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One-pot three-component highly diastereoselective synthesis of isoindolin-1-one-3-phosphonates under solvent and catalyst free-conditions

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ABSTRACT

The one-pot three-component reaction of 2-formylbenzoic acid with (*S*)- and (*R*)-methylbenzylamine and dimethyl phosphite (Kabachnik–Fields reaction) proceeded in short reaction times under solvent and catalyst free-conditions to afford the corresponding (3*R*,1′*S*)- and (3*S*,1′*R*)-isoindolin-1-one-3-phosphonates **3**, respectively, in good yield and with high diastereoselectivity (95:5 dr). The use of a solvent decreases the diastereoselectivity and slows the reaction rate. The reaction rate was also influenced by CO_2H functionality through protonation of the imine intermediate. The absolute configuration at the new stereogenic center was determined by X-ray crystal analysis, and a mechanism was proposed to explain the high diastereoselectivity.

1. Introduction

α-Aminophosphonic acids are analogs of α-amino acids in which the planar carboxylic acid (CO_2H) has been replaced by a sterically more demanding tetrahedral phosphonic acid group [$P(O)(OH)_2$]. This replacement results in not only significant differences in molecular shape and size, but also in acidity and other properties. α-Aminophosphonic acids are currently attracting a great deal of interest in medicinal chemistry and agrochemistry, due to their excellent biological and pharmacological properties. Thus, some of these compounds and their derivatives, including the short peptides that incorporate them, have found application as antibacterial, antiviral and antifungal agents, as well as insecticides and herbicides. Additionally, other aminophosphonic acids have shown potential anticancer activity or have been demonstrated to be effective in the treatment of osteoporosis.[1,2]

The relevant properties exhibited by α-aminophosphonic acids and their derivatives have stimulated the development of several synthetic methods for these compounds.[1,2a,3] Over the last few decades, much effort has been dedicated to the preparation of the phosphonic analogs of the 20 proteinogenic α-amino acids and, as a result, procedures for the synthesis of most of them are currently available.[4] Once this goal has been achieved, the remaining challenge is to search for new structures, other than those analogous to the encoded α-amino acids. In this context, a wide variety of non-coded α-amino acids have been synthesized in recent years by the introduction of different types of modifications on proteinogenic residues and have provided an invaluable source of inspiration. In particular, those non-proteinogenic α-amino acids that have already shown exceptional properties are ideal candidates to serve as models for the construction of new α-aminophosphonic acids.

On the other hand, the isoindolinone core is a key structural feature of a great number of natural compounds with important biological activities.[5,6] In particular, the ethyl isoindolin-1-one-3-carboxylate **1** bearing the (*S*)-α-methylbenzylamine fragment, a benzannulated analog of pyroglutamate, is a valuable synthetic intermediate in the synthesis of chiral spirobutyrolactone derivatives **2**.[7] Additionally, isoindolin-1-one-3-carboxylates have been used for the synthesis of other complex compounds.[8] Despite the diverse biological activities displayed by the α-aminophosphonic acids, the stereoselective synthesis of isoindolin-1-one-3-phosphonates **3** has not yet been reported.[9]

In connection with our current research interest in the development of new synthetic methodologies[10] and the preparation of novel α-aminophoshonic acids,[11] we herein report the one-pot three-component highly diastereoselective synthesis of dimethyl (3*R*,1′*S*)- and (3*S*,1′*R*)-isoindolin-1-one-3-phosphonate **3** under solvent and catalyst free-conditions.

