Unprecedented Alkene Transposition in Phthalate-Amino Acid Adducts

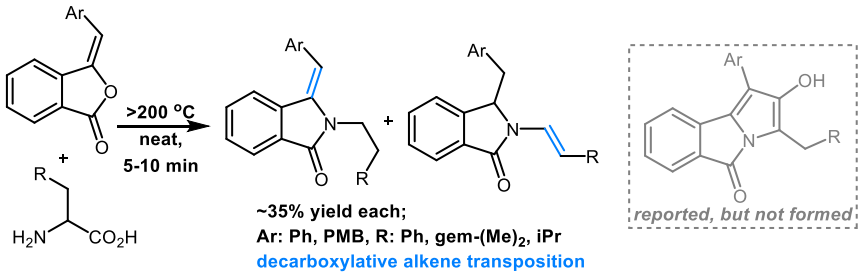
Ishika Saha[a]
Ian R. Baxendale*[a]
Marcus Baumann*[b]

[a] Department of Chemistry, Durham University, South Road, DH1 3LE, Durham, United Kingdom.

[b] School of Chemistry, University College Dublin, Science Centre South, Belfield, Dublin 4, Ireland.

marcus.baumann@ucd.ie

Click here to insert a dedication.

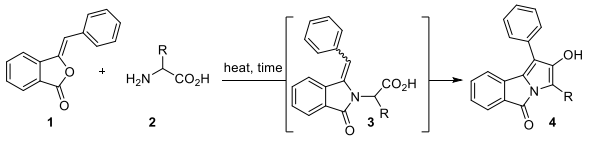


Received:
Accepted:
Published online:
DOI:

Abstract A detailed account on the outcome of the thermal reaction between benzylidene phthalides and various amino acid derivatives is reported. It was discovered that the tricyclic pyrroles as previously described are not the products formed in these reactions. Instead under high-temperature conditions decarboxylated phthalamide adducts are formed within 5-10 minutes. Additionally, an unprecedented alkene transposition mechanism has been identified leading to the final products of these reactions.

Key words phthalide, phthalamide, tricyclic pyrrole, alkene transposition

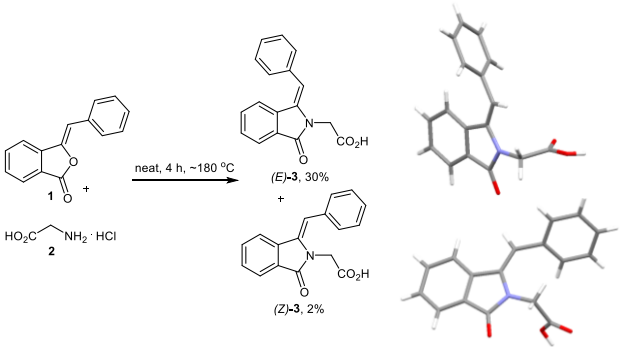
The effective assembly of versatile heterocyclic scaffolds [1] remains at the forefront of modern chemical synthesis especially if complex targets can be generated efficiently in a short sequence of steps from readily available starting materials [2]. We recently embarked on such an endeavor, targeting functionalized tricyclic pyrrole-based products [3] that hold promise as drug-like scaffolds. We specifically favored a process in which the formation of the heterocyclic system would be achieved via a one pot condensation of benzylidene phthalide (**1**) and amino acid (**2**) inputs. Such a high temperature cyclo-condensation process was expected to proceed via a phthalamide intermediate (**3**) that upon ring-closure would yield a fully substituted pyrrole embedded in the desired tricyclic ring system (Scheme 1).



Scheme 1: Anticipated route to tricyclic pyrroles **4**.

A literature search uncovered a study by Hassan and co-workers [4] that reported such a transformation furnishing high yields (90-92%) of the desired products **4** generated in a short heating sequence of **1** with various amino acids **2** under neat melt conditions. To this end we decided to reproduce the reported reactions to create sets of related products and concomitantly explore the scope and robustness of this process in the context of an ongoing medicinal chemistry program.

We commenced our studies by heating mixtures of benzylidene phthalide **1** with different amino acids **2** (Val, Gly, Leu; in a 1:1 stoichiometry) using a standard hot plate set-up with internal temperature control. Although we aimed for heating this mixture at between 220-240 °C for 5-10 minutes akin to the conditions reported by Hassan *et al.* we noticed that this temperature was not reached leading to a maximum internal temperature of only 180-190 °C. Furthermore, we encountered sublimation of the benzylidene phthalide at these temperatures. To circumvent this problem, we decided to add a 1:1 mixture of both starting materials into a pre-heated flask maintained at 240 °C. Although this method ensured the reaction would start at the desired temperature we again noticed a rapid temperature drop to ~190 °C along with sublimation of benzylidene phthalide within 5 minutes. In both cases we analyzed the crude reaction products by ^{1}H-NMR which indicated the presence of a singlet at 6.80 ppm which is diagnostic for a benzylidene proton but differing from the signal in the starting material **1**.



Scheme 2: Reaction with glycine giving *E*- and *Z*-configured **3** as shown by single crystal X-ray analysis.

