.1 (d, J = 5.5 Hz). ^{31}P NMR (81 MHz, DMSO-d_6): δ = 14.5.

1-[(7-(4-Fluorophenyl)aminocarbonyl)isoindolin-1-one-2-yl]-1-phenylmethylphosphonic Acid (9a)

Yield 46%; white solid; mp > 250°C (MeOH). Anal. Calcd. for $C_{22}H_{18}N_2O_5FP$ (440.37): C, 60.01; H, 4.12; P, 7.03. Found: C, 59.94; H, 4.03; P, 6.97%. m/z (M+1) 441. IR (KBr, cm^{-1}) ν_{max}: 1642 (NCO), 1642, 1583 (RNHC=O), 1207 (P=O). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.55 (d, J = 19.2 Hz, 1H, CH_2), 5.07 (d, J = 19.2 Hz, 1H, CH_2), 5.71 (d, J = 21.4 Hz, 1H, NCHP), 7.23 (t, J = 9.0 Hz, 2H, 4-FC_6H_4), 7.31–7.45 (m, 3H, Ph), 7.64 (d, J = 7.3 Hz, 2H, Ph), 7.75–7.89 (m, 4H, 4-FC_6H_4, H_4, H_5), 8.19 (d, J = 7.7 Hz, 1H, H_6), 12.94 (s, 1H, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 48.9, 54.3 (d, J = 149 Hz), 115.9 (d, J = 22.0 Hz), 121.9 (d, J = 7.7 Hz), 127.0, 127.8, 128.4, 129.0, 129.7 (d, J = 6.8 Hz), 130.4, 132.3, 132.7, 135.5 (d, J = 2.2 Hz), 135.9 (d, J = 2.7 Hz), 143.9, 158.7 (d, J = 241 Hz), 162.7, 168.4 (d, J = 5.8 Hz). ^{31}P NMR (81 MHz, DMSO-d_6): δ = 15.5.

1-[(7-(4-Fluorophenylmethyl)aminocarbonyl)isoindolin-1-one-2-yl]-1-phenylmethyl-phosphonic Acid (9b)

Yield 55%; white solid; mp 154–156°C (CH_3CN). Anal. Calcd. for $C_{23}H_{20}N_2O_5FP$ (454.40): C, 60.80; H, 4.44; P, 6.82. Found: C, 60.87; H, 4.46; P, 6.85%. m/z (M+1) 455. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.52 (d, J = 19.1 Hz, 1H, CH_2), 4.58 (m, 2H, 4-$FC_6H_4\underline{CH_2}NH$), 5.03 (d, J = 19.1 Hz, 1H, CH_2), 5.65 (d, J = 21.2 Hz, 1H, NCHP), 7.16 (t, J = 8.8 Hz, 2H, 4-FC_6H_4), 7.29–7.46 (m, 5H, 4-FC_6H_4, Ph), 7.60 (d, J = 7.7 Hz, 2H, Ph), 7.75 (t, J = 7.7 Hz, 1H, H_5), 7.82 (d, J = 7.7 Hz, 1H, H_4), 8.20 (d, J = 7.7 Hz, 1H, H_6), 11.39 (t, J = 5.7 Hz, 1H, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 42.2, 48.4, 53.9 (d, J = 150 Hz), 115.0 (d, J = 21.1 Hz), 126.2, 127.4, 127.8, 128.5, 129.0, 129.1, 129.2 (d, J = 8.0 Hz), 130.2, 131.7 (d, J = 6.0 Hz), 135.0 (d, J = 2.0 Hz), 135.3 (d, J = 3.0 Hz), 143.5, 161.1 (d, J = 243 Hz), 163.8, 167.9 (d, J = 5.6 Hz). ^{31}P NMR (81 MHz, DMSO-d_6): δ = 15.4.

1-[(7-Phenylaminocarbonyl)isoindolin-1-one-2-yl]-1-(4-fluorophenyl)methylphosphonic Acid (10a)

Yield 30%; pale solid; mp > 250°C (*i*-PrOH/DMF/H_2O = 1/1/4). Anal. Calcd. for $C_{22}H_{18}N_2O_5FP$ (440.37): C, 60.01; H, 4.12; P, 7.03. Found: C, 60.09; H, 4.13; P, 7.14%. m/z (M+1) 441. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 4.54$ (d, $J = 19.0$ Hz, 1H, CH_2), 5.07 (d, $J = 19.0$ Hz, 1H, CH_2), 5.72 (d, $J = 21.8$ Hz, 1H, NCHP), 7.13 (t, $J = 7.8$ Hz, 1H, Ph), 7.24 (t, $J = 9.0$ Hz, 2H, 4-FC_6H_4), 7.40 (t, $J = 7.8$ Hz, 2H, Ph), 7.69 (dd, $J = 9.0$ Hz, 5.5 Hz, 2H, 4-FC_6H_4), 7.76–7.89 (m, 4H, Ph, H_4, H_5), 8.21 (d, $J = 7.6$ Hz, 1H, H_6), 12.91 (s, 1H, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta =$ 48.4, 53.2 (d, $J = 150$ Hz), 115.3 (d, $J = 21.4$ Hz), 119.6, 126.3, 127.2, 128.7, 130.0, 131.2 (d, $J = 7.6$ Hz), 131.3, 131.7, 132.3, 138.9, 143.3, 161.5 (d, $J = 245$ Hz), 162.0, 167.8 (d, $J = 5.7$ Hz). ^{31}P NMR (81 MHz, DMSO-d_6): $\delta = 14.4$.