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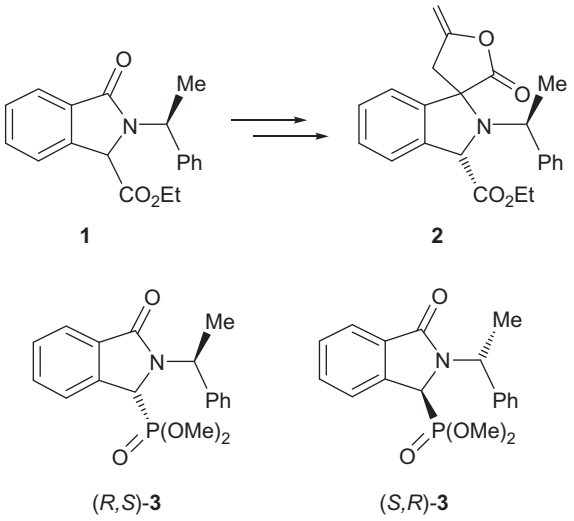
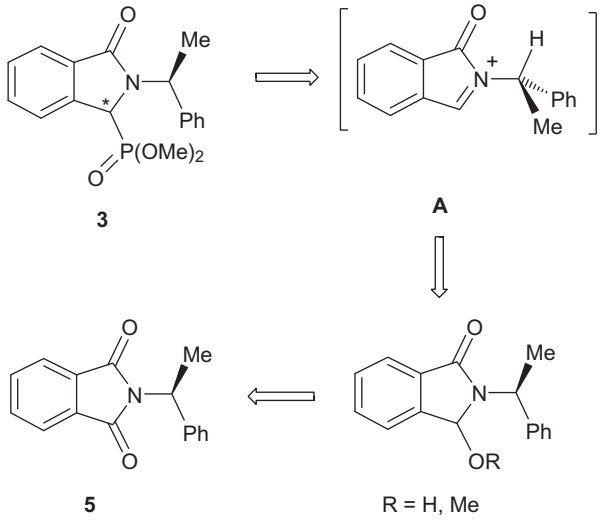


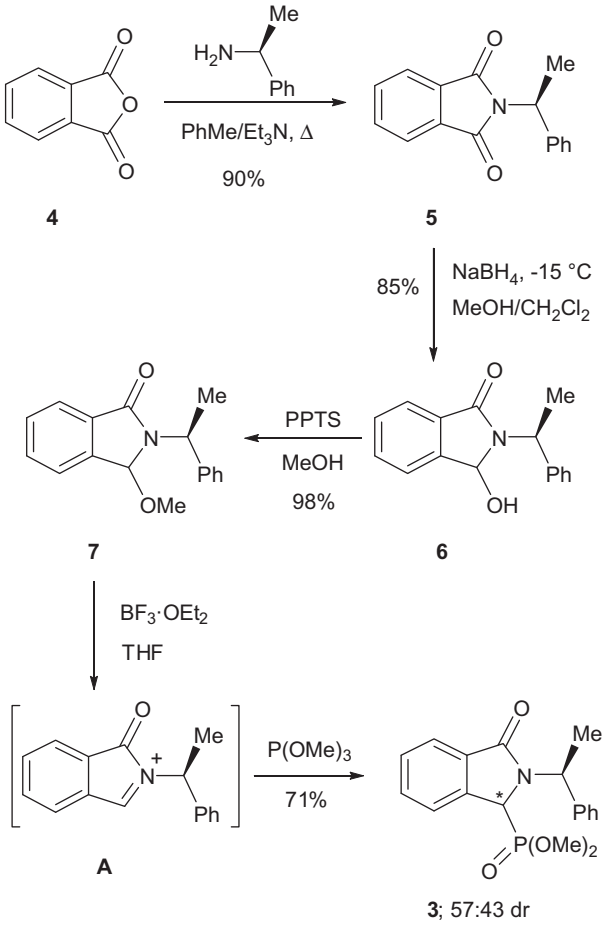
2. Results and discussion

For the stereoselective synthesis of target compounds **3**, we initially proposed a chiral *N*-acyliminium ion **A** as a suitable precursor (Scheme 1), considering that the well-known reduction of the carbonyl group at the C1 position of phthalimide derivatives and their subsequent transformation into *N*-acyliminium salts, through the corresponding hemiaminals, provides a useful synthetic intermediate. It has been reported that this intermediate is highly electrophilic; this allows the addition of various nucleophiles to afford numerous 3-substituted isoindolin-1-one derivatives.[12]



Scheme 1.

Taking this into consideration, the synthesis of the required aminal **7** was accomplished by a three-step sequence as outlined in Scheme 2. The starting *N*-(α-methylbenzyl)imide[13,14] **5** although not commercially available was easily prepared in 90% yield from the condensation of (*S*)-α-methylbenzylamine [(*S*)-MBA] and phthalic anhydride **4** in the presence of a catalytic amount of Et_3N in toluene at reflux under azeotropic removal of water. Following the procedure reported by Liu et al.[15] the regioselective reduction of the phthalimide **5** was carried out with sodium borohydride in a methanol–dichloromethane mixture at −15 °C,