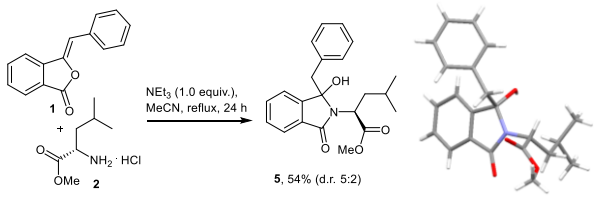
Evidently the desired tricyclic pyrrole product **4** had not formed in any significant amounts. Indeed upon recrystallizing of the main product of these reactions from aqueous acetic acid the material was identified by NMR, HRMS and elemental analysis as the benzylidene phthalamide adduct **3** of the corresponding amino acid component (Scheme 2), the majority of which displayed an *E*-configured alkene moiety as established through NOESY experiments and X-ray crystallography. This finding was consistently found when reacting similarly valine, glycine and leucine in an analogous manner.

Based upon these results we pursued a more in-depth study in order to reconcile this contrasting result and to explore different reaction conditions as reported by Ibrahim [5] using acetic acid as a high boiling solvent for the process.

Hence an equimolar ratio of benzylidene phthalide (**1**) and glycine as its HCl salt were heated in refluxing acetic acid for 8 hours. Aliquots of the reaction mixture were systematically sampled over time and analyzed by LC-MS and ^{1}H-NMR. This experiment showed the steady formation of the expected adduct **3**, however, the desired tricyclic pyrrole **4** was not identified at any point during the reaction. Additionally, it was noted that using acetic acid as a solvent led to a much cleaner reaction albeit at the expense of lower conversions (~30%, isolated yield 15% for (*E*)-**3**). Using fractional crystallization techniques, it was possible to obtain single crystals of the individual *E*- and *Z*-isomers allowing for proof of their respective structures through X-ray diffraction experiments. As previously identified, the *E*-isomer formed preferentially with typical E/Z ratios being in excess of 5:1. Furthermore, the gradual conversion of the isolated *Z*-isomer into the corresponding *E*-isomer was observed in NMR samples prepared in DMSO over a period of several days.

Furthermore, it should be noted that the same products (**3**) were isolated in 83% as a mixture of *E*- and *Z*-isomers by Napolitano [6] when refluxing benzylphthalide with potassium glycinate in a mixture of dioxane and water for 8 hours. This implies that the higher temperature used by Hasan (220 °C) might be a stronger contributing factor than the pH of the medium.

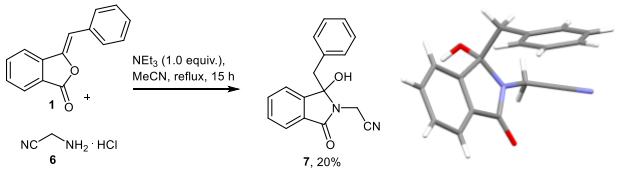
To further extend our studies we decided to attempt the synthesis and isolation of the cyclic aminal structure **5** that upon dehydration would yield benzylidene phthalamide adducts of type **3** (Scheme 3).



Scheme 3: Reaction of **1** with an amino ester with X-ray structure of the aminal adduct (**5a**).

We therefore heated at reflux stoichiometric amounts of substrate **1** with amino ester HCl salt **2** in the presence of triethylamine in acetonitrile. This led to the formation of the expected aminal structures as mixtures of diastereomers which could be separated using column chromatography allowing determination of the absolute configuration of the major diastereomer (original *d.r.* 5:2 by ^{1}H NMR) via X-ray crystallography. This proved that the initial stages of the expected mechanism proceed through predictable intermediates (i.e. **5** → **3**).

In an analogous fashion the aminonitrile HCl salt **6** was used as a replacement of amino acid or ester inputs furnishing again the expected cyclic aminal adduct (**7**) upon reflux in acetonitrile (Scheme 4).

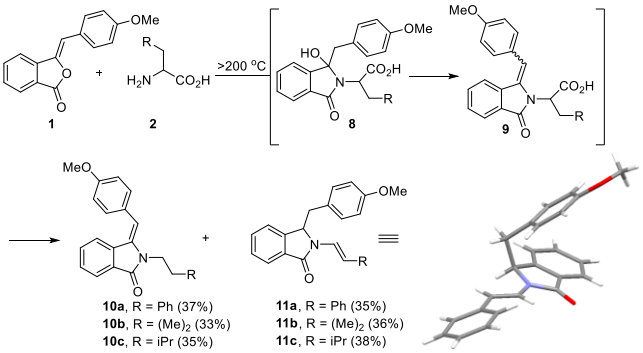


Scheme 4: Reaction of **1** with aminoacetonitrile hydrochloride and X-ray structure of product **7**.

Having secured comprehensive supporting evidence that the condensation reaction between benzylidene phthalides (**1**) and amino acid derivatives (**2**) proceeds indeed through the expected early stages we surmised that a critical point that determines the outcome of this sequence could be the subsequent high temperature fusion process in which the embedded enamine would formally cyclize into the carboxylic acid moiety to generate the subsequent pyrrole.

