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ORIGINAL PAPER

Synthesis of 3-alkylideneisoindolinones and isoindolones by a Horner–Wadsworth–Emmons reaction

Miguel Ángel Reyes-González · Ángel Zamudio-Medina · Oscar Abelardo Ramírez-Marroquín · Mario Ordóñez

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Abstract A series of 3-alkylideneisoindolinones was prepared by a Horner–Wadsworth–Emmons (HWE) reaction of aromatic aldehydes with *N*-(ω-hydroxyalkyl)-substituted 3-phosphoisoindolin-1-ones, obtained in one-pot synthesis from 2-formylbenzoic acid. Additionally, the intramolecular HWE reaction of the *N*-(ω-formylalkyl)-substituted phosphoisoindolin-1-ones afforded the corresponding isoindolone derivatives.

Keywords Phosphonates · Three-component reaction · Wittig reaction · Heterocycles

Introduction

In recent years, the 3-methyleneisoindolin-1-ones and their derivatives have been the subject of growing interest because they are present in numerous natural products or are designed as pharmaceutical compounds with a wide range of biological activities. For example, AKS 186 was found to inhibit vasoconstriction induced by a thromboxane A2 analog [1, 2], whereas the derivatives **1** [3] and **2** [4–6] are useful intermediates in the synthesis of important heterocyclic compounds, and the isoindolin-1-ones of type **3** have attracted interest in the field of medicinal chemistry [7–10] (Fig. 1). Other isoindolin-1-ones have also shown a remarkably wide array of biological activities [11–15]. Due to the biological importance of 3-methyleneisoindolin-1-ones, several methods for their synthesis have been developed [16–24], but the preparation of tricyclic isoindolin-1-ones of type **3** (R = H) has been seldom studied, and only the radical cyclization cascade of ynamides [25, 26] and cyclization of *N*-(iodoalkyl) cyclic imides with SmI_2 [27] have been reported.

Recently, we reported a practical synthesis of *N*-substituted isoindolin-1-ones [28] and 3-(arylmethylene)isoindolin-1-ones under mild reaction conditions [29]. As part of our interest in the development of practical and efficient synthesis methods in an environmentally friendly manner, we herein report an alternative simple route for the synthesis of *N*-(ω-hydroxyalkyl)-substituted 3-(arylmethylene)isoindolin-1-ones **7** and **8** and tricyclic compounds type **3** from easily obtained dimethyl isoindolin-1-one-3-ylphosphonates. The process involves a 'one-pot' three-component reaction of 2-formylbenzoic acid [30] with the appropriate amino alcohol and dimethyl phosphite, followed by an intermolecular HWE reaction. Otherwise, subsequent oxidation of the hydroxy moiety, and finally an intramolecular HWE reaction provides the respective tricyclic compounds.

Results and discussion

For the synthesis of the target compounds **3**, **7**, and **8**, our strategy started with the preparation of dimethyl isoindolin-1-one-3-ylphosphonates **6a–6d**, which were obtained in good yields by means of a 'one-pot' three-component reaction of 2-formylbenzoic acid (**4**) with the corresponding amino alcohol **5** and dimethyl phosphite in methanol under microwave irradiation in an open flask (55 °C/180 W, 10 min) [28]. Remarkably, this process did not need any catalyst (Scheme 1).

With the isoindolin-1-one-3-phosphonates **6a** and **6b** in hand, we focused our attention on the intermolecular HWE

M. Á. Reyes-González · Á. Zamudio-Medina · O. A. Ramírez-Marroquín · M. Ordóñez (✉)
Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, Cuernavaca, Mexico
e-mail: palacios@uaem.mx

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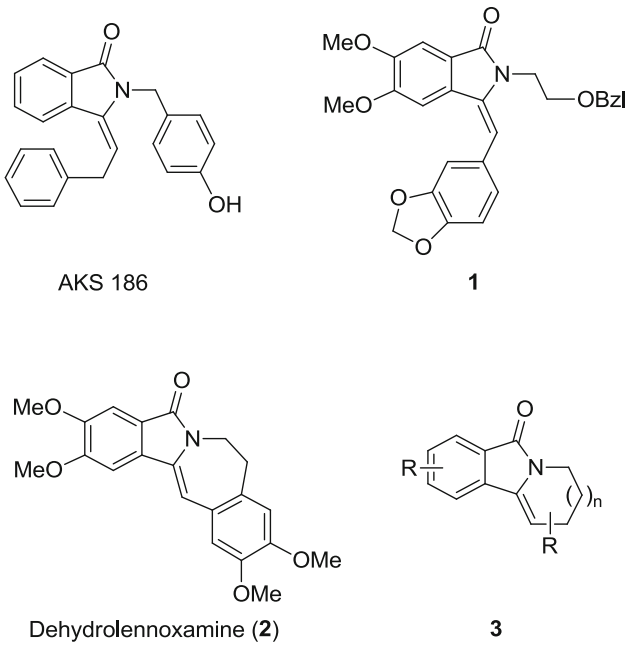
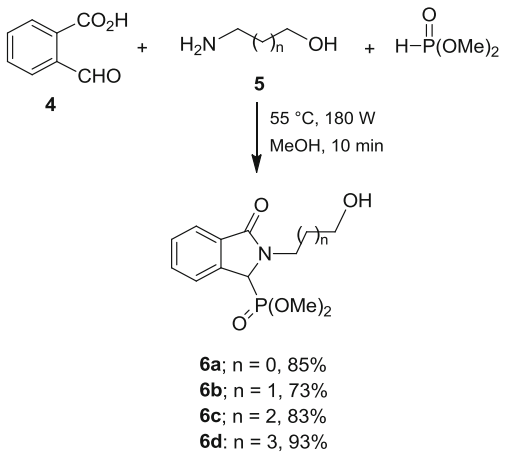