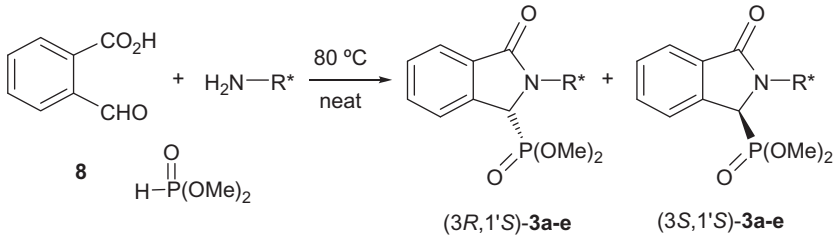


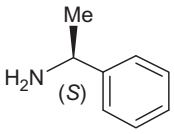
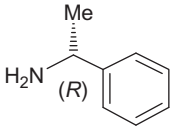
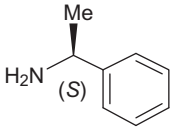
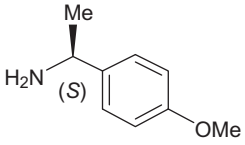
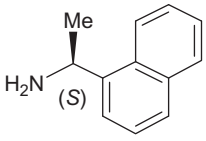
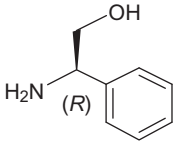
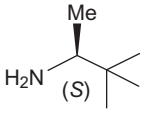
Scheme 2.

obtaining the 3-hydroxy-isoindolin-1-one **6** in 85% yield. The transformation into the corresponding aminal **7** was easily carried out by the reaction of **6** with methanol in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) at room temperature. Product **7** was obtained in almost quantitative yield.[16] Finally, in the last step, treatment of aminal **7** with boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) generated a highly reactive *N*-acyliminium salt **A**, which reacted with trimethyl phosphite to give the target compound **3**, in 71% yield and a 57:43 diastereoisomeric ratio (dr).[17] Similar results were obtained using $TiCl_4$ as the catalyst in this transformation (62% yield and 54:46 dr).

Although this synthetic procedure proved to be a suitable methodology to obtain target compound **3**, the low diastereoselectivity prompted us to explore a new method for its preparation in a highly diastereoselective manner. With this purpose in mind, and looking for alternative protocols under mild and environmentally friendly reaction conditions, we decided to explore the use of 2-formylbenzoic acid **8** as a starting material, taking into account its recent application in the synthesis of 3-substituted isoindolin-1-ones derivatives.[18] In this context, we initially explored the one-pot three-component reaction of 2-formylbenzoic acid **8**, (*S*)-α-methylbenzylamine as the chiral source, and $HP(O)(OMe)_2$ under solvent and catalyst free-conditions. Thus, 2-formylbenzoic acid **8** and (*S*)-α-MBA were stirred for 10 min at room temperature followed by the addition of dimethyl phosphite and stirred at 80 °C for 0.5–1.0 h, obtaining the expected isoindolin-1-one-3-phosphonates (3*R*,1′*S*)-**3** and (3*S*,1′*S*)-**3** in 75% yield and 95:5 dr (Table 1, entry 1). It should be emphasized that the same stereoselectivity was obtained using the oppositely configured amine (*R*)-α-MBA,

Table 1
Synthesis of isoindolin-1-one-3-phosphonates **3a–e**



Entry	Chiral amine	Product	Yield (%)	(3*R*,1′*S*):(3*S*,1′*S*)[a]
1		**3a**	75	95:05
2		**3a**	73	95:05[b]
3		**3a**	80	75:25[c]
4		**3b**	73	56:44
5		**3c**	70	75:25
6		**3d**	70	53:47[d]
7		**3e**	40	>98:02

[a] (3*R*,1′*S*):(3*S*,1′*S*) ratio was determined by ^{31}P NMR at 81 MHz in the crude product.
[b] The (3*S*,1′*R*)-diastereoisomer was the major product.
[c] The reaction was carried out in PhMe.
[d] The (3*S*,2′*R*)-diastereoisomer was the major product.

obtaining the (3*S*,1′*R*)-**3** and (3*R*,1′*R*)-**3** diastereoisomers in 71% yield and 95:5 dr (Table 1, entry 2). The diastereoisomeric ratio was determined by ^{31}P NMR spectroscopy at 81 MHz, and the absolute configuration of the isoindolin-1-one-3-phosphonates (3*R*,1′*S*)-**3** and (3*S*,1′*R*)-**3** were unambiguously determined by X-ray crystallographic analysis (Fig. 1).[19,20] In order to determine the optimal conditions, the reaction was carried out at different temperatures (25, 50, 70, 80, and 90 °C). The results of these experiments showed no remarkable differences in reactivity, yield or diastereoselectivity in this temperature range, excluding the reaction rate, which was extremely slow at 25 °C. Additionally, when the one-pot three-component reaction was carried out in toluene at 80 °C, 6 h were necessary to complete the reaction; the isoindolin-1-one-3-phosphonates (3*R*,1′*S*)-**3** and (3*S*,1′*S*)-**3** were obtained in 80% yield and 75:25 dr (Table 1, entry 3).