To test this conjecture, we decided to apply more forcing conditions when attempting the reaction between benzylidene phthalide **1** and different amino acids. In a series of solvent-free reactions phthalide **1** (Ar = Ph, 4-OMe-Ph [7], 1 equiv.) was premixed and blended with the amino acid component (Phe, Leu or Val, 1-2 equiv.) in a thick-walled glass tube followed by rapid heating with a standard laboratory heat gun (reaching 230-250 °C, IR thermometer detection [8]). Within 5 minutes the yellow powdered starting material mixture turned into an amber viscous liquid. This process was accompanied by formation of gas which was expected to be water (from dehydration) and CO_2 (from decarboxylation). Upon further heating over an additional 5 minutes the gas evolution ceased, and a light brown oil formed that rapidly solidified upon cooling. To analyze the reaction progress in each case samples were taken after 5 and 10 minutes and studied by ^{1}H-NMR and COSY experiments. These data revealed that after 5 minutes a complex mixture of intermediates had formed. Based on comparison with previously prepared structures (see above section) we were able to identify both diastereomeric intermediates **5**, *E* and *Z* isomers of the subsequent adducts (**3**) as well as residual amounts of the starting materials. NMR spectra obtained for samples taken after heating for 10 minutes indicated that both starting materials and intermediates (**3** and **5**) were largely consumed and had been converted into 2 new species possessing distinct NMR shifts for their respective alkyl and alkenyl moieties. After separation of these entities by silica column chromatography these two new species were identified

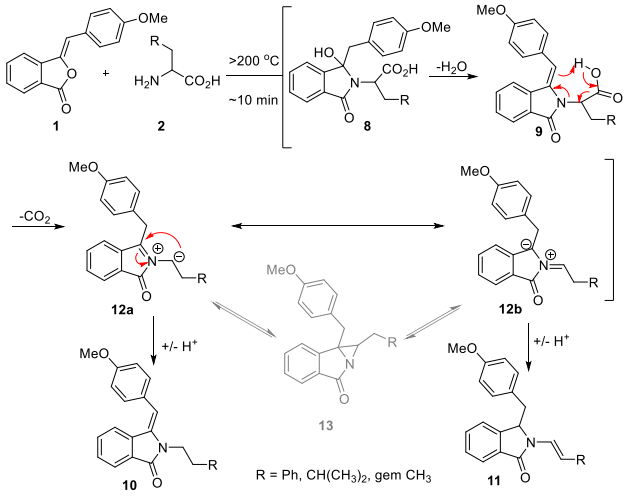
as the products **10** and **11** respectively, which are isomeric compounds based on decarboxylated species (Scheme 5).



Scheme 5: Neat fusion reactions of **1** with amino acids.

Using NOESY techniques the alkene configuration of product **10** was determined to be of the *E* form. The structure of the unexpected isomer **11a** was secured by means of single crystal X-ray diffraction experiments. Analyzing the original mixtures, we determined that it had formed in equal amounts with respect to the isomer **10** (isolated yield about 35% each). This finding was also corroborated when employing different amino acid components (Phe, Val, Leu) as well as amino ester HCl salts, specifically LeuOMe·HCl, in an analogous fusion process, observing principally decarboxylated phthalamide products. Importantly, in none of these experiments were any of the originally specified tricyclic pyrrole products observed.

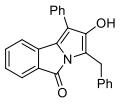
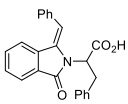
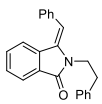
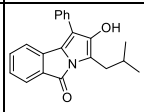
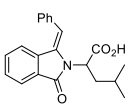
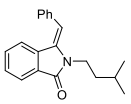
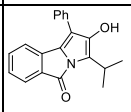
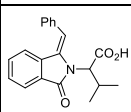
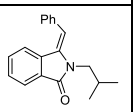
To account for the reaction outcome of this high-temperature reaction between benzylidene phthalides and amino acids (esters) the following ylide-based mechanism is proposed (Scheme 6). In accordance with our prior studies we suggest initial formation of a phthalamide adduct **8** that upon loss of water forms acid species **9**. Upon continued heating this material decarboxylates to form a zwitter-ionic structure **12a** that can exist in its mesomeric form **12b** and both can potentially interconvert via the putative tricycle **13**. Proton transfer then furnishes the two isolated products **10** and **11** arising from the zwitter-ionic precursors. It is postulated that the equimolar ratio of products **10** and **11** obtained in these reactions reflects the similar free energies for their respective formations.



Scheme 6: Proposed reaction mechanism furnishing **10** and **11**.

Based on the discovery of this unexpected and unprecedented reaction pathway leading to two distinct isomeric alkene products (**10** and **11**) instead of the anticipated pyrrole products (**4**) as reported by Hassan [4], we undertook a comparison of the available data on these products. In the original report Hassan presented IR data, uncorrected melting points and nitrogen content established through elemental analysis. Although on its own none of these would be sufficient proof of the correct structure, we decided to compare the nitrogen content reported by Hassan to the calculated value for different products we obtained. As depicted in Table 1 the reported values are close to those required for the tricyclic pyrrole structures (entry 2 and 3), however, it appears that the alternative products **3**, **10** and **11** possess similar values for nitrogen. Unfortunately, Hassan and co-workers do not report elemental analysis data for carbon and hydrogen which would have helped to confirm the assignments.

Table 1: Calculated nitrogen content of different products compared to reported data by [4].