1-[(7-Benzylaminocarbonyl)isoindolin-1-one-2-yl]-1-(4-fluorophenyl)methylphosphonic Acid (10b)

Yield 50%; white solid; mp > 250°C (CH_3CN). Anal. Calcd. for $C_{23}H_{20}N_2O_5FP$ (454.40): C, 60.80; H, 4.44; P, 6.82. Found: C, 60.75; H, 4.56; P, 6.94%. m/z (M-1) 453. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta =$ 4.50 (d, $J = 19.0$ Hz, 1H, CH_2), 4.60 (m, 2H, Ph$\underline{CH_2}$NH), 5.00 (d, $J =$ 19.0 Hz, 1H, CH_2), 5.64 (d, $J = 21.4$ Hz, 1H, NCHP), 7.15–7.29 (m, 3H, 4-FC_6H_4, Ph), 7.30–7.41 (m, 4H, Ph), 7.64 (dd, $J = 8.8$ Hz, 5.7 Hz, 2H, 4-FC_6H_4), 7.75 (t, $J = 7.7$ Hz, 1H, H_5), 7.81 (d, $J = 7.7$ Hz, 1H, H_4), 8.21 (d, $J = 7.7$ Hz, 1H, H_6), 11.39 (t, $J = 5.1$ Hz, 1H, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 43.0$, 48.2, 53.1 (d, $J = 150$ Hz), 115.3 (d, $J = 21.3$ Hz), 126.2, 126.8, 127.2, 127.3, 128.3, 130.3, 131.2, 129.2 (d, $J = 7.0$ Hz), 131.7, 131.8, 139.1, 143.5, 161.6 (d, $J = 244$ Hz), 163.7, 167.9 (d, $J = 5.7$ Hz). ^{31}P NMR (81 MHz, DMSO-d_6): $\delta = 15.2$.

Synthesis of Diethyl (2-Benzylisoindolin-1-one-3-yl) phosphonate (18)

Compound **18** was synthesized in analogy to a published procedure.[21] A mixture of 2-benzyl-3-hydroxy-isoindolin-1-one **17** (0.83 g, 3 mmol) and trifluoroacetic anhydride (3 mL) was stirred for 1 h under argon. After the excess trifluoroacetic anhydride and the resulting trifluoroacetic acid were removed under reduced pressure, triethyl phosphite (1.04 mL, 6 mmol) in 10 mL of anhydrous chloroform was added to the residue, and the resulting mixture was stirred for 4 h. The reaction mixture was quenched with aqueous $NaHCO_3$ (saturated, 50 mL). The organic layer was washed with water and dried over Na_2SO_4, and the solvent was evaporated. The residue obtained was dried for 1.5 h at

80°C under reduced pressure (0.1 mm Hg) to give 0.75 g of **18** as a pale oil. Yield: 70%. IR (KBr, cm^{-1}) ν_{max}: 1707 (NCO), 1259 (P=O). Anal. Calcd. for $C_{19}H_{22}NO_4P$ (359.37): C, 63.50; H, 6.17; P, 8.62. Found: C, 63.43; H, 6.10; P, 8.64%. m/z (M+1) 360. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.10$ (t, $J = 7.2$ Hz, 3H, CH_3), 1.14 (t, $J = 7.2$ Hz, 3H, CH_3), 3.84–4.08 (m, 4H, OCH_2), 4.61 (d, $J = 15.5$ Hz, 1H, Ph$\underline{CH_2}$N), 5.06 (d, $J = 14.2$ Hz, 1H, NCHP), 5.27 (d, $J = 15.5$ Hz, 1H, Ph$\underline{CH_2}$N), 7.19–7.38 (m, 5H, C_6H_4), 7.55–7.64 (m, 1H, C_6H_4), 7.64–7.72 (m, 2H, C_6H_4), 7.81 (d, $J = 7.5$ Hz, 1H, C_6H_4). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 16.1$ (d, $J = 5.5$ Hz), 16.2 (d, $J = 5.5$ Hz), 44.6, 56.4 (d, $J = 153$ Hz), 62.8 (d, $J = 7.2$ Hz), 62.9 (d, $J = 7.2$ Hz), 123.2 (d, $J = 1.4$ Hz), 124.5 (d, $J = 2.5$ Hz), 127.2, 127.5, 128.5, 128.8 (d, $J = 2.1$ Hz), 131.3 (d, $J = 4.2$ Hz), 131.7 (d, $J = 2.7$ Hz), 136.9, 139.0 (d, $J = 6.0$ Hz), 167.8 (d, $J = 3.5$ Hz). ^{31}P NMR (81 MHz, DMSO-d_6): $\delta = 18.4$.