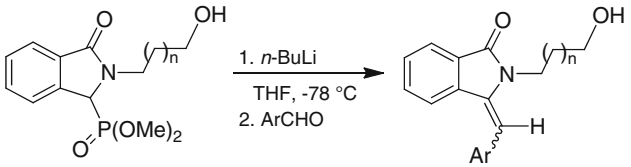
Fig. 1 Structure of biologically active 3-isoindolin-1-ones

Scheme 1



reaction with several aromatic aldehydes in order to obtain the desired 3-(arylmethylene)isoindolin-1-ones **7a**–**7e** and **8a**–**8e**, using the protocol that we have already reported [29]. Thus, treatment of the isoindolin-1-one-3-phosphonates **6a** and **6b** with *n*-BuLi in dry THF at −78 °C followed by the addition of the corresponding aromatic aldehyde afforded the 3-(arylmethylene)isoindolin-1-ones **7a**–**7e** and **8a**–**8e** in good yield and with moderate to good (*E*):(*Z*) selectivity. The results are summarized in Table 1. It is worth mentioning that for this process it was not necessary to protect the OH moiety of substrates, nor to use an excess of *n*-BuLi.

Table 1 Synthesis of 3-(arylmethylene)isoindolin-1-ones **7a**–**7e** and **8a**–**8e**



6a; n = 0
6b; n = 1

7a-7e; n = 0
8a-8e; n = 1

Entry	Product	Yield/%	Ratio (*E*):(*Z*)
1	**7a**, $n = 0$, Ar = C_6H_5	85	83:17
2	**7b**, $n = 0$, Ar = 4-$MeOC_6H_4$	95	20:80
3	**7c**, $n = 0$, Ar = 4-ClC_6H_4	92	19:81
4	**7d**, $n = 0$, Ar = 3,4-$(MeO)_2C_6H_3$	81	67:33
5	**7e**, $n = 0$, Ar = 3,4-$(OCH_2O)C_6H_3$	80	57:43
6	**8a**, $n = 1$, Ar = C_6H_5	86	79:21
7	**8b**, $n = 1$, Ar = 4-$MeOC_6H_4$	88	83:17
8	**8c**, $n = 1$, Ar = 4-ClC_6H_4	91	77:23
9	**8d**, $n = 1$, Ar = 3,4-$(MeO)_2C_6H_3$	92	87:13
10	**8e**, $n = 1$, Ar = 3,4-$(OCH_2O)C_6H_3$	95	75:25

The stereochemistry assignment in the compounds **7a**–**7e** and **8a**–**8e** was performed based on our previously reported results [29]. Additionally, 2-D NOESY spectra and X-ray crystallographic analysis of compound **7c** permitted us to unambiguously assign it as the (*Z*)-isomer (Fig. 2).

Inspired by these results, we turned our attention to the synthesis of tricyclic compounds **10b**–**10d**, which were obtained through an intramolecular HWE reaction with the aldehydes **9b**–**9d**. Thus, in order to obtain the starting aldehydes, initially the isoindolin-1-one-3-phosphonates **6** were treated with pyridinium chlorochromate (PCC) in dichloromethane at room temperature, obtaining the corresponding aldehydes **9** in low yield and unidentified products. In order to improve the chemical yield, we successfully attempted the oxidation using the Dess–Martin periodinane (DMP). In this context, **6b** was reacted with DMP in dry dichloromethane at room temperature obtaining the aldehyde **9b** in 89 % yield. Under the identical conditions, the oxidation of the alcohols **6c** and **6d** afforded the corresponding aldehydes **9c** and **9d** in 89 and 88 % yield, respectively. The compound **9b** was not stable when it was purified through flash column chromatography, and for that reason the crude product was directly used in the next step. With the aldehydes **9b**–**9d** in hand, we carried out the intramolecular HWE reaction using the same protocol described above. Thus, the reaction of aldehyde **9b** with *n*-BuLi solution in dry THF at −78 °C gave the

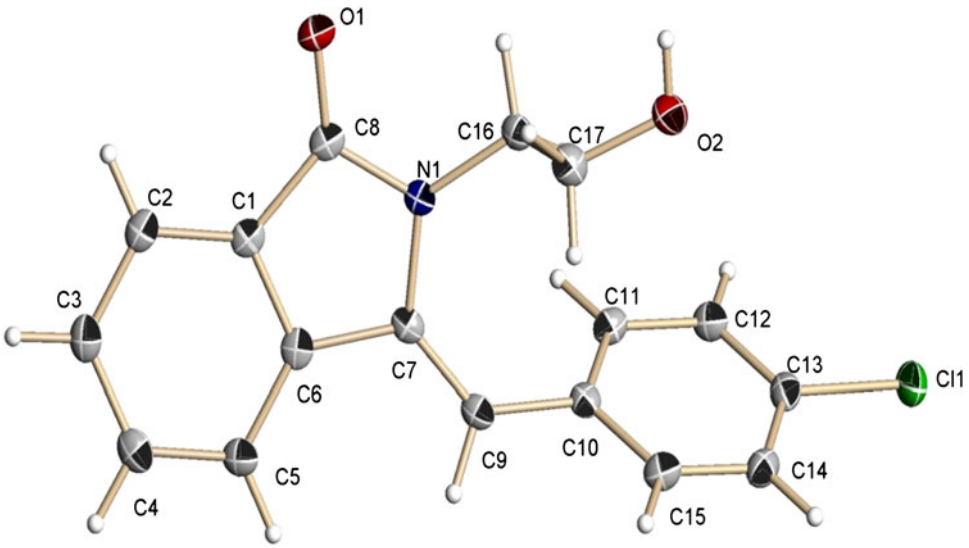
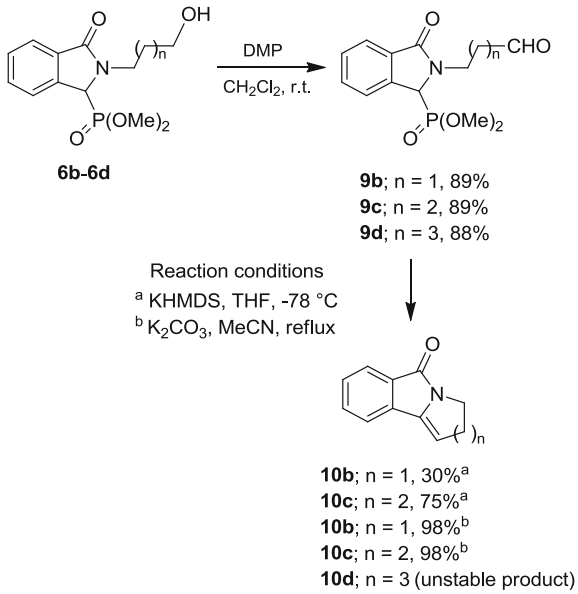