	Pyrrole **4**	reported N content	Acid adducts **3**	Products **10** (and **11**)
1	 N = 3.99%	N = n.a.	 N = 3.79%	 N = 4.30%
2	 N = 4.41%	N = 4.35%	 N = 4.18%	 N = 4.81%
3	 N = 4.62%	N = 4.51%	 N = 4.36%	 N = 5.05%

Additionally, Hassan's report lists IR stretching frequencies of 1695-1730 cm^{-1} and 3300-3425 cm^{-1} for the product obtained. Whilst the former can be assigned to the amide carbonyl that is present in either structure **3**, **4**, **10** or **11**, the latter assigned for the hydroxy group was not identified by us. Due to the lack of NMR data presented in Hassan's report and the persisting discrepancies regarding the true nature of the pyrrole products that reportedly were isolated in 90-92% yield we are unable to account for the correct structural assignment. However, based on our experiments and the complete characterization provided for products **10** and **11** that include key X-ray structural data, we can confirm that a competitive and possibly alternative process readily occurs in the fusion reaction between benzylidene phthalides and various amino acids. This process is accompanied by concomitant loss of water and carbon dioxide and involves an unprecedented alkene transposition leading to isomeric products in a combined yield of ~70%.

In conclusion, we provide evidence (by NMR, HR-MS and X-ray crystallography) of an unprecedented decarboxylative condensation reaction between benzylidene phthalides and amino acids under high temperature fusion conditions. In this process a phthalamide adduct is readily formed that upon loss

of carbon dioxide generates a zwitter-ionic intermediate rendering after proton-transfer the isolated alkene isomers in a 1:1 ratio as principal reaction products. This outcome contrasts with literature reports suggesting tricyclic pyrrole products that we were unable to observe. Several modifications to this process were made allowing the isolation and characterization of key intermediates supporting the proposed reaction pathway, however, attempts to rectify the experimentally determined reaction outcome were ultimately unsuccessful.

Acknowledgment

We are grateful to Dr Andrei Batsanov and Dr Dmitry Yufit (both Durham University, Department of Chemistry) for solving the X-ray crystal structures reported. We furthermore acknowledge generous support by the Royal Society (to IRB) and the School of Chemistry at University College Dublin (to MB).

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

References and Notes

(1) (a) Taylor, R.D.; MacCoss, M.; Lawson, A.D.G. *J. Med. Chem.* **2014**, *57*, 5845. (b) Baumann, M.; Baxendale, I.R. *Beilstein J. Org. Chem.* **2013**, *9*, 2265. (c) Baumann, M.; Baxendale, I.R.; Ley, S.V.; Nikbin, N. *Beilstein J. Org. Chem.* **2011**, *7*, 442. (d) Silverman, R.B. *The Organic Chemistry of Drug Design and Drug Action*; Elsevier Academic Press: Burlington, MA, **2004**. (e) Li, J.J. *Heterocyclic Chemistry in Drug Discovery*; Wiley: New York, **2013**.

(2) (a) Taylor, A.P.; Robinson, R.P.; Fobian, Y.M.; Blakemore, D.C.; Jones, L.H.; Fadeyi, O. *Org. Biomol. Chem.* **2016**, *14*, 6611. (b) Mendez-Lucio, O.; Medina-Franco, J.L. *Drug Disc. Today* **2017**, *22*, 120. (c) Jorgensen, W.L. *Acc. Chem. Res.* **2009**, *42*, 724.

(3) For recent examples, please see: (a) Yamamoto, Y.; Hayashi, H. *Tetrahedron* **2007**, *63*, 10149. (b) Mondal, S.K.; Mandal, A.; Manna, S.K.; Ali, S.A.; Hossain, M.; Venugopal, V.; Jana, A.; Samanta, S. *Org. Biomol. Chem.* **2017**, *15*, 2411. (c) Zheng, Z.; Tu, H.; Zhang, L. *Chem. Eur. J.* **2014**, *20*, 2445. (d) Rihak, K.J.; Bissember, A.C.; Smith, J.A. *Tetrahedron* **2018**, *74*, 1167. (e) Mir, N.A.; Choudharry, S.; Ramaraju, P.; Singh, D.; Kumar, I. *RSC Adv.* **2016**, *6*, 39741. (f) Guirguis, D.B. *Eur. Chem. Bull.* **2013**, *2*, 797.

(4) Hassan, K.M.; El-Garby Younes, M.; El-Maghraby, M.A. *Ind. J. Chem.* **1974**, *12*, 1031.

(5) Ibrahim, T.M. *Arch. Pharm. Res.* **1991**, *14*, 342.

(6) Napolitano, E.; Fiaschi, R.; Scartoni, V.; Marsili, A. *J. Chem. Soc., Perkin Trans 1* **1986**, *5*, 781.

(7) We opted to use this 4-methoxyphenyl-substituted phthalide to facilitate ^{1}H-NMR analysis of crude reaction mixtures due to the characteristic signal of the methoxy group.

(8) A hand-held IR thermometer from Extech Instruments was used (type K, model 42515, temperature range -58 to 1472 F).

