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ORIGINAL PAPER

Synthesis of 3-substituted *N*-allylisoindolinone derivatives by the acetate method

Ibrahim A. I. Ali

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Abstract A series of *N*-allylisoindolinone derivatives were prepared by a novel sequential reaction of 2-allyl-3-oxoisoindolin-1-yl acetate with C-nucleophiles in the presence of trimethylsilyl trifluoromethanesulfonate. The nucleophiles included arenes, alkenes, and active methylene to give 3-substituted *N*-allylisoindolinone products. This method was applied to synthesize cyclohexane-fused indolizidine alkaloid mimics using Grubbs' catalyst.

Keywords Isoindolinones · Acetate · Grubbs' catalyst · C–C bond formation · C-nucleophiles · Trimethylsilyl trifluoromethanesulfonate (TMSOTf)

Introduction

Isoindolinones are the core structures of numerous natural alkaloids [1–3] and biologically active compounds (Fig. 1). For example, the alkaloid fumaridine is a secophthalideisoquinoline ene lactam [4]; DN-2574 is an isoindoloquinoline derivative used as a cognition-enhancing agent [5]; and many drug candidates, such as pagoclone [6], are isoindolinones. They demonstrate a remarkably wide array of biological activities [7], including anti-inflammatory [7], anti-hypertensive [8], antipsychotic [9], vasodilatory [10], and antileukemic [11] effects, meaning that the development of new synthetic routes to these heterocycles is particularly attractive. While several methods have been reported for the preparation of isoindolinones [12], some lead to the synthesis of natural products [13] and compound libraries [14]. Additionally, 3-methyleneisoindolin-1-one is a key intermediate in the total synthesis of lennoxamine [15].

Trichloroacetimidates and an acetate method have been widely used to activate anomeric oxygen exchange reactions. The consequent glycosidic bond formation is useful in glycoside synthesis [16]. Ali et al. [16–19] reported the reaction of *O*-phthalimidomethyl trichloroacetimidate with C-nucleophiles to afford N-substituted phthalimides. In the work described in the present report, we extended the scope of this process, enabling efficient and selective carbon–carbon bond formation. This research offers the development of a series of 3-substituted 2-allylisoindolinone via C–C bond formation using the acetate method.

Results and discussion

The trichloroacetimidate method was applied by our group to synthesize a series of N-protected nonproteinogenic α-amino acid esters via C–C bond formation. The base-catalyzed addition reaction of trichloroacetonitrile to the hydroxyl group of 2-allyl-3-hydroxyisoindolin-1-one (**1**) [19, 20] failed to afford the trichloroacetimidate **2** but gave *N*-(2-allyl-3-oxoisoindolin-1-yl)-trichloroacetamide (**3**) instead (Scheme 1).

The alternative simple method that was applied to perform the structural modification of 2-allylisoindolinone was the acetate coupling method. The acetylation of hydroxyisoindolin-1-one **1** by acetic anhydride in pyridine afforded 2-allyl-3-oxoisoindolin-1-yl acetate (**4**). The reaction of **4** with C-nucleophiles in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) at room temperature readily afforded the isoindolinone products in 65–89 % yield.

I. A. I. Ali (✉)
Department of Chemistry, Faculty of Science, Suez Canal University, Ismailia, Egypt
e-mail: ibrahim3369@yahoo.com