Fig. 2 The X-ray crystal structure for (*Z*)-**7c**

desired tricyclic compound **10b** in 26 % yield and other unidentified products. In order to use a less nucleophilic base that only abstracts the α-phosphonate hydrogen, the reaction of the aldehyde **9b** was performed using potassium bis(trimethylsilyl)amide (KHMDS) in dry THF at −78 °C, obtaining in this case **10b** in 30 % yield, whereas the treatment of **9c** with KHMDS in dry THF at −78 °C provided the tricyclic compound **10c** in 75 %. However, the reaction of **9d** afforded only unstable products. In an effort to improve the chemical yield of the HWE reaction and to implement easier handling reaction conditions, we carried out the intramolecular HWE reaction of **9b–9d** using K_2CO_3 [31] as base in acetonitrile at reflux, obtaining the desired tricyclic compounds **10b** and **10c** in quantitative yield (Scheme 2).

Scheme 2



Conclusions

In conclusion, we report an efficient procedure for the synthesis of *N*-(ω-hydroxyalkyl)-substituted 3-(arylmethylene)isoindolin-1-ones by means of a HWE reaction between dimethyl isoindolin-1-one-3-ylphosphonates and aromatic aldehydes without previous protection of the OH moiety. This process expands the synthesis utility of dimethyl isoindolin-1-one-3-ylphosphonates, and could be applied to the preparation of biologically active compounds, such as the dehydrolennoxamine derivatives. Additionally, we report the utility of dimethyl isoindolin-1-one-3-ylphosphonates in the synthesis of tricyclic compounds by means of an oxidation followed by an intramolecular HWE reaction under easy handling, metal-free conditions, and excellent chemical yields. The main advantage of this protocol is the easy access to the required dimethyl isoindolin-1-one-3-ylphosphonates, which are obtained on a large scale in only one step under microwave irradiation in open flask and catalyst-free conditions.

Experimental

All commercial materials were used as received from commercial sources without further purification. Melting points were registered in a Fisher-Johns apparatus. Flash chromatography was performed using 230–400 mesh Silica Flash 60® silica gel. Thin layer chromatography was performed with pre-coated TLC sheets of silica gel (60F254, Merck). NMR spectra were recorded in a Varian System

instrument (400 MHz for ^{1}H, and 100 MHz for ^{13}C) and in a Mercury instrument (81 MHz for ^{31}P), and calibrated with $CDCl_3$ as the solvent and TMS as the internal standard signal. Chemical shifts (δ) are reported in parts per million. Multiplicities are recorded as: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, td = triplet of doublets, bs = broad singlet, q = quartet, and m = multiplet. Coupling constants (J) are given in Hz. High resolution FAB$^+$ and CI$^+$ mass spectra (HRMS) were obtained in a JEOL HRMStation JHRMS-700. The X-ray was obtained in an APEX-Bruker at 173(2) K. Spectroscopic data for **6a–6c** [29], **10b**, and **10c** [25–27] were identical to those reported in the literature.

*Dimethyl [2-(5-hydroxypentyl)-3-oxoisoindolin-1-yl]-phosphonate (**6d**, $C_{15}H_{22}NO_5P$)*

To a solution of 1.0 g 2-formylbenzoic acid (6.7 mmol) in 10 cm^3 methanol was added 686 mg 5-amino-1-pentanol (6.7 mmol). The reaction mixture was irradiated in a CEM microwave at 55 °C and 180 W for 5 min. After this time, 880 mg dimethyl phosphite (0.7 cm^3, 8.0 mmol) was added and the reaction mixture was irradiated again at 55 °C, 180 W for 5 min. The crude product was purified by flash column chromatography (AcOEt 100 % and then acetone 100 %), obtaining 2.02 g (93 %) of **6d** as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34–1.45 (m, 2H), 1.55-1.81 (m, 4H), 3.52–3.64 (m, 1H), 3.58 (d, J = 10.8 Hz, 3H, $(CH_3O)_2P$), 3.66–3.77 (m, 2H), 3.73 (d, J = 10.8 Hz, 3H, $(CH_3O)_2P$), 4.06–4.14 (m, 1H), 4.47 (bs, 1H, OH), 4.94 (d, J = 13.6 Hz, 1H, $CHP(OCH_3)_2$), 7.53 (t, J = 7.6 Hz, 1H, H_{arom}), 7.59 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H, H_{arom}), 7.74 (ddd, J = 7.6, 7.2, 0.8 Hz, 1H, H_{arom}), 7.86 (d, J = 8.4 Hz, 1H, H_{arom}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2, 22.8, 27.3, 36.9, 48.9 (d, J = 7.6 Hz, $(CH_3O)_2P$), 49.0 (d, J = 7.6 Hz, $(CH_3O)_2P$), 52.9 (d, J = 154.5 Hz, $CHP(OCH_3)_2$), 57.5, 119.1, 119.5, 124.2, 126.9, 127.3, 133.4, 164.1 ppm; ^{31}P NMR (81 MHz, $CDCl_3$): δ = 20.25 ppm; HRMS [CI$^+$]: *m/z* calculated for $C_{15}H_{23}NO_5P$ $[M + H]^+$ 328.1200, found 328.1289.