Synthesis of (2-Benzylisoindolin-1-one-3-yl)phosphonic Acid (19)

To a solution of the phosphonate **18** (0.36 g, 1 mmol) in 10 mL of anhydrous dichloromethane, Me_3SiBr (0.40 mL, 3 mmol) was added. The reaction mixture was allowed to stand overnight, and subsequently the solvent was evaporated. The residue was dissolved in 10 mL of aqueous dioxane (1:1), and after 1 h the solvent was evaporated again. After crystallization from EtOAc/*i*-PrOH (4/1) 0.22 g of **19** was obtained as a white solid. Yield 73%; mp 228–229°C. IR (KBr, cm^{-1}) ν_{max}: 1602 (NCO), 1194 (P=O). Anal. Calcd. for $C_{15}H_{14}NO_4P$ (303.26): C, 59.41; H, 4.65; P, 10.21. Found: C, 59.49; H, 4.68; P, 10.20%. m/z (M-1) 302. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 4.56$ (d, $J = 15.5$ Hz, 1H, NCHP), 4.67 (d, $J = 15.1$ Hz, 1H, Ph$\underline{CH_2}$N), 5.30 (d, $J = 15.1$ Hz, 1H, Ph$\underline{CH_2}$N), 7.18–7.37 (m, 5H, Ph), 7.52 (d, $J = 7.5$ Hz, 1H, C_6H_4), 7.60 (d, $J = 7.5$ Hz, 1H, C_6H_4), 7.66 (d, $J = 7.5$ Hz, 1H, C_6H_4), 7.75 (d, $J = 7.5$ Hz, 1H, C_6H_4). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 44.1$, 57.6 (d, $J = 148$ Hz), 122.8, 124.4 (d, $J = 2.4$ Hz), 127.2, 127.7, 128.1 (d, $J = 1.9$ Hz), 128.5, 131.2 (d, $J = 2.1$ Hz), 131.5 (d, $J = 3.8$ Hz), 137.3, 140.6 (d, $J = 5.5$ Hz), 167.7 (d, $J = 3.2$ Hz). ^{31}P NMR (81 MHz, DMSO-d_6): $\delta = 15.1$.

Aromatization of 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 (11)

Treatment with 85% H_3PO_4

A suspension of the epoxyisoindolyl phosphonate **11** (0.39 g, 1 mmol) in 85% H_3PO_4 (5 mL) was stirred at 80°C for 4 h, cooled, diluted with water (50 mL), and left to stand overnight. After drying, filtration of

the precipitate gave a 0.15 g mixture of compounds **11**, **13**, and **14** as a pale solid.

Epoxyisoindolyl Phosphonate 11. MS: m/z (M+1) 394. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.61$ (d, $J = 9.1$ Hz, 1H, H_b), 2.94 (d, $J = 9.1$ Hz, 1H, H_a), 3.77 (d, $J = 10.6$ Hz, 3H, OCH_3), 3.78 (d, $J = 10.6$ Hz, 3H, OCH_3), 3.98 (d, $J = 5.7$ Hz, 1H, PCHN), 4.21 (d, $J = 16.2$ Hz, 1H, CH_2N), 5.02 (d, $J = 16.2$ Hz, 1H, CH_2N), 5.07 (br s, 1H, H_c), 6.51 (dd, $J = 5.7$ Hz, 1.6 Hz, 1H, CH=CH), 6.58 (d, $J = 5.7$ Hz, 1H, CH=CH), 7.20–7.44 (m, 5H, Ph). ^{31}P NMR (81 MHz, DMSO-d_6): $\delta = 21.9$.

Dimethyl (2-Benzyl-7-carboxyisoindolin-1-one-3-yl)phosphonate (13). MS: m/z (M+1) 376. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 3.66$ (d, $J = 10.8$ Hz, 3H, OCH_3), 3.67 (d, $J = 10.8$ Hz, 3H, OCH_3), 4.71 (d, $J = 15.6$ Hz, 1H, Ph$\underline{CH_2}$N), 5.27 (d, $J = 15.6$ Hz, 1H, Ph$\underline{CH_2}$N), 5.57 (d, $J = 16.6$ Hz, 1H, NCHP), 7.20–7.44 (m, 5H, Ph), 7.81–7.96 (m, 2H, H_4, H_5), 8.08–8.20 (m, 1H, H_6). ^{31}P NMR (81 MHz, DMSO-d_6): $\delta = 19.8$.