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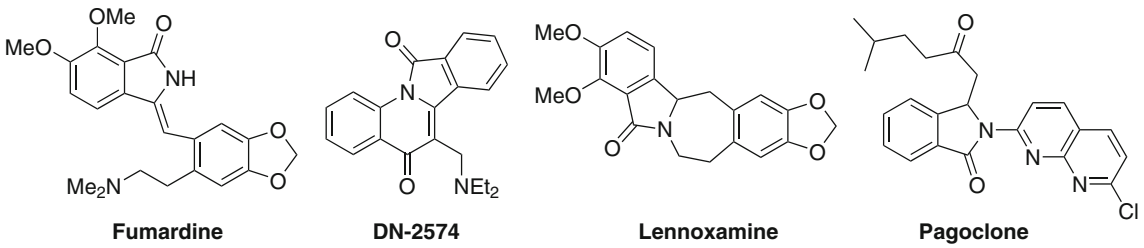
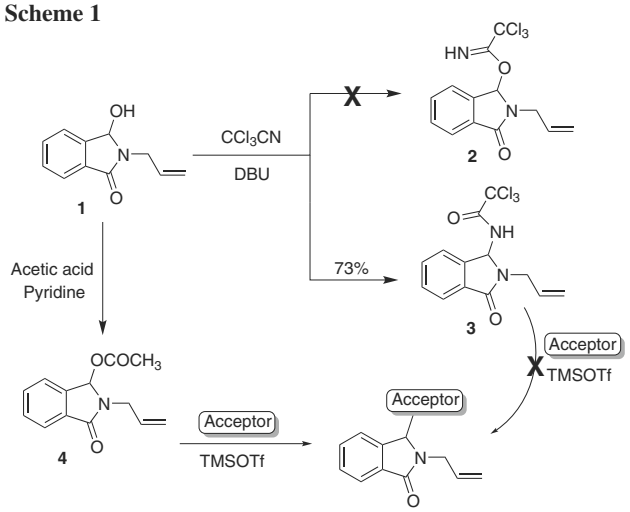


Fig. 1 Structures of some natural products and biologically active 3-isoindolin-1-one compounds

Scheme 1



Thus, acetate **4** was reacted with a series of substituted benzene derivatives **5a**–**5c** and styrene in the presence of TMSOTf to give the 3-substituted 2-allylisoindolin-1-ones **6a**–**6c** and **8** in 65–89 % yield (Scheme 2).

Structure assignment of 2-allyl-3-(2,4-dimethoxyphenyl)-1-isoindolinone (**6b**) was based on ^{1}H and ^{13}C NMR spectral and physicochemical analysis. The ^{1}H NMR spectrum clearly confirms the selective aromatic electrophilic substitution site. Thus, the ^{1}H NMR spectrum of **6b** gave two singlet signals at $\delta = 3.73$ and 3.72 ppm, associated with two OCH_3 groups. The ^{1}H NMR spectrum also presented an important signal at 5.10 ppm that is typically associated with CH, confirming C–C linkage generation. The ^{13}C NMR spectrum of **6b** displayed signals at $\delta = 55.4$, 55.2, and 63.9 ppm, associated with two OCH_3 and CH groups, respectively.

Similarly, functionalized ester and ketone moieties can be introduced onto 2-allylisoindolinones at position 3 by the reaction of **4** with silylated reagents such as 1-(trimethylsiloxy)cyclohexene (**9**), 1-phenyl-1-(trimethylsiloxy)ethylene (**11**), 2-(trimethylsiloxy)pent-2-en-4-one (**13**), or 1-methoxy-2-methyl-1-(trimethylsiloxy)propene (**15**) in the presence of TMSOTf to give **10**, **12**, **14**, and **16** in 79–83 % yield (Scheme 3).

The structure assignment of cyclohexanone **10** is based on ^{1}H and ^{13}C NMR spectral analysis. The ^{1}H NMR spectrum gave multiplet signals at δ 2.80-1.20 ppm, attributed to cyclohexane moiety, while the ^{13}C NMR spectrum of **10** displays signals at δ 44.1, 41.5, 25.8, 24.3, 24.2 and 53.6 ppm associated with four CH_2 and CH groups, respectively. The structure of ketone **14** was established by analyzing the ^{1}H and ^{13}C NMR spectra; the ^{1}H NMR spectrum showed signals at 1.28, 2.29, 5.10 and 5.42 ppm, revealing the presence of 2 CH_3 and 2 CH groups, while the ^{13}C NMR spectrum presented signals at 22.7, 24.0, 57.8 and 104.9 ppm, which arise from the generated C-C linkage.

Methyl 2-(2-allyl-3-oxo-2,3-dihydro-1H-1-isoindolyl)-2-methylpropanoate (**16**) was identified by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum showed newly introduced methyl propanoate group signals at 0.90, 1.20 and 3.73 ppm. The ^{13}C NMR spectrum displays signals at δ 19.4, 22.8, and 52.1 corresponding to two CH_3 and OCH_3 groups, respectively.