*General procedure for the synthesis of 3-benzylideneisoindolinones **7a–7e** and **8a–8e***

A solution of *n*-BuLi (1.0 equiv) was added dropwise to a stirred solution of the isoindolin-1-one-3-ylphosphonates **6** (1.0 equiv) in 15 cm^3 THF at −78 °C under nitrogen. The solution was stirred for 15 min at this temperature, followed by the addition of the corresponding aldehyde (1.0 equiv). The reaction mixture was stirred at −78 °C for 15 min, and at room temperature for 1 h. The reaction mixture was quenched by the addition of saturated solution of NH_4Cl and extracted with AcOEt (2 × 20 cm^3). The organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was analyzed by ^{1}H NMR and then purified by flash chromatography AcOEt:hexanes (2:1), obtaining the corresponding 3-benzylideneisoindolin-1-ones **7a–7e** and **8a–8e**.

*3-Benzylidene-2-(2-hydroxyethyl)isoindolin-1-one (**7a**, $C_{17}H_{15}NO_2$)*

Yield: 237 mg (85 %), (*E*):(*Z*) isomer ratio 83:17. After chromatographic separation, the (*E*)-isomer was obtained as a white solid; m.p.: 111–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.75 (bs, 1H, OH), 3.47 (t, J = 5.6 Hz, 2H, CH_2N), 3.80 (t, J = 6.0 Hz, 2H, CH_2OH), 6.82 (s, 1H, CH), 7.31–7.35 (m, 3H, H_{arom}), 7.38–7.42 (m, 2H, H_{arom}), 7.49 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H, H_{arom}), 7.60 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H, H_{arom}), 7.74 (d, J = 8.0 Hz, 1H, H_{arom}), 7.82 (d, J = 7.2 Hz, 1H, H_{arom}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.8, 61.2, 106.9, 119.3, 123.3, 127.8, 128.3, 129.1, 129.5, 132.1, 133.9, 134.6, 135.1, 138.4, 170.4 ppm; HRMS [CI$^+$]: *m/z* calculated for $C_{17}H_{16}NO_2$ $[M + H]^+$ 266.1103, found 266.1171.

*3-(4-Methoxybenzylidene)-2-(2-hydroxyethyl)isoindolin-1-one (**7b**, $C_{18}H_{17}NO_3$)*

Yield: 294 mg (95 %), (*E*):(*Z*) isomer ratio 20:80. After chromatographic separation, the (*Z*)-isomer was obtained as a white solid; m.p.: 157–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.95 (bs, 1H, OH), 3.49–3.51 (m, 2H, CH_2N), 3.84 (s, 3H, CH_3O), 3.85 (t, J = 5.2 Hz, 2H, CH_2O), 6.78 (s, 1H, CH), 6.92 (AA'BB', J = 8.6 Hz, 2H, H_{arom}), 7.25 (AA'BB', J = 8.6 Hz, 2H, H_{arom}), 7.48 (dd, J = 7.6, 7.6 Hz, 1H, H_{arom}), 7.59 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H, H_{arom}), 7.73 (d, J = 7.6 Hz, 1H, H_{arom}), 7.82 (d, J = 7.6 Hz, 1H, H_{arom}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.0, 55.5, 61.3, 107.5, 114.0, 119.5, 123.4, 126.7, 128.0, 129.1, 130.9, 132.3, 134.6, 138.6, 159.4, 170.8 ppm; HRMS [CI$^+$]: *m/z* calculated for $C_{18}H_{18}NO_3$ $[M + H]^+$ 296.1208, found 296.1275.

The (*E*)-isomer was obtained as a yellow solid; m.p.: 131–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.90 (bs, 1H, OH), 3.88 (s, 3H, CH_3O), 3.97 (t, J = 5.6 Hz, 2H, CH_2N), 4.09 (t, J = 5.6 Hz, 2H, CH_2OH), 6.61 (s, 1H, CH), 6.96 (d, J = 8.8 Hz, 2H, H_{arom},), 7.31–7.39 (m, 4H, H_{arom}), 7.42 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H, H_{arom}), 7.83 (d, J = 7.2 Hz, 1H, H_{arom}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.8, 55.6, 61.5, 111.1, 114.4, 123.3, 123.6, 127.3, 129.4, 130.1, 131.0, 131.9, 134.3, 135.4, 159.6, 168.0 ppm; HRMS [CI$^+$]: *m/z* calculated for $C_{18}H_{18}NO_3$ $[M + H]^+$ 296.1208, found 296.1278.