After optimization of the experimental conditions with (*S*)-α-MBA, we extended this three-component reaction to other chiral amines, such as (*S*)-4-methoxy-α-methylbenzylamine, (*S*)-1-(1′-naphthyl)ethylamine, (*R*)-phenylglycinol and (*S*)-3,3-dimethyl-2-butylamine. The reaction with the first three chiral amines provided the isoindolin-1-one-3-phosphonates **3** in good yield but with only moderate diastereoselectivity (Table 1, entries 4–6); however, only the (3*R*,1′*S*)-diastereoisomer **3e** was detected by ^{1}H and ^{31}P NMR, using the (*S*)-3,3-dimethyl-2-butylamine in this three component process (Table 1, entry 7). The stereochemistry in compounds **3b–e** was established by correlation of the spectro-

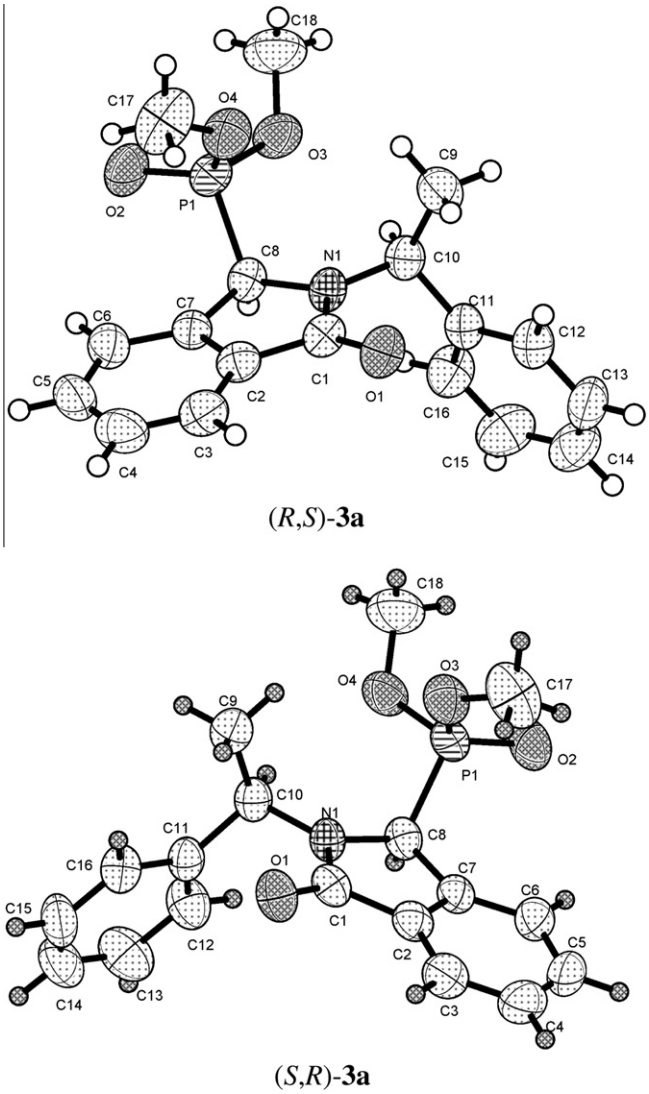
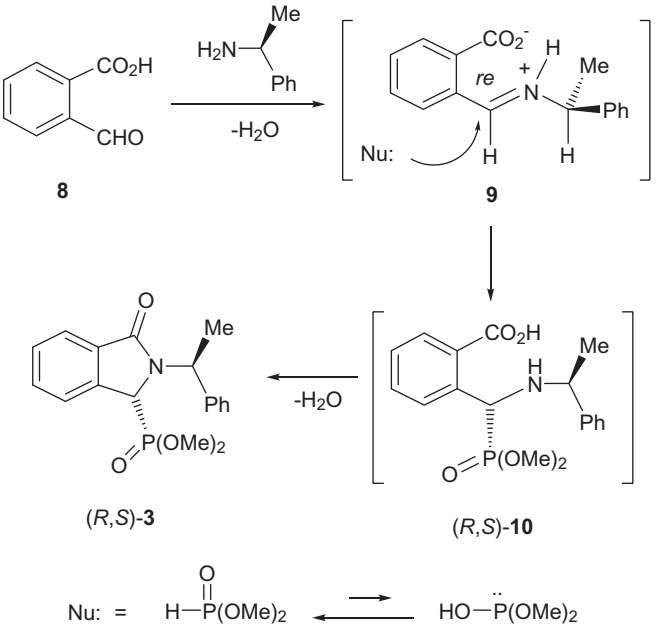