(2-Benzyl-7-carboxyisoindolin-1-one (14). MS: m/z (M+1) 268. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 4.63$ (s, 2H, PhCH_2N), 4.86 (s, 1H, ArCH_2N), 7.20–7.44 (m, 5H, Ph), 7.81–7.96 (m, 2H, H_4, H_5), 8.08–8.20 (m, 1H, H_6).

Treatment with NaOMe/MeOH

Epoxyisoindolyl phosphonate **11** (0.39 g, 1 mmol) was dissolved in 10 mL of a 3M solution of NaOMe in MeOH and left at room temperature overnight. The solvent was evaporated, and the residue was dissolved in water and neutralized with HCl. A gum-like precipitate was formed, which became crystalline upon decantation and treatment with a new portion of water. After drying, filtration gave 0.17 g mixture of compounds **13**, **14**, and **15** as a white solid. The NMR data for compounds **13** and **14** are reported above.

Monomethyl (2-Benzyl-7-carboxyisoindolin-1-one-3-yl) phosphonate (15). MS: m/z (M+1) 362. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 3.54$ (d, $J = 10.9$ Hz, 3H, OCH_3), 4.82 (d, $J = 15.4$ Hz, 1H, Ph$\underline{CH_2}$N), 5.21 (d, $J = 17.5$ Hz, 1H, NCHP), 5.30 (d, $J = 15.4$ Hz, 1H, Ph$\underline{CH_2}$N), 7.26–7.44 (m, 5H, Ph), 7.77–7.98 (m, 2H, H_4, H_5), 8.08–8.20 (m, 1H, H_6). ^{31}P NMR (81 MHz, DMSO-d_6): $\delta = 14.0$.

Treatment with Bromotrimethylsilane

To a solution of epoxyisoindolyl phosphonate **11** (0.39 g, 1 mmol) in 20 mL of anhydrous dichloromethane, Me_3SiBr (0.66 mL, 5 mmol) was added, and the reaction mixture was kept overnight. Subsequently

the solvent was evaporated, the residue was dissolved in 10 mL of aqueous dioxane (1:1); after 1 h the solvent was evaporated again, and the residue was dried for 1 h at 80°C under reduced pressure (18 mm Hg) to give 0.25 g mixture of compounds **14** and **16** as a colorless clear melt. NMR data for compound **14** are reported above.

*(N-Benzyl-3-aza-6-carboxy-10-oxa-*exo*-tricyclo[5.2.1.0^{1,5}]-4-oxodec-8-en-2-yl)-*endo*-phosphonic Acid (16).* MS: m/z (M+1) 366. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.58$ (d, $J = 9.1$ Hz, 1H, H_b), 2.86 (d, $J = 9.1$ Hz, 1H, H_a), 3.55 (d, $J = 6.5$ Hz, 1H, PCHN), 4.33 (d, $J = 15.8$ Hz, 1H, CH_2N), 5.03 (br s, 1H, H_c), 5.05 (d, $J = 15.8$ Hz, 1H, CH_2N), 6.45 (dd, $J = 6.0$ Hz, 1.6 Hz, 1H, CH=CH), 6.71 (d, $J = 6.0$ Hz, 1H, CH=CH), 7.20–7.42 (m, 5H, Ph). ^{31}P NMR (81 MHz, DMSO-d_6): $\delta = 15.1$.

Aromatization of Dimethyl *N*-Benzyl-3-aza-6-methoxycarbonyl-10-oxa-*exo*-tricyclo[5.2.1.0^{1,5}]-4-oxodec-8-en-2-yl-*endo*-phosphonate (23) and *N*-Benzyl-3-aza-6-[(morpholine-4-yl)carbonyl]-10-oxa-*exo*-tricyclo [5.2.1.0^{1,5}]-4-oxodec-8-en-2-yl-*endo*-phosphonate (24) in Trifluoroacetic Acid

A sample (30 mg) of epoxyisoindolyl phosphonate **23** or **24** was dissolved in TFA (1 mL) and heated at 70°C for 14 h. The ^{31}P NMR spectrum of the reaction mixture showed only one signal at 0 ppm. The ^{1}H NMR (300 MHz, DMSO-d_6) spectrum of the solid residue obtained after evaporation of TFA and additional drying under reduced pressure showed the signals of compound **14** (see above). The LCMS spectrum showed m/z (M+1) 268 for the major peak.

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