*3-(4-Chlorobenzylidene)-2-(2-hydroxyethyl)isoindolin-1-one (**7c**, $C_{17}H_{14}ClNO_2$)*

Yield: 263 mg (92 %), (*E*):(*Z*) isomer ratio 19:81. After chromatographic separation, the (*Z*)-isomer was obtained

as a yellow solid; m.p.: 139–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.73 (bs, 1H, OH), 3.49 (t, J = 5.6 Hz, 2H, CH_2N), 3.81 (t, J = 5.6 Hz, 2H, CH_2OH), 6.72 (s, 1H, CH), 7.27 (AA'BB', J = 8.0 Hz, 2H, H_{arom}), 7.37 (AA'BB', J = 8.0 Hz, 2H, H_{arom}), 7.49 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H, H_{arom}), 7.61 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H, H_{arom}), 7.73 (d, J = 7.6 Hz, 1H, H_{arom}), 7.82 (d, J = 7.6 Hz, 1H, H_{arom}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.9, 61.1, 105.7, 119.6, 123.6, 128.1, 128.8, 129.5, 131.0, 132.5, 133.2, 134.0, 135.6, 138.4, 170.6 ppm; HRMS [CI$^+$]: *m/z* calculated for $C_{17}H_{15}ClNO_2$ $[M + H]^+$ 300.0713, found 300.0793.

Summary of the crystallographic data (CCDC 978159): triclinic, space group P-1, a = 7.2380(10) Å, b = 8.6727(12) Å, c = 11.7007(17) Å, V = 705.17(17) Å^3, Z = 2, D_c = 1.412 Mg/m^3, 6,697 reflections collected, 2,487 unique (R_{int} = 0.0516), data/parameters: 2,487/1/191; final R indices R_1 = 0.0484, wR_2 = 0.1240, R indices (all data): R_1 = 0.0516, wR_2 = 0.1266, goodness-of-fit: 1.106.

*3-(3,4-Dimethoxybenzylidene)-2-(2-hydroxyethyl)-isoindolin-1-one (**7d**, $C_{19}H_{19}NO_4$)*

Yield: 275 mg (81 %), (*E*):(*Z*) isomer ratio 67:33; yellow solid; m.p.: 86–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.93* (bs, 1H, OH), 3.08 (bs, 1H, OH), 3.55* (t, J = 5.2 Hz, 2H, CH_2N), 3.86 (s, 3H, CH_3O), 3.89* (t, J = 5.6 Hz, 2H, CH_2OH), 3.90* (s, 3H, CH_3O), 3.92* (s, 3H, CH_3O), 3.95 (s, 3H, CH_3O), 3.97 (t, J = 6 Hz, 2H, CH_2N), 4.08 (t, J = 6 Hz, 2H, CH_2OH), 6.64 (s, 1H, CH), 6.79* (s, 1H, CH), 6.86* (s, 1H, H_{arom}), 6.89-6.92 (m, 1H, H_{arom}), 6.95 (d, J = 8.4 Hz, 1H, H_{arom}), 7.01 (d, J = 8 Hz, 1H, H_{arom}), 7.33 (t, J = 8 Hz, 1H, H_{arom}), 7.41 (t, J = 7.6 Hz, 2H, H_{arom}), 7.48* (t, J = 7.6 Hz, 1H, H_{arom}), 7.60* (t, J = 8 Hz, 1H, H_{arom}), 7.74* (d, J = 7.6 Hz, 1H, H_{arom}), 7.83 (t, J = 7.6 Hz, 1H, H_{arom}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.6, 45.1*, 56.1, 61.1, 61.5*, 107.5*, 111.1*, 111.2, 111.4, 112.6*, 112.7, 119.4*, 122.3, 122.4*, 123.3, 123.4, 123.5*, 127.0*, 127.5, 128.0*, 129.2, 129.4, 130.1*, 131.7, 132.3*, 134.7*, 135.3, 136.2, 138.6*, 148.9, 149.0, 149.1, 167.8, 170.8* ppm (asterik denotes minor isomer); HRMS [CI$^+$]: *m/z* calculated for $C_{19}H_{20}NO_4$ $[M + H]^+$ 326.1300, found 326.1380.

*3-[(Benzo[d][1, 3]dioxol-5-yl)methylene]-2-(2-hydroxyethyl)isoindolin-1-one (**7e**, $C_{18}H_{15}NO_4$)*

Yield: 165 mg (80 %), (*E*):(*Z*) isomer ratio 57:43; yellow solid; m.p.: 142–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.83 (bs, 1H, OH), 2.92* (bs, 1H, OH), 3.56* (m, 2H, CH_2N), 3.89 (t, J = 5.6 Hz, 2H, CH_2N), 3.95* (t, J = 4.8 Hz, 2H, CH_2OH), 4.06 (t, J = 5.6 Hz, 2H, CH_2OH), 6.01 (s, 2H, OCH_2O), 6.03* (s, 2H, OCH_2O), 6.56* (s, 1H, CH), 6.71 (s, 1H, CH), 6.78–6.93 (m, 3H, H_{arom}), 7.34* (dd, J = 7.6, 7.6, 1.2 Hz, 1H, H_{arom}), 7.39–7.43* (m, 2H, H_{arom}), 7.48 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H, H_{arom}), 7.59 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H, H_{arom}), 7.72 (d, J = 8 Hz, 1H, H_{arom}), 7.82 (dd, J = 7.2, 7.2 Hz, 1H, H_{arom}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.3*, 29.6, 42.5*, 44.9, 61.1*, 61.3, 101.2*, 101.3, 106.8*, 108.2, 108.6*, 109.6, 109.7, 110.5*, 119.2, 123.1*,123.2, 127.9*, 128.1, 128.6*, 128.9, 129.1, 130.0*, 131.6*, 132.0, 134.9, 135.1*, 136.4*, 138.4, 147.3, 147.4*, 147.7, 147.9*, 167.6*, 170.4 ppm (asterik denotes minor isomer); HRMS [CI$^+$]: *m/z* calculated for $C_{18}H_{16}NO_4$ $[M + H]^+$ 310.1000, found 310.1069.