Figure 1. X-ray structure of (3*R*,1′*S*)- and (3*S*,1′*R*)-**3a**.

scopic data with those obtained for the aminophosphonate **3a** and considering a general mechanism for this reaction.

Based on our previous work on three-component reactions (aldehyde, chiral amine, and dimethyl phosphite) in solvent and catalyst free-conditions,[10] the 1,3-induction of chirality in the reaction of 2-formylbenzoic acid **8**, (*S*)-α-MBA and $HP(O)(OMe)_2$ can be explained as illustrated in Scheme 3. The initial condensation reaction of 2-formylbenzoic acid **8** and (*S*)-α-MBA gives a protonated imine **9**, which adopts a conformation where the hydrogen of the chiral fragment is eclipsed with the imine double bond, as should be expected from the 1,3-allylic strain model.[21] The conformation with C–Ph or C–Me eclipsed with the N=C–H fragment is appreciably higher in energy. Consequently, nucleophilic attack of dimethyl phosphite to the protonated imine **9** takes place at the *re* face (less hindered face) to afford the phosphonate (3*R*,1′*S*)-**10** as the major diastereoisomer, which by ring closure afforded the (3*R*,1′*S*)-isoindolin-1-one-3-phosphonate **3**. We considered that the determining step in this transformation involves nucleophilic attack of the dimethyl phosphite to the protonated imine **9** by taking into account that the three component reaction of methyl 2-formylbenzoate, (*S*)-α-MBA and $HP(O)(OMe)_2$ gave the isoindolin-1-one-3-phosphonate **3** in 70% and 95:5 dr, but after 6 h of reaction.



Scheme 3.

3. Conclusions

In conclusion, a new and mild one-pot three-component reaction under catalyst and solvent free-conditions was developed to give access to chiral isoindolin-1-one-3-phosphonates **3** in good yields with high diastereoselectivity. This procedure may find wide application in the large scale synthesis of cyclic α-aminophosphonates. Further investigations are currently in progress to demonstrate the potential of this methodology in the diastereoselective preparation of isoindolin-1-ones bearing phosphonate functionality of biological interest.

4. Experimental

4.1. General

All commercial materials were used as received without further purification. Melting points were registered in a Fisher–Johns apparatus and are uncorrected. 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 (60 F254, Merck). NMR spectra were recorded with a Varian System instrument (400 MHz for ^{1}H, and 100 MHz for ^{13}C) and 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, br s = 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. Microanalyses were determined in an Elemental VARIO EL III machine.

4.2. General procedure for the synthesis of isoindolin-1-one-3-phosphonates 3a–e

The chiral amine (1.05 equiv) was added to 2-formylbenzoic acid (1.0 equiv), and the mixture was stirred at room temperature for 15 min prior to the addition of dimethyl phosphite (1.15 equiv). The reaction mixture was stirred at 80 °C, and the progress of the

reaction was monitored by TLC. The crude product was analyzed by ^{1}H and ^{31}P NMR spectroscopy. Finally, the crude product was purified by column chromatography.