Similarly, functionalized hydrocarbon moieties can be introduced onto 2-allylisoindolinones at position 3 by the reaction of **4** with silylated reagents such as benzyltrimethylsilane (**17**), allyltrimethylsilane (**19**), and propargyltrimethylsilane (**21**) in the presence of TMSOTf to give **18**, **20** [20], and **22** in 76-88 % yield (Scheme 4).

Alkaloids incorporating indolizidine skeletons comprise a large group of natural compounds with an interesting range of biological activities [21]. In this context, we perceive that the present synthetic route to benzoindolizidine alkaloid mimics is highly applicable. We constructed the desired indolizidine **23** in 64 % yield from 2,3-diallyl-1-isoindolinone (**20**) by ring-closing metathesis followed by olefin hydrogenation with Grubbs' catalyst.

Tricyclic isoindol-6-one **24** was obtained by selective reduction using catalytic hydrogenation of the indolizidine **23** [20, 22–24] in the presence of H_2/Pd/C. Treatment of **24** with lithium aluminum hydride in THF led to the reduction of the amide group to the corresponding amine, affording **25** [25] (Scheme 5).

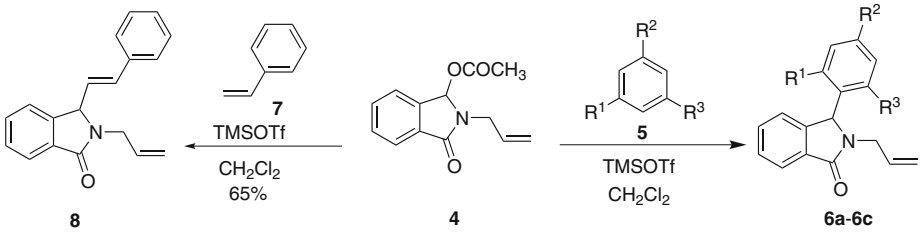
The overall sequential reaction achieved by the acetate coupling method and 2,3-diallyl-1-isoindolinone cyclo-

condensation by Grubbs' catalyst proved to be a versatile method for the synthesis of tricyclic systems of promising biological activity. This was further applied to perform the synthesis of decahydropyrido[2,1-*a*]isoindol-6-one **30**.

Reduction of 2-allylhexahydro-2*H*-isoindole-1,3-dione (**26**) with sodium borohydride in methanol afforded monoselective reduction and gave 2-allyl-3-hydroxyoctahydroisoindol-1-one (**27**). Treatment with acetic anhydride in pyridine furnished acetate **28** in 63 % yield. This acetate was reacted with allyltrimethylsilane **21** as a C-nucleophile in the presence of TMSOTf as catalyst to afford 2,3-diallyloctahydroisoindol-1-one (**29**). The ring closure metathesis of **29** under the influence of Grubbs' catalyst was successful and gave the tricyclic ring system **30** in 72 % yield (Scheme 6).