*3-Benzylidene-2-(3-hydroxypropyl)isoindolin-1-one (**8a**, $C_{18}H_{17}NO_2$)*

Yield: 240 mg (86 %), (*E*):(*Z*) isomer ratio 79:21; yellow solid; m.p.: 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33* (quint, J = 6.4 Hz, 2H, CH_2CH_2N), 1.94 (quint, J = 6.4 Hz, 2H, CH_2CH_2N), 3.20* (bs, 1H, OH), 3.26* (t, J = 5.6 Hz, 2H, CH_2N), 3.62 (t, J = 5.6 Hz, 2H, CH_2N), 3.75 (bs, 1H, OH), 3.80* (t, J = 6.4 Hz, 2H, CH_2OH), 4.07 (t, J = 6.4 Hz, 2H, CH_2OH), 6.63 (s, 1H, CH), 6.85* (s, 1H, CH), 7.30-7.46 (m, 8H, H_{arom}), 7.51* (ddd, J = 7.2, 7.2 Hz, 1H, H_{arom}), 7.62* (ddd, J = 7.6, 7.6, 1.2 Hz, 1H, H_{arom}), 7.76* (d, J = 8 Hz, 1H, H_{arom}), 7.82–7.86* (m, 1H, H_{arom}), 7.84 (d, J = 7.6 Hz, 1H, H_{arom}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.7, 31.0*, 35.6, 37.5*, 58.4, 58.6*, 107.5*, 111.1, 119.3*, 123.2, 123.3*, 127.8*, 128.0, 128.2, 128.7, 129.1, 129.3, 129.4*, 129.5, 129.8, 131.7, 132.1, 132.2*, 134.1*, 135.0, 135.9*, 167.2*, 167.8, 171.0* ppm (asterik denotes minor isomer); HRMS [CI$^+$]: *m/z* calculated for $C_{18}H_{18}NO_2$ $[M + H]^+$ 280.1259, found 280.1338.

*3-(4-Methoxybenzylidene)-2-(3-hydroxypropyl)isoindolin-1-one (**8b**, $C_{19}H_{19}NO_3$)*

Yield: 639 mg (88 %), (*E*):(*Z*) isomer ratio 83:17. After chromatographic separation, the (*E*)-isomer was obtained as a white solid; m.p.: 134–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (quint, J = 6.0 Hz, 2H, CH_2CH_2N), 2.89 (bs, 1H, OH), 3.27 (t, J = 6.0 Hz, 2H, CH_2N), 3.85 (s, 3H, CH_3O), 3.86 (t, J = 6.4 Hz, 2H, CH_2OH), 6.80 (s, 1H, CH), 6.93 (AA'BB', J = 8.2 Hz, 2H, H_{arom}), 7.27 (AA'BB', J = 8.2 Hz, 2H, H_{arom}), 7.49 (ddd, J = 7.6, 7.6, 0.8 Hz, 1H, H_{arom}), 7.60 (ddd, J = 7.6, 7.6, 0.8 Hz, 1H, H_{arom}), 7.74 (d, J = 7.6 Hz, 1H, H_{arom}), 7.84 (d, J = 7.6 Hz, 1H, H_{arom}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.0, 37.4, 55.3, 58.5, 107.6, 113.7, 119.3, 123.3, 126.5, 127.8, 128.9, 130.7, 132.1, 134.1, 138.3, 159.2, 169.7 ppm; HRMS [CI$^+$]: *m/z* calculated for $C_{19}H_{20}NO_3$ $[M + H]^+$ 310.1365, found 310.1447.

The (*Z*)-isomer was obtained as a yellow solid; m.p.: 95–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (quint,

$J = 6.0$ Hz, 2H, CH_2CH_2N), 3.58 (t, $J = 6.0$ Hz, 2H, CH_2N), 3.85 (s, 3H, CH_3O), 4.02 (t, $J = 6.0$ Hz, 2H, CH_2OH), 6.55 (s, 1H, CH), 6.94 (AA'BB', $J = 8.8$ Hz, 2H, H_{arom}), 7.29-7.41 (m, 5H, H_{arom}), 7.80 (d, $J = 7.6$ Hz, 1H, H_{arom}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.9$, 35.8, 55.5, 58.6, 111.4, 114.3, 123.3, 123.4, 127.1, 129.3, 130.0, 131.0, 131.8, 135.3, 135.5, 159.5, 168.0 ppm; HRMS [CI^+]: *m/z* calculated for $C_{19}H_{20}NO_3$ $[M + H]^+$ 310.1365, found 310.1447.

*3-(4-Chlorobenzylidene)-2-(3-hydroxypropyl)isoindolin-1-one (**8c**, $C_{18}H_{16}ClNO_2$)*