4.2.1. Dimethyl (3*R*,1′*S*)-2-(1′-methylbenzyl)isoindolin-1-one-3-yl)phosphonate (3*R*,1′*S*)-3a

2-Formylbenzoic acid (2.5 g, 17 mmol), (*S*)-α-methylbenzylamine (2.2 g, 2.5 mL, 18 mmol) and dimethyl phosphite (2.3 g, 3.0 mL, 21 mmol) were stirred at 80 °C for 1.0 h. The product (*R*,*S*)-**3a** was obtained (4.3 g, 75%) as a white solid in a 95:05 dr. The major diastereoisomer was crystallized in a methanol–dichloromethane mixture. Mp 193–194 °C. $[\alpha]_D = -19.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.05 (d, *J* = 7.6 Hz, 3H, CH_3CH), 3.52 (d, *J* = 10.6 Hz, 3H, $(CH_3O)_2P$), 3.61 (d, *J* = 10.6 Hz, 3H, $(CH_3O)_2P$), 4.91 (d, *J* = 12.8 Hz, 1H, $CHP(OMe)_2$), 5.35 (q, *J* = 7.2 Hz, 1H, $NCHCH_3$), 7.20–7.86 (m, 9H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.6 (CH_3CH), 53.8 (d, *J* = 7.6 Hz, $(CH_3O)_2P$), 54.0 (d, *J* = 7.6 Hz, $(CH_3O)_2P$), 55.5 ($CHCH_3$), 58.3 (d, *J* = 156.2 Hz, $CHP(OMe)_2$), 124.0, 124.5, 127.3, 127.5, 128.6, 129.1, 131.8, 133.3, 138.6, 141.8, 169.8 (C=O). ^{31}P NMR (81 MHz, $CDCl_3$) δ: 21.4. HRMS [CI^+]: Calcd $C_{18}H_{21}NO_4P$ 346.1208. Found 346.1209. Anal. Calcd for $C_{18}H_{20}NO_4P$: C, 62.60; H, 5.84; N, 4.06. Found: C, 62.96; H, 5.54; N, 4.25.

4.2.2. Dimethyl (3*S*,1′*R*)-2-(1′-methylbenzyl)isoindolin-1-one-3-yl)phosphonate (3*S*,1′*R*)-3a

2-Formylbenzoic acid (2.5 g, 17 mmol), (*R*)-α-methylbenzylamine (2.2 g, 2.5 mL, 18 mmol) and dimethyl phosphite (2.3 g, 3.0 mL, 21 mmol) were stirred at 80 °C for 1.0 h. The product (*R*,*S*)-**3a** was obtained (4.2 g, 73%) as a white solid in 95:05 dr. The major diastereoisomer was crystallized in a methanol–dichloromethane mixture. Mp 193–194 °C. $[\alpha]_D = +19.2$ (*c* 1.0, $CHCl_3$). Spectroscopy data for (*S*,*R*)-**3a** were identical to (*R*,*S*)-**3a**.

4.2.3. Dimethyl (3*R*,1′*S*)- and (3*S*,2′*S*)-2-(1′-methyl-*p*-methoxybenzyl)isoindolin-1-one-3-yl)phosphonate 3b

2-Formylbenzoic acid (200 mg, 1.33 mmol), (*S*)-4-methoxy-α-methylbenzylamine (212 mg, 0.21 mL, 1.40 mmol), and dimethyl phosphite (154 mg, 0.13 mL, 1.40 mmol) were stirred at 80 °C for 1 h. The diastereoisomeric mixture **3b** was obtained (365 mg, 73%) as a white solid in 56:44 dr. Asterik denotes minor diastereoisomer. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.86* (d, *J* = 7.4 Hz, 3H, CH_3CH), 2.03 (d, *J* = 7.0 Hz, 3H, CH_3CH), 3.46–3.70 (m, 12H, $(CH_3O)_2P$), 3.76 (s, 3H, CH_3OPh), 3.80* (s, 3H, CH_3OPh), 4.61* (d, *J* = 13.6 Hz, 1H, $CHP(OCH_3)_2$), 4.90 (d, *J* = 13.2, Hz, 1H, CH-P), 5.27 (q, *J* = 7.6 Hz, 1H, $NCHCH_3$), 5.57* (q, *J* = 7.2 Hz, 1H, $CHCH_3$), 6.81–6.89 (m, 4H, H_{arom}), 7.37–7.88 (m, 12H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.0* (CH_3), 18.8 (CH_3), 53.3 (CH_3–O), 53.7* (d, *J* = 6.1 Hz, $(CH_3O)_2P$), 53.8 (d, *J* = 7.6 Hz, $(CH_3O)_2P$), 55.2* (CH–CH_3), 55.4 (CH–CH_3), 57.2* (d, *J* = 156.2 Hz, $CHP(OCH_3)_2$), 58.4 (d, *J* = 156.3 Hz, $CHP(OCH_3)_2$), 123.9, 124.5, 124.8*, 128.6, 129.0, 129.5, 131.7, 132.0*, 132.6*, 133.5*, 134.0*, 138.6, 139.2*, 158.9, 159.0*, 169.6. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 21.5, 21.9*. HRMS [FAB^+]: Calcd $C_{19}H_{23}NO_5P$ 376.1314. Found 376.1304. Anal. Calcd for $C_{19}H_{22}NO_5P$: C, 60.80; H, 5.91; N, 3.73. Found C, 60.45; H, 5.68; N, 3.79.