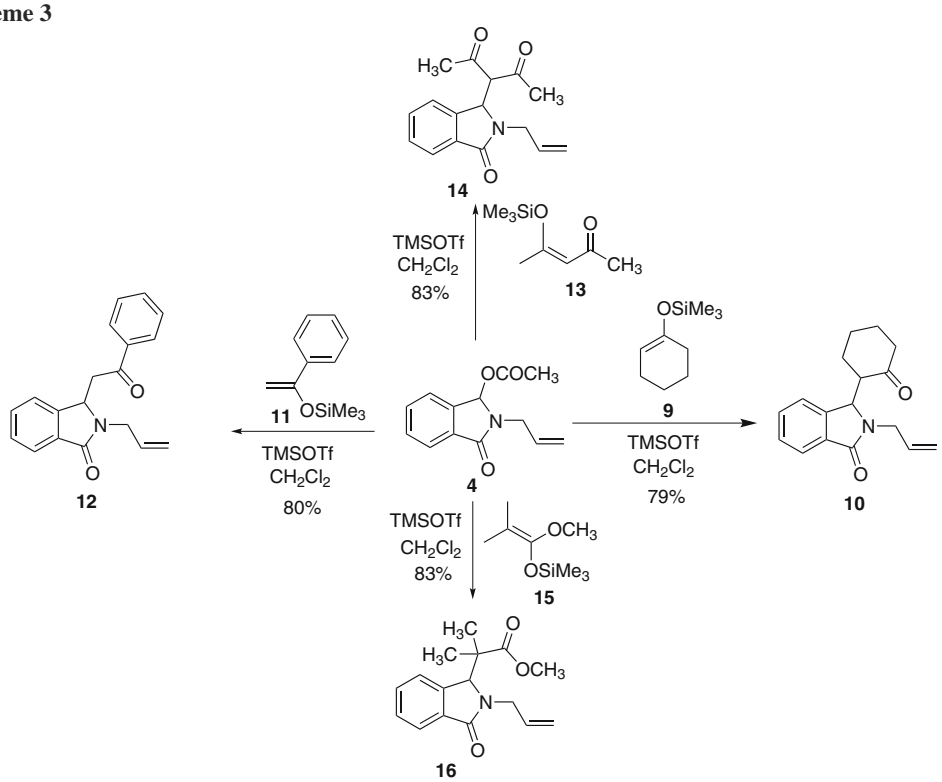
Structure assignment of decahydropyrido[2,1-*a*]isoindol-6-one (**30**) was based on spectral analysis (Fig. 2). The