Yield: 669 mg (91 %), (*E*):(*Z*) isomer ratio 77:23; white solid; m.p.: 76–80 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.35$* (quint, $J = 6$ Hz, 2H, CH_2CH_2N), 1.91 (quint, $J = 6.0$ Hz, 2H, CH_2CH_2N), 2.63* (bs, 1H, OH), 2.85 (bs, 1H, OH), 3.29* (t, $J = 6$ Hz, 2H, CH_2N), 3.59 (t, $J = 5.6$ Hz, 2H, CH_2N), 3.81* (t, $J = 6$ Hz, 2H, CH_2OH), 4.02 (t, $J = 6$ Hz, 2H, CH_2OH), 6.51 (s, 1H, CH), 6.74* (s, 1H, CH), 6.81* (AA'BB', $J = 8.4$ Hz, 2H, H_{arom}), 7.07* (AA'BB', $J = 8.4$ Hz, 2H, H_{arom}), 7.27–7.43 (m, 7H, H_{arom}), 7.62* (ddd, $J = 7.6$, 7.6, 0.8 Hz, 1H, H_{arom}), 7.74* (d, $J = 7.6$ Hz, 1H, H_{arom}), 7.81 (d, $J = 7.2$ Hz, 1H, H_{arom}), 7.84* (d, $J = 7.6$ Hz, 1H, H_{arom}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.9$, 35.7*, 35.9, 37.4*, 58.4*, 58.7, 105.9*, 109.7, 119.4*, 123.1*, 123.3, 123.5, 128.5*, 129.2, 129.3*, 129.6*, 129.8, 130.1, 130.9*, 131.1, 131.7*, 132.0, 132.3*, 133.0*, 133.6, 134.1, 134.8*, 135.0, 136.6, 138.1*, 167.8*, 167.9 ppm (asterik denotes minor isomer); HRMS [CI^+]: *m/z* calculated for $C_{18}H_{17}ClNO_2$ $[M + H]^+$ 314.0870, found 314.0949.

*3-(3,4-Dimethoxybenzylidene)-2-(3-hydroxypropyl)-isoindolin-1-one (**8d**, $C_{20}H_{21}NO_4$)*

Yield: 732 mg (92 %), (*E*):(*Z*) isomers ratio 87:13; yellow oil; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.41$ (quint, $J = 6.0$ Hz, 2H, CH_2CH_2N), 1.95* (quint, $J = 6$ Hz, 2H, CH_2CH_2N), 2.14 (bs, 1H, OH), 3.30 (t, $J = 6.0$ Hz, 2H, CH_2N), 3.62* (t, $J = 6.0$ Hz, 2H, CH_2N), 3.87* (s, 3H, CH_3O), 3.87–3.91 (m, 2H, CH_2OH), 3.90 (s, 3H, CH_3O), 3.93 (s, 3H, CH_3O), 3.96* (s, 3H, CH_3O), 4.06* (t, $J = 5.6$ Hz, 2H, CH_2OH), 6.60* (s, 1H, CH), 6.82 (s, 1H, CH), 6.87–6.97 (m, 4H, H_{arom}), 7.03* (d, $J = 8.0$ Hz, 1H, H_{arom}), 7.35* (ddd, $J = 8.0$, 8.0, 1.2 Hz, 1H, H_{arom}), 7.42–7.46* (m, 2H, H_{arom}), 7.50 (dd, $J = 7.6$, 7.6 Hz, 1H, H_{arom}), 7.61 (ddd, $J = 7.6$, 7.6, 0.8 Hz, 1H, H_{arom}), 7.75 (d, $J = 8.0$ Hz, 1H, H_{arom}), 7.84* (d, $J = 8.0$ Hz, 1H, H_{arom}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.8$*, 31.3, 35.7*, 37.6, 55.9, 55.96*, 55.99*, 56.0, 58.6*, 58.7, 107.2, 110.9*, 111.1, 111.5*, 112.8*, 112.9, 119.1, 122.1*, 122.2, 123.14*, 123.2, 123.21*, 127.0, 127.4*, 127.9, 128.9*, 129.1*, 129.9, 131.5*, 131.9, 134.2, 135.1*, 135.6*, 138.3, 148.8, 148.9, 149.1*, 149.2*, 167.6*, 169.6 ppm (asterik denotes minor isomer); HRMS [CI^+]: *m/z* calculated for $C_{20}H_{22}NO_4$ $[M + H]^+$ 340.1471, found 340.1559.

*3-[(Benzo[d][1,3]dioxol-6-yl)methylene]-2-(3-hydroxypropyl)isoindolin-1-one (**8e**, $C_{19}H_{17}NO_4$)*

Yield: 719 mg (95 %), (*E*):(*Z*) isomer ratio 75:25. After chromatographic separation, the (*E*)-isomer was obtained as a yellow solid; m.p.: 99–102 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.93$ (quint, $J = 6.0$ Hz, 2H, CH_2OH), 2.16 (bs, 1H, OH), 3.61 (t, $J = 5.6$ Hz, 2H, CH_2N), 4.04 (t, $J = 6.4$ Hz, 2H, CH_2CH_2N), 6.04 (s, 2H, OCH_2O), 6.53 (s, 1H, CH), 6.86-6.94 (m, 3H, H_{arom}), 7.35–7.46 (m, 3H, H_{arom}), 7.42–7.46 (m, 2H, H_{arom}), 7.83 (d, $J = 7.6$ Hz, 1H, H_{arom}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.7$, 35.6, 58.4, 101.3, 108.6, 109.7, 111.0, 123.2, 123.3 (2), 128.4, 129.3, 129.8, 131.7, 134.9, 135.7, 147.4, 147.9, 167.7 ppm; HRMS [CI^+]: *m/z* calculated for $C_{19}H_{18}NO_4$ $[M + H]^+$ 324.1158, found 324.1242.

The (*Z*)-isomer was obtained as a yellow solid; m.p.: 119–121 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.42$ (quint, $J = 5.6$ Hz, 2H, CH_2OH), 2.90 (bs, 1H, OH), 3.31 (t, $J = 5.6$ Hz, 2H, CH_2N), 3.89 (t, $J = 6.0$ Hz, 2H, CH_2CH_2N), 6.02 (s, 2H, OCH_2O), 6.74 (s, 1H, CH), 6.80-6.86 (m, 3H, H_{arom}), 7.49 (ddd, $J = 7.2$, 7.2, 1.2 Hz, 1H, H_{arom}), 7.60 (ddd, $J = 7.2$, 7.2, 1.2 Hz, 1H, H_{arom}), 7.72 (d, $J = 7.6$ Hz, 1H, H_{arom}), 7.84 (d, $J = 7.6$ Hz, 1H, H_{arom}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 31.1$, 37.4, 58.6, 101.3, 107.3, 108.1, 109.7, 119.3, 123.2, 123.3, 127.8, 128.0, 129.0, 132.1, 134.4, 138.2, 147.3, 147.5, 169.8 ppm; HRMS [CI^+]: *m/z* calculated for $C_{19}H_{18}NO_4$ $[M + H]^+$ 324.1158, found 324.1242.