(9) ***General procedure for products 3***: Equimolar amounts of benzylidene phthalide **1** and glycine were heated (~180-190 °C) and stirred in a round-bottomed flask for 4 h. After cooling, the reaction mixture was dissolved in DCM and a base wash was conducted using saturated aqueous $NaHCO_3$ (10 ml × 3). Aqueous HCl (1 M, ~50 ml) was used to back-extract the acidic species from the aqueous layer into DCM. After drying the organic layer with anhydrous Na_2SO_4 the solvent was removed *in vacuo*. The remaining semi-solid product was recrystallised from a 1:1 mixture of acetic acid and water furnishing crystals of the *E*-isomer (30% isolated yield). The mother liquor subsequently yielded single crystals of the *Z*-isomer (2% isolated yield).

***E*-2-(3-benzylidene-1-oxoisoindolin-2-yl)-acetic acid, (*E*)-3:** Orange crystalline solid; melting range: 201.8-202.5 °C; ^{1}H-NMR (600 MHz, d_6-DMSO) δ/ppm 13.00 (br s, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.51 (app t, *J* = 7.4 Hz, 1H), 7.41-7.48 (m, 5H), 7.36-7.40 (m, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 6.71 (s, 1H), 4.62 (s, 2H). ^{13}C-NMR (150 MHz, d_6-DMSO) δ/ppm 169.9 (C), 165.9 (C), 135.5 (C), 135.2 (C), 135.1 (C), 132.6 (CH), 130.2 (CH), 129.9 (C), 128.3 (CH), 129.7 (2CH), 129.2 (2CH), 123.4 (CH), 123.1 (CH), 111.4 (CH), 41.2 (CH_2). IR ν/ cm^{-1} 2981 (br), 1752 (m), 1670 (s), 1655 (m), 1643 (m); ES$^+$ *m/z* 280.1 [M+H]$^+$, ES$^-$ *m/z* 278.1 [M-H]$^+$; HRMS (ES-TOF$^+$) calculated for $C_{17}H_{14}NO_3$ 280.0968, found 280.0974; CHN-analysis for $C_{17}H_{13}NO_3$ requires C, 73.11; H, 4.69; N, 5.02, found C, 72.67; H, 4.66; N, 4.97; Crystal data CCDC 1863430: Space group: P 2_1/n; a = 9.4136(8), b = 14.1529(12), c = 10.1118(8) Å; α = 90, β = 97.034(3), γ = 90°.

***Z*-2-(3-benzylidene-1-oxoisoindolin-2-yl)-acetic acid, (*Z*)-3:** White crystalline solid; melting range: 174.6-176.1 °C; ^{1}H-NMR (600 MHz, d_6-DMSO) δ/ppm 12.73 (br s, 1H), 8.07 (app dd, *J* = 7.8, 0.9 Hz, 1H), 7.81 (app dt, *J* = 7.1, 1.0 Hz, 1H), 7.76 (app td, *J* = 7.6, 1.2 Hz, 1H), 7.40-7.48 (m, 5 H), 7.33-7.36 (m, 1H), 7.07 (s, 1H), 4.17 (s, 2H). ^{13}C-NMR (150 MHz, d_6-DMSO) δ/ppm 169.7 (C), 168.3 (C), 138.6 (C), 134.6 (C), 134.5 (C), 133.1 (CH), 130.1 (2CH), 129.9 (2CH), 129.6 (CH), 128.1 (CH), 127.7 (C), 123.2 (CH), 120.8 (CH), 107.5 (CH), 43.9 (CH_2). IR ν/ cm^{-1} 2981 (br), 1710 (m), 1642 (s), 1249 (s), 760 (s); Crystal data CCDC 1863431: space group: Pbca; a = 9.4099(5), b = 8.4569(5), c = 33.1462(19) Å; α = 90, β = 90, γ = 90.

(10) ***General procedure for products 5:*** To a pre-stirred mixture of *L*-leucine methyl ester hydrochloride (4.5 mmol) and triethylamine (4.5 mmol) in acetonitrile (12 ml) was added benzylidene phthalide (**1**, 4.5 mmol) and the solution was allowed to reflux for 24 hours. After cooling to ambient temperature, a base wash with sat. $NaHCO_3$ (~5 ml) was conducted to create the free base form of triethylamine, which was subsequently removed *in vacuo*. The compounds in the remaining mixture were separated by silica column chromatography using a gradient in the eluent system, Hex:EtOAc (6:4 to 7:3). The isomers were recrystallised from a mixture of EtOAc and hexane. The major isomer **5a** was found by single crystal X-ray diffraction to have (2*S*3*R*) configuration. A diastereomeric ratio of ~5:2 was established by ^{1}H-NMR of the unseparated mixture. The combined yield for both diastereomers was 54%, 0.90 g.