4.2.4. Dimethyl (3*R*,1′*S*)- and (3*S*,1′*S*)-2-(1′-(naphthalen-1-yl) ethyl)isoindolin-1-one-3-yl)phosphonate 3c

2-Formylbenzoic acid (200 mg, 1.33 mmol), (*S*)-1-(1-naphthyl)ethylamine (240 mg, 0.23 mL, 1.40 mmol), and dimethyl phosphite (154 mg, 0.13 mL, 1.40 mmol) were stirred at 80 °C for 2 h. The diastereoisomeric mixture **3c** was obtained (362 mg, 70%) as a yellow oil in 75:25 dr. Asterik denotes minor diastereoisomer. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.09 (d, *J* = 7.2 Hz, 3H, CH_3CH), 2.24* (d, *J* = 7.2 Hz, 3H, CH_3CH), 3.43 (d, *J* = 10.8 Hz, 3H, $(CH_3O)_2P$), 3.60 (d, *J* = 10.8 Hz, 3H, $(CH_3O)_2P$), 3.61* (d, *J* = 11.2 Hz, 3H, $(CH_3O)_2P$), 3.73* (d, *J* = 11.2 Hz, $(CH_3O)_2P$), 4.03 (d, *J* = 13.6, Hz, 1H, $CHP(OCH_3)_2$), 4.83* (d, *J* = 12.4, Hz, 1H, $CHP(OCH_3)_2$), 6.27* (q, *J* = 7.6 Hz, 1H, $NCHCH_3$), 6.35 (q, *J* = 7.2 Hz, 1H, CH–CH_3), 7.26–7.62 (m, 13H, H_{arom}), 7.75–8.29 (m, 9H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.3 (CH_3–CH), 19.7* (CH_3–CH), 49.4 (CH–CH_3), 52.2*(CH–CH_3), 53.6 (d, *J* = 6.0 Hz, $(CH_3O)_2P$), 53.8 (d, *J* = 7.5 Hz, $(CH_3O)_2P$), 54.3* (d, *J* = 6.0 Hz, $(CH_3O)_2P$), 56.6 (d, *J* = 154.7 Hz, CH-P), 58.7* (d, *J* = 154.7 Hz, CH-P), 122.5, 122.8*, 124.0*, 124.1, 124.9, 125.0, 125.2, 125.6*, 125.8, 126.7*, 126.9, 127.3, 128.3, 128.9, 129.0, 129.1, 129.2, 131.2, 131.6*, 131.8*, 131.9*, 133.7, 134.0*,134.1, 137.5, 139.4, 169.7, 170.3*. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 21.6*, 21.8. HRMS [FAB^+]: Calcd $C_{22}H_{23}NO_4P$ 396.1365. Found 396.1367.

4.2.5. Dimethyl (3*S*,2′*R*)- and (3*R*,2′*R*)-2-(2′-phenyl-ethanol)isoindolin-1-one-3-yl)phosphonate 3d

2-Formylbenzoic acid (200 mg, 1.33 mmol), (*R*)-2-phenylglycinol (192 mg, 1.40 mmol), and dimethyl phosphite (154 mg, 0.13 mL, 1.40 mmol) were stirred at 80 °C for 2 h. The diastereoisomeric mixture **3d** was obtained (337 mg, 70%) as a white solid in 53:47 dr, which was purified by flash column chromatography (AcOEt/hexane = 1:1).