Scheme 2

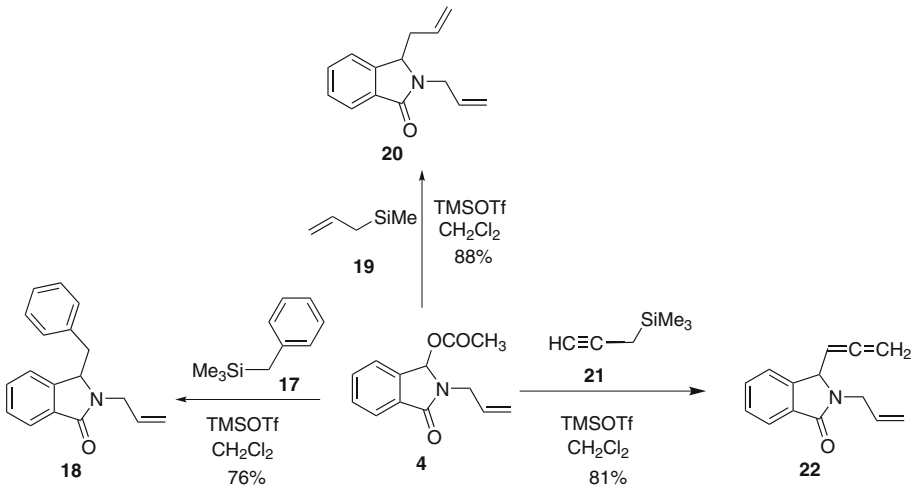


5, 6	R^1	R^2	R^3	
a	H	OCH_3	H	68%
b	OCH_3	OCH_3	H	77%
c	OCH_3	OCH_3	OCH_3	89%

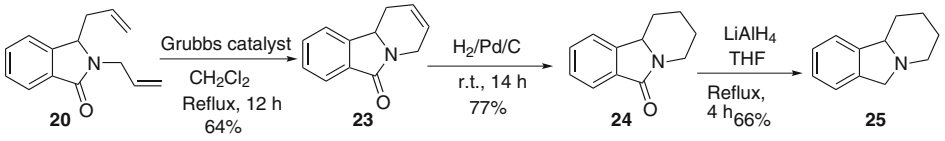
Scheme 3



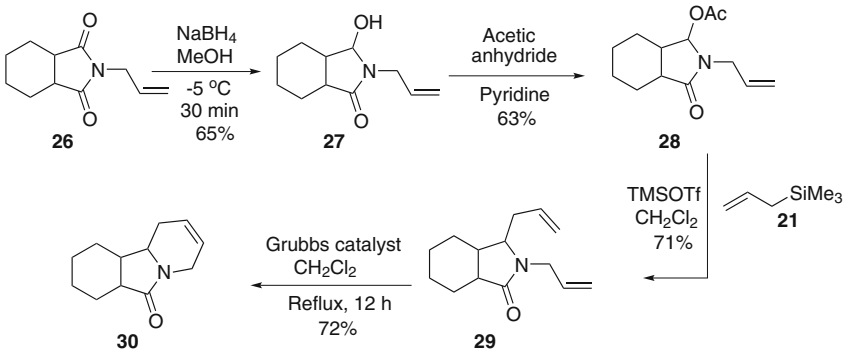
Scheme 4



Scheme 5



Scheme 6



^{1}H NMR spectrum of **30** exhibited signals at 5.77–5.50, 4.20, and 2.41–2.01 ppm, corresponding to CH_{d+c}, CH_e, and CH_b, respectively. The ^{13}C NMR spectrum of **30** showed signals at 175.3, 123.9, 123.6 ppm, attributable to CO, C_d, and C_c, respectively.

Conclusions

A general method has been developed for the formation of isoindolinone derivatives by a novel sequential reaction of acetate **4** with C-nucleophiles. These derivatives are then used for the synthesis of benzo- and cyclohexane-fused indolizidine alkaloid mimics. The prepared compounds may represent novel potential chemotherapeutic agents.

Experimental

Solvents were purified and dried in the usual way. The boiling range of the petroleum ether used was 40–60 °C.

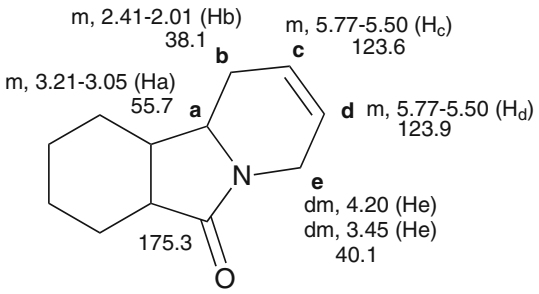


Fig. 2 Selected ^{1}H NMR and ^{13}C NMR spectral data for **30**

Thin-layer chromatography (TLC) utilized silica gel 60 F254 plastic plates (E. Merck, layer thickness 0.2 mm). Detection was by UV absorption. Melting points were determined on a Büchi 510 melting point apparatus. NMR spectra were measured with a Bruker AC 250 (250 MHz) using TMS (0.00 ppm) as the internal standard. Mass spectra were measured on a GC-MSQP (1000EX, Shimadzu). Elemental analyses were performed on a Flash EA-1112 instrument at the Microanalytical Laboratory, Faculty of Science, Suez Canal University, Ismailia, Egypt.

N-(2-Allyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)-2,2,2-trichloroacetamide (**3**, $C_{13}H_{11}Cl_3N_2O_2$)

A stirred solution of 0.94 g **1** (5.0 mmol) in 20 cm^3 dry dichloromethane and 2.5 cm^3 trichloroacetonitrile (25 mmol) was treated with 35 mm^3 DBU at room temperature and then left for 2 h. The solvent was evaporated and the product was purified by column chromatography using 2 % triethylamine in toluene as eluent to give a yellow oil. Yield 1.22 g (73 %); $R_f = 0.53$ (3 % triethylamine in toluene); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 4.15$ (d, $J = 6.2$ Hz, 2H, NCH_2), 5.00–5.20 (m, 3H, CH_2, CH), 5.98–6.05 (m, 1H, CH), 7.30–7.55 (m, 4H, Ar–H), 7.88 (d, $J = 8.0$ Hz, 1H, NH) ppm; ^{13}C NMR (62.5 MHz): $\delta = 43.0$ (CH_2), 80.2 (CH), 91.1 (CCl_3), 118.1 (CH_2), 123.0, 124.1, 129.1, 132.1 (C–Ar), 129.3 (CH), 142.0 (C–Ar), 160.3, 169.4 (2 CO) ppm.