2-(*S*)-(3-(*R*)-benzyl-3-hydroxy-1-oxoisoindolin-2-yl)-4-methylpentanoate, 5a: White crystalline solid; ^{1}H-NMR (700 MHz, d_6-DMSO) δ/ppm 7.58 (app dt, *J* = 7.5, 1.0 Hz, 1H), 7.43 (app tt, *J* = 7.4, 1.2 Hz, 1H), 7.37 (app td, *J* = 7.5, 1.2 Hz, 1H), 7.21-7.25 (m, 3H), 7.14-7.18 (m, 2H), 6.62 (s, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 4.30 (dd, *J* = 8.3, 5.8 Hz, 1H), 3.61 (s, 3H), 3.43 (d, *J* = 13.8 Hz, 1H), 2.80 (dd, *J* = 13.8, 1.6 Hz, 1H), 2.05-2.10 (m, 1H), 1.91-1.96 (m, 1H), 1.72 (dddd, *J* = 13.2, 12.0, 8.4, 6.5 Hz, 1H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H); ^{13}C-NMR (175 MHz, d_6-DMSO) δ/ppm 172.0 (C), 165.7 (C), 147.2 (C), 136.5 (C), 132.1 (CH), 131.4 (2CH), 131.1 (C), 129.5 (CH), 127.9 (2CH), 127.0 (CH), 123.5 (CH), 123.4 (CH), 90.5 (C), 52.5 (CH_3), 52.0 (CH), 44.4 (CH_2), 39.1 (CH_2), 24.8 (CH), 23.3 (CH_3), 22.4 (CH_3). IR ν/ cm^{-1} 3188 (br), 2954 (w), 1749 (m), 1672 (s), 1420 (m); ES$^+$ *m/z* 368.1 [M+H]$^+$, HRMS (ES-TOF$^+$) calculated for $C_{22}H_{26}NO_4$ 368.1856, found 368.1875; Crystal data CCDC 1863432: space group: P-1; a = 9.6024(13), b = 11.2692(15), c = 19.438(3) Å; α = 95.240(6), β = 98.235(6), γ =110.172(6)°.

2-(*S*)-*2*-((3*S*)-3-benzyl-3-hydroxy-1-oxoisoindolin-2-yl)-4-methylpentanoate , 5b: White crystalline solid; IR ν/ cm^{-1} 3342 (br), 2955 (w), 1735 (m), 1675 (s), 1420 (m). ^{1}H-NMR (700 MHz, d_6-DMSO) δ/ppm 7.55 (app dt, *J* = 7.5, 1.0 Hz, 1H), 7.44 (m, 1H), 7.39 (app td, *J* = 7.5, 1.3 Hz, 1H), 7.18-7.20 (m, 3H), 7.03-7.06 (m, 2H), 6.67 (app dt, *J* = 7.6, 1.0 Hz, 1H), 6.66 (d, *J* = 1.0 Hz, 1H), 4.39 (dd, *J* = 7.9, 6.5 Hz, 1H), 3.57 (s, 3H), 3.47 (d, *J* = 13.8 Hz, 1H), 2.83 (dd, *J* = 13.8, 1.0 Hz, 1H), 2.18-2.25 (m, 1H), 1.85-1.91 (m, 1H), 1.78 (dt, *J* = 13.4, 6.7 Hz, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H); ^{13}C-NMR (175 MHz, d_6-DMSO) δ/ppm 172.1 (C), 166.7

(C), 146.7 (C), 136.1 (C), 131.7 (C), 131.6 (CH), 131.0 (2CH), 129.6 (CH), 128.0 (2CH), 127.1 (CH), 124.2 (CH), 122.7 (CH), 91.1 (C), 52.1 (CH), 51.8 (CH_3), 44.5 (CH_2), 39.3 (CH_2), 25.5 (CH), 23.2 (CH_3), 22.6 (CH_3).

(11) ***General procedure for product 7:*** To a pre-stirred mixture of 2-aminoacetonitrile hydrochloride (4.5 mmol) and triethylamine (4.5 mmol) in acetonitrile (12 ml) was added benzylidene phthalide (**1**, 4.5 mmol) at room temperature. After refluxing for 15 hours the mixture was cooled to room temperature. A base wash with sat. $NaHCO_3$ (~5 ml) was conducted to create the free base form of triethylamine, which was subsequently removed *in vacuo*. The remaining mixture was purified by silica column chromatography using an eluent system of Hex:EtOAc (7:3). The title compound was obtained as a pale solid and recrystallised from EtOAc:Hex (2:5); yield = 20% (0.253 g).

2-(3-Benzyl-3-hydroxy-1-oxoisonidolin-2-yl)-acetonitrile, 7: White crystalline solid; melting range: 144.7-147.9 °C; IR ν/ cm^{-1} 3356 (br), 1690 (s), 1616 (w), 1411 (m), 1070 (m); ^{1}H-NMR (700 MHz, $CDCl_3$) δ/ppm 7.48-7.51 (m, 2H), 7.39-7.45 (m, 1H), 7.11-7.21 (m, 4H), 6.95-7.00 (m, 2H), 4.31 (dd, *J* = 17.6, 0.9 Hz, 1H), 4.17 (br s, 1H), 4.07 (d, *J* = 17.6 Hz, 1H), 3.49 (d, *J* = 14.1 Hz, 1H), 3.12 (d, *J* = 14.1 Hz, 1H); ^{13}C-NMR (175 MHz, $CDCl_3$) δ/ppm 167.0 (C), 146.3 (C), 133.8 (C), 132.9 (CH), 130.3 (2CH), 129.9 (2CH+CH), 129.6 (C), 127.4 (CH), 123.6 (CH), 123.2 (CH), 115.5 (C), 90.8 (C), 43.4 (CH_2), 26.1 (CH_2). ES$^+$ *m/z* 279.2 $[M+H]^+$, HRMS (ES-TOF$^+$) calculated for $C_{17}H_{15}N_2O_2$, 279.1128, found 279.1134. Crystal data CCDC 1863433: space group: C 2/c; a = 23.0705(13), b = 8.1188(4), c = 15.8975(9) Å; α = 90, β = 108.421(2), γ = 90.