Less polar diastereoisomer (3*S*,2′*R*): Mp 106–108 °C. $[\alpha]_D = +64$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.65 (d, *J* = 10.3 Hz, 3H, $(CH_3O)_2P$), 3.76 (d, *J* = 11.3 Hz, 3H, $(CH_3O)_2P$), 4.18 (dd, *J* = 12.8, 3.6 Hz, 1H, CH_2CH), 4.54 (dd, *J* = 12.8, 8.0 Hz, 1H, $CHCH_2$), 4.71 (d, *J* = 13.6 Hz, 1H, $CHP(OCH_3)_2$), 5.38 (dd, *J* = 8.0, 3.6 Hz, 1H, CH_2CH), 7.24–7.34 (m, 5H, H_{arom}), 7.53–7.65 (m, 3H, H_{arom}), 7.91 (d, *J* = 7.6 Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.8 (d, *J* = 7.6 Hz, $(CH_3O)_2P$), 54.5 (d, *J* = 7.6 Hz, $(CH_3O)_2P$), 59.0 (d, *J* = 153.2 Hz, $CHP(OCH_3)_2$), 64.6 ($CHCH_2$), 64.7 (CH_2CH), 124.3, 124.5, 127.4, 128.2, 129.0, 129.3, 132.3, 132.5, 137.7, 139.0, 170.6. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 20.9. HRMS [FAB^+]: Calcd $C_{18}H_{21}NO_5P$ 362.1157. Found 362.1170.

More polar diastereoisomer (3*R*,2′*R*): Mp 165–168 °C. $[\alpha]_D = +32$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.42 (d, *J* = 11.2 Hz, 3H, $(CH_3O)_2P$), 3.45 (d, *J* = 11.0 Hz, 3H, $(CH_3O)_2P$), 4.13 (dd, *J* = 11.2, 4.4 Hz, 1H, CH_2CH), 4.66 (dd, *J* = 11.2, 9.6 Hz, 1H, $CHCH_2$), 4.92 (d, *J* = 13.6, Hz, 1H, $CHP(OCH_3)_2$), 5.29 (dd, *J* = 9.6, 4.4 Hz, 1H, CH_2CH), 7.24–7.84 (m, 9H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.8 (d, *J* = 6.1 Hz, $(CH_3O)_2P$), 53.8 (d, *J* = 7.6 Hz, $(CH_3O)_2P$), 60.0 (d, *J* = 156.3 Hz, $CHP(OCH_3)_2$), 63.2 ($CHCH_2$), 63.4 (CH_2CH), 124.0, 124.5, 127.7, 128.3, 128.5, 129.2, 132.1, 132.3, 137.3, 139.0, 170.9 ^{31}P NMR (81 MHz, $CDCl_3$) δ: 21.4. HRMS [FAB^+]: Calcd $C_{18}H_{21}NO_5P$ 362.1157. Found 362.1169. Anal. Calcd for $C_{18}H_{20}NO_5P$: C, 59.83; H, 5.58; N, 3.88. Found C, 59.67; H, 5.38; N, 3.91.

4.2.6. Dimethyl (3*R*,2′*S*)-2(2′-(3,3-dimethylbuthyl)isoindolin-1-one-3-yl)phosphonate 3e

2-Formylbenzoic acid (200 mg, 1.33 mmol), (*S*)-3,3-dimethyl-2-butylamine (142 mg, 0.2 mL, 1.40 mmol), and dimethyl phosphite (154 mg, 0.15 mL, 1.40 mmol) were stirred at 80 °C for 3 h. Compound **3e** was obtained (170 mg, 40%) as a white solid in a >98:02 dr. Mp 144–147 °C. $[\alpha]_D = +9.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02 (s, 9H, $(CH_3)_3$), 1.72 (d, *J* = 6.8 Hz, 3H, CH_3CH), 3.55 (d, *J* = 10.4 Hz, 3H, $(CH_3O)_2P$), 3.72 (d, *J* = 10.8 Hz, 3H, $(CH_3O)_2P$), 3.76 (q, *J* = 7.2 Hz, 1H, $NCHCH_3$), 4.91 (d, *J* = 12.8 Hz, 1H, $CHP(OMe)_2$), 7.48–7.83 (m, 4H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.6 (CH_3CH), 28.3 (($CH_3)_3$), 53.8 (d, *J* = 7.6 Hz, $(CH_3O)_2P$), 53.9 (d, *J* = 6.1 Hz, $(CH_3O)_2P$), 61.7 (d, *J* = 151.7 Hz, $CHP(OMe)_2$), 62.8 ($NCHCH_3$), 123.7, 124.4, 129.0, 131.3, 134.1, 138.0, 169.1 ^{31}P NMR (81 MHz, $CDCl_3$) δ: 21.9. HRMS [FAB^+]: Calcd $C_{16}H_{25}NO_4P$ 326.1521. Found 326.1530. Anal. Calcd for $C_{16}H_{24}NO_4P$: C, 59.07; H, 7.44; N, 4.31. Found C, 59.42; H, 7.12; N, 4.48.

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