2-Allyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl acetate (**4**, $C_{13}H_{13}NO_3$)

Compound **1** (5.3 mmol) was dissolved in 5 cm^3 pyridine, treated with 2.5 cm^3 acetic anhydride, and then the mixture was stirred at room temperature for 24 h. The solvent was removed in vacuo and then coevaporated with toluene. The residue was purified by flash chromatography using petroleum ether/ethyl acetate as eluent. White powder; yield 0.91 g (74 %); $R_f = 0.32$ (petroleum ether/ethylacetate, 3/1); m.p.: 55 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.09$ (s, 3H, CH_3), 3.86–3.96 (m, 1H, NCH), 4.27–4.35 (m, 1H, NCH), 5.14–5.20 (m, 2H, CH_2), 5.73–5.85 (m, 1H, CH), 6.96 (s, 1H, CH), 7.50–7.85 (m, 4H, Ar–H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 20.7$ (CH_3), 42.7 (CH_2), 80.6 (CH), 117.5 (CH_2), 123.3, 123.6, 129.9, 131.5 (C–Ar), 132.3 (CH), 140.7 (C–Ar), 167.2, 170.6 (2 CO) ppm.

*General procedure for reaction of acetate **4** with C-nucleophiles*

A solution of 0.33 g acetate **4** (1.4 mmol) and C-nucleophile as acceptor (1.4 mmol) in 40 cm^3 dry dichloromethane was stirred at room temperature, and then 13 mm^3 TMSOTf (0.06 mmol) were added. After 20–90 min, the reaction mixture was neutralized with solid sodium bicarbonate, filtered, and concentrated in vacuum. The residue was purified by flash chromatography.

*2-Allyl-3-(4-methoxyphenyl)-1-isoindolinone (**6a**)*

Colorless oil; yield 0.29 g (68 %); $R_f = 0.54$ (petroleum ether/ethylacetate, 3/1); NMR data agree with those given in [20].

2-Allyl-3-(2,4-dimethoxyphenyl)-1-isoindolinone (**6b**, $C_{19}H_{19}NO_3$)

Colorless oil; yield 0.34 g (77 %); $R_f = 0.38$ (petroleum ether/ethylacetate, 3/1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 3.34$–3.50 (m, 1H, NCH), 3.72 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 4.36–4.52 (m, 1H, NCH), 4.92–5.10 (m, 3H, CH_2, CH), 5.52–5.73 (m, 1H, CH), 6.27–6.48 (m, 3H, Ar–H), 7.35–7.83 (m, 4H, Ar–H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 42.6$ (CH_2), 55.2, 55.4 (2 CH_3), 63.9 (CH), 98.7, 104.8 (C–Ar), 105.9, 116.6 (C–Ar), 117.2 (CH_2), 122.8, 123.2, 127.7, 128.1, 129.3 (C–Ar), 131.4 (CH), 146.0, 158.7, 160.7 (C–Ar), 168.5 (CO) ppm.

*2-Allyl-3-(2,4,6-trimethoxyphenyl)-1-isoindolinone (**6c**)*

White powder; yield 0.43 g (89 %); $R_f = 0.31$ (petroleum ether/ethylacetate, 3/1); m.p.: 129–130 °C (128–130 °C [20]).

(Z)-2-Allyl-3-(2-phenyl-1-ethenyl)-1-isoindolinone (**8**, $C_{19}H_{17}NO$)

Colorless oil; yield 0.26 g (65 %); $R_f = 0.22$ (petroleum ether/ethylacetate, 4/1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 3.59$–3.70 (m, 1H, NCH), 4.51–4.60 (m, 1H, NCH), 5.00–5.32 (m, 3H, CH_2, CH), 5.65–5.80 (m, 2H, CH, CH), 6.82 (d, $J = 15.6$ Hz, 1H, CHPh), 7.15–7.90 (m, 9H, Ar–H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 42.7$ (CH_2), 62.9 (CH), 117.6 (CH_2), 123.1 (CH), 125.5, 126.5 (CH), 128.3, 128.4, 128.6 (C–Ar), 131.6, 133.1 (C–Ar), 135.6 (CH), 167.7 (CO) ppm.