(12) ***General procedure for products 10 and 11:*** A homogeneous mixture of benzylidene phthalide (**1**, 1 equiv.) and an amino acid HCl-salt (Phe, Val, Leu; 1-2 equiv.) was prepared in a thick-walled glass tube and heated with a heat gun to about 240 °C. After 10 minutes gas formation ceased and an amber oil resulted, which solidified upon cooling. The crude residue was dissolved in a minimal amount of EtOH and subjected to silica column chromatography (5-10% EtOAc/hexanes) yielding the individual products **10** and **11** as yellow oils.

(*E*)-3-(4-Methoxybenzylidene)-2-phenethylisoindolin-1-one, 10a: Pale yellow oil, 37% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm 7.85 (dt, J = 7.7, 1.0 Hz, 1H), 7.41 (ddd, J = 7.5, 6.3, 2.0 Hz, 1H), 7.35 – 7.22 (m, 9H), 6.99 – 6.92 (m, 2H), 6.38 (s, 1H), 4.15 – 4.09 (m, 2H), 3.88 (s, 3H), 3.09 – 3.02 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ/ppm 166.4 (C), 159.3 (C), 138.8 (C), 135.6 (C), 135.1 (C), 131.4 (CH), 130.8 (2CH), 130.3 (C), 129.0 (CH), 128.9 (2CH), 128.6 (2CH), 127.3 (C), 126.6 (CH), 123.1 (2CH), 114.1 (2CH), 110.3 (CH), 55.4 (CH_3), 41.2 (CH_2), 34.9 (CH_2). IR (ν/cm^{-1}; neat) 3028 (w), 2957 (w), 1703 (s), 1605 (m), 1509 (s), 1454 (m), 1346 (m), 1250 (s), 1173 (m), 1105 (m), 1031 (m), 832 (w), 756 (m), 697 (m). HRMS (AP+) calculated for $C_{24}H_{22}NO_2$ 356.1651, found 356.1626.

(*E*)-2-Isobutyl-3-(4-methoxybenzylidene)isoindolin-1-one, 10b: Pale yellow oil, 33% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ/ppm 7.82 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.39 (td, *J* = 7.4, 1.1 Hz, 1H), 7.37 – 7.33 (m, 3H), 7.30 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 2H), 6.48 (s, 1H), 3.87 (s, 3H), 3.71 (d, *J* = 7.6 Hz, 2H), 2.22 (sept, *J* = 6.0 Hz, 1H), 1.00 (d, *J* = 6.8 Hz, 6H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ/ppm 166.8 (C), 159.2 (C), 136.2 (C), 135.0 (C), 131.3 (CH), 130.8 (2CH), 130.2 (C), 128.9 (CH), 127.4 (C), 123.1 (CH), 123.0 (CH), 114.1 (2CH), 110.4 (CH), 55.3 (CH3), 46.8 (CH2), 27.8 (CH), 20.3 (2CH3). IR (ν/cm^{-1}; neat) 2959 (m), 1698 (s), 1606 (m), 1510 (s), 1407 (m), 1248 (s), 1175 (m), 1095 (m), 1033 (m), 768 (m), 697 (m), 562 (m). HRMS (AP+) calculated for $C_{20}H_{22}NO_2$ 308.1651, found 308.1652.

(*E*)-2-Isopentyl-3-(4-methoxybenzylidene)isoindolin-1-one, 10c: Pale yellow oil, 35% yield. ^{1}H-NMR (600 MHz, $CDCl_3$) δ/ppm 7.82 (dt, J = 7.5, 1.0 Hz, 1H), 7.41 – 7.34 (m, 4H), 7.30 (ddd, J = 8.1, 7.2, 1.2 Hz, 1H), 6.97 (d, J = 8.7 Hz, 2H), 6.47 (s, 1H), 3.91 – 3.88 (m, 2H), 3.88 (s, 3H), 1.71 (sept, J = 6.0 Hz, 1H), 1.66 – 1.59 (m, 2H), 1.01 (d, J = 6.0 Hz, 6H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ/ppm 166.4 (C), 159.3 (C), 135.7 (C), 135.1 (C), 131.2 (CH), 130.8 (2CH), 130.4 (C), 128.9 (CH), 127.4 (C), 123.0 (2xCH), 114.1 (2CH), 110.0 (CH), 55.3 (CH_3), 37.9 (CH_2), 37.2 (CH_2), 26.2 (CH), 22.6 ($2CH_3$). IR (ν/cm^{-1}; neat) 2956 (w), 1698 (s), 1606 (m), 1510 (m), 1407 (m), 1248 (s), 1174 (m), 1096 (m), 1033 (m), 837 (m), 767 (m), 696 (m). HRMS (AP+) calculated for $C_{21}H_{24}NO_2$ 322.1807, found 322.1813.