*General procedure for the synthesis of aldehydes **9b-9d***

A solution of the hydroxyphosphonates **6b–6d** (1.67 mmol) in 10 cm^3 dry dichloromethane was added to a stirred solution of Dess–Martin-Periodinane reagent (1.5 equiv), and the reaction mixture was stirred at room temperature overnight. The solvent was then removed under reduced pressure, and the crude product was purified by flash chromatography (AcOEt:acetone 50:50), yielding the desired aldehydes **9b–9d**. Aldehyde **9c** was unstable.

*Dimethyl 2-(2-formylethyl)-3-oxoisoindolin-1-ylphosphonate (**9b**, $C_{13}H_{16}NO_5P$)*

Yield: 443 mg (89 %) as a white solid; m.p.: 103–105 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.77$ (dddd, $J = 18.4$, 6.0, 6.0, 1.6 Hz, 1H, CH_2CHO), 3.08 (dddd, $J = 18.4$, 6.8, 6.8, 1.2 Hz, 1H, CH_2CHO), 3.52 (d, $J = 10.8$ Hz, 3H, $(CH_3O)_2P$), 3.72 (d, $J = 10.8$ Hz, 3H, $(CH_3O)_2P$), 3.98 (ddd, $J = 14.4$, 6.0, 6.0 Hz, 1H, CH_2N), 4.12 (ddd, $J = 14.4$, 6.0, 6.0 Hz, 1H, CH_2N), 5.01 (d, $J = 13.2$ Hz, 1H, $CHP(OCH_3)_2$), 7.47 (ddd, $J = 7.6$, 7.6, 1.2 Hz, 1H,

H_{arom}), 7.54 (ddd, $J = 7.6$, 7.6, 1.2 Hz, 1H, H_{arom}), 7.68–7.71 (m, 1H, H_{arom}), 7.79 (d, $J = 1.2$ Hz, 1H, H_{arom}), 9.75 (t, $J = 1.2$ Hz, 1H, CHO) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 36.3$, 42.4, 53.6 (d, $J = 7.6$ Hz, $(CH_3O)_2P$), 53.7 (d, $J = 7.6$ Hz, $(CH_3O)_2P$), 57.8 (d, $J = 153.7$ Hz, $CHP(OCH_3)_2$), 123.7, 124.3, 128.9, 131.7, 131.8, 138.5, 168.8, 200.2 ppm; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 18.4$ ppm; HRMS [CI^+]: *m/z* calculated for $C_{13}H_{17}NO_5P$ $[M + H]^+$ 298.0800, found 298.0836.

*Dimethyl 2-(4-formylbutyl)-3-oxoisoindolin-1-ylphosphonate (**9d**, $C_{15}H_{20}NO_5P$)*

Yield: 631 mg (88 %) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.58$–1.78 (m, 4H), 2.49–2.54 (m, 2H), 3.55–3.62 (m, 4H), 3.75 (d, $J = 10.8$ Hz, 3H, $(CH_3O)_2P$), 4.10–4.13 (m, 1H), 4.94 (d, $J = 13.6$ Hz, 1H, $CHP(OCH_3)_2$), 7.51–7.55 (m, 1H), 7.57–7.61 (m, 1H), 7.75–7.77 (m, 1H), 7.86–7.88 (m, 1H), 9.76 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.1$, 27.2, 41.3, 43.1, 53.6 (d, $J = 5.9$ Hz, $(CH_3O)_2P$), 53.7 (d, $J = 7.3$ Hz, $(CH_3O)_2P$), 56.9 (d, $J = 155.2$ Hz, $CHP(OCH_3)_2$), 123.8, 124.3, 128.9, 131.5, 132.1, 138.2, 168.7, 201.6 ppm; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 18.3$ ppm; HRMS [CI^+]: *m/z* calculated for $C_{15}H_{21}NO_5P$ $[M + H]^+$ 326.1100, found 326.1141.

*General procedure for the synthesis of isoindolones **10b–10d***

Method A: a solution of KHMDS in toluene (0.5 M, 2 equiv) was added dropwise to a stirred solution of the corresponding aldehydes **9b–9d** (1.0 equiv) in 15 cm^3 THF at −78 °C under nitrogen. The reaction mixture was stirred for 15 min and then warmed at room temperature over a period of 1 h. The reaction mixture was quenched by the addition of saturated solution of NH_4Cl and extracted with AcOEt (2 × 20 cm^3). The organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was analyzed by ^{1}H NMR and then purified by flash column chromatography (AcOEt:hexanes 2:1), yielding the corresponding tricyclic compounds **10b–10d**. Compound **10d** was unstable.

Method B [31]: to a solution of the corresponding aldehydes **9b–9d** (1.0 equiv) in 10 cm^3 acetonitrile was added K_2CO_3 (1.5 equiv), and the reaction mixture was heated at 85 °C for 2.5 h. The reaction mixture was filtered and the solvent was evaporated under reduced pressure until complete dryness, yielding the corresponding tricyclic compounds **10b** and **10c** in 98 % yield. Spectroscopic data were identical to those reported in Refs. [25–27].

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