(*E*)-3-(4-Methoxybenzyl)-2-styrylisoindolin-1-one, 11a: Beige solid, 35% yield; melting range 161.3-164.0 °C (hexanes/Et_2O). ^{1}H-NMR (600 MHz, $CDCl_3$) δ/ppm 7.81 (d, *J* = 15.2 Hz, 1H), 7.76 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.52 (td, *J* = 7.5, 1.1 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.25 – 7.22 (m, 1H), 7.21 (dt, *J* = 7.7, 0.9 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.69 (d, *J* = 8.6 Hz, 2H), 6.30 (d, *J* = 15.1 Hz, 1H), 5.15 (dd, *J* = 7.3, 3.1 Hz, 1H), 3.73 (s, 3H), 3.47 (dd, *J* = 14.2, 3.2 Hz, 1H), 3.15 (dd, *J* = 14.1, 7.2 Hz, 1H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ/ppm 166.4 (C), 158.5 (C), 145.0 (C), 136.5 (C), 132.0 (CH), 131.3 (C), 130.6 (2CH), 128.8 (2CH), 128.5 (CH), 126.7 (CH), 126.5 (C), 125.7 (2CH), 124.1 (CH), 122.9 (CH), 122.7 (CH), 113.6 (2CH), 112.7 (CH), 59.6 (CH), 55.1 (CH_3), 36.6 (CH_2). IR (ν/cm^{-1}; neat) 3067 (w), 2933 (w), 1700 (s), 1646 (s), 1609 (m), 1508 (s), 1390 (s), 1298 (m), 1242 (s), 1140 (m), 1029 (m), 948 (m), 834 (s), 747 (s), 697 (s), 618 (m). HRMS (ES+) calculated for $C_{24}H_{22}NO_2$ 356.1651, found 356.1675. Crystal data CCDC 1863434: space group: Pbca; a = 9.7463(4), b = 14.9772(7), c = 25.1292(11) Å; α = 90, β = 90, γ = 90.

3-(4-Methoxybenzyl)-2-(2-methylprop-1-en-1-yl)isoindolin-1-one, 11b: Colourless oil, 36% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm 7.80 (ddd, *J* = 5.6, 3.0, 0.8 Hz, 1H), 7.41 (dd, *J* = 5.6, 3.1 Hz, 2H), 6.96 – 6.90 (m, 3H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.01 – 5.98 (m, 1H), 4.88 (dd, *J* = 8.5, 4.3 Hz, 1H), 3.77 (s, 3H), 3.35 (dd, *J* = 13.8, 4.3 Hz, 1H), 2.68 (dd, *J* = 13.8, 8.5 Hz, 1H), 1.88 (d, *J* = 1.5 Hz, 3H), 1.74 (d, *J* = 1.5 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ/ppm 158.5 (C), 145.0 (C), 133.1 (C), 132.0 (C), 131.1 (CH), 130.6 (2CH), 128.2 (CH), 128.0 (C), 123.8 (CH), 123.0 (CH), 117.7 (CH), 113.8 (2CH), 62.9 (CH), 55.2 (CH_3), 38.0 (CH_2), 23.1 (CH_3), 19.0 (CH_3) [1 C not observed]. IR (ν/cm^{-1}; neat) 2962 (w), 2914 (w), 1698 (s), 1612 (m), 1513 (s), 1402 (m), 1301 (m), 1249 (s), 1178 (m), 1034 (m), 826 (m), 746 (m), 692 (m). HRMS (AP+) calculated for $C_{20}H_{22}NO_2$ 308.1651, found 308.1650.

(*E*)-3-(4-Methoxybenzyl)-2-(3-methylbut-1-en-1-yl)isoindolin-1-one, 11c: Yellow oil, 38% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm 7.73 (dt, *J* = 7.4, 1.0 Hz, 1H), 7.46 (td, *J* = 7.5, 1.3 Hz, 1H), 7.38 (ddd, *J* = 8.0, 7.4, 0.9 Hz, 1H), 7.12 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.04 (ddd, *J* = 14.8, 1.2, 0.6 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.7 Hz, 2H), 5.32 (dd, *J* = 14.8, 7.3 Hz, 1H), 4.97 (dd, *J* = 7.4, 3.1 Hz, 1H), 3.74 (s, 3H), 3.40 (dd, *J* = 13.9, 3.1 Hz, 1H), 2.99 (dd, *J* = 13.9, 7.4 Hz, 1H), 2.54 (dsext, *J* = 13.6, 6.8 Hz, 1H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ/ppm 166.2 (C), 158.5 (C), 145.0 (C), 131.8 (C), 131.5 (CH), 130.5 (2CH), 128.3 (CH), 127.0 (C), 123.9 (CH), 122.8 (CH), 121.2 (CH), 120.5 (CH), 113.6 (2CH), 59.4 (CH), 55.1 (CH_3), 36.3 (CH_2), 29.9 (CH), 23.5 (CH_3), 23.2 (CH_3). IR (ν/cm^{-1}; neat) 2957 (m), 1698 (s), 1663 (m), 1513 (s), 1467 (m), 1393 (m), 1249 (s), 1178 (m), 1035 (m), 826 (m), 747 (m), 697 (m). HRMS (AP+) calculated for $C_{21}H_{24}NO_2$ 322.1807, found 322.1812.