2-Allyl-3-(2-oxocyclohexyl)-1-isoindolinone (**10**, $C_{17}H_{19}NO_2$)

Colorless oil; yield 0.30 g (79 %); $R_f = 0.32$ (petroleum ether/ethylacetate, 4/1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.20$–2.13 (m, 6H, 3 CH_2), 2.21–2.30 (m, 1H, CH),

2.48–2.55 (m, 1H, CH), 2.70–2.80 (m, 1H, CH), 3.42–3.62 (m, 1H, NCH), 4.29–4.40 (m, 1H, NCH), 5.00–5.11 (m, 2H, CH_2), 5.41 (s, 1H, CH), 5.72–5.90 (m, 1H, CH), 7.28–7.47 (m, 2H, Ar–H), 7.70 (d, $J = 7.4$ Hz, 1H, Ar–H), 7.77 (d, $J = 7.4$ Hz, 1H, Ar–H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 24.2$, 24.3, 25.8, 41.5, 44.1 (CH_2), 53.6 (CH), 56.9, (CH), 117.8 (CH_2), 121.1, 123.4, 128.0, 131.5 (C–Ar), 132.8 (CH), 144.9 (C–Ar), 169.0, 209.2 (2 CO) ppm.

2-Allyl-3-(2-oxo-2-phenylethyl)-1-isoindolinone (**12**, $C_{19}H_{17}NO_2$)
Yellow oil; yield 0.33 g (80 %); $R_f = 0.27$ (petroleum ether/ethylacetate, 4/1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.96$–3.13 (m, 1H, NCH), 3.28–3.44 (m, 1H, NCH), 3.70–3.80 (m, 1H, CHPh), 4.24–4.32 (m, 1H, CHPh), 4.92–5.10 (m, 3H, CH_2, CH), 5.60–5.70 (m, 1H, CH), 7.21–7.83 (m, 9H, Ar–H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 41.7$, 43.0 (CH_2), 55.5 (CH), 117.4 (CH_2), 122.6, 123.2, 127.2, 128.0, 128.5, 128.8, 129.8, 131.4, 132.8 (C–Ar), 133.4 (CH), 167.7, 196.8 (2 CO) ppm.

3-(2-Allyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)-2,4-pentanedione (**14**, $C_{16}H_{17}NO_3$)
Colorless oil; yield 0.34 g (83 %); $R_f = 0.16$ (petroleum ether/ethylacetate, 4/1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.28$ (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 3.28–3.46 (m, 1H, NCH), 4.50–4.65 (m, 1H, NCH), 5.00–5.10 (m, 3H, CH_2, CH), 5.42 (s, 1H, CH), 5.69–5.80 (m, 1H, CH), 7.24 (d, $J = 8.8$ Hz, 1H, Ar–H), 7.39–7.46 (m, 2H, Ar–H), 7.79 (d, $J = 6.8$ Hz, 1H, Ar–H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 22.7$, 24.0 (2 CH_3), 42.2 (CH_2), 57.8 (CH), 104.9 (CH), 117.8 (CH_2), 122.0, 123.7, 128.5, 131.9, 132.1 (C–Ar), 133.2 (CH), 144.9 (C–Ar), 167.6, 189.6, 197.4 (3 CO) ppm.

Methyl 2-(2-allyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)-2-methylpropanoate (**16**, $C_{16}H_{19}NO_3$)
Colorless oil; yield 0.32 g (83 %); $R_f = 0.28$ (petroleum ether/ethylacetate, 4/1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.90$ (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 3.50 (d, $J = 7.0$ Hz, 1H, NCH), 3.73 (s, 3H, OCH_3), 4.58–4.70 (m, 1H, NCH), 5.03–5.21 (m, 3H, CH_2, CH), 5.60–5.70 (m, 1H, CH), 7.28–7.81 (m, 4H, Ar–H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 19.4$, 22.8 (2 CH_3), 44.0 (*C*-CH_3), 45.9 (CH_2), 52.1 (OCH_3), 64.1 (NCH), 117.1 (CH_2), 123.6, 128.3, 130.9 (C–Ar), 132.7 (CH), 142.8 (C–Ar), 169.2, 176.6 (2 CO) ppm.

2-Allyl-3-benzyl-1-isoindolinone (**18**, $C_{18}H_{17}NO$)
Yellow oil; yield 0.29 g (76 %); $R_f = 0.45$ (petroleum ether/ethylacetate, 4/1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.03$ (s, 2H, CH_2Ph), 3.20–3.35 (m, 1H, NCH), 4.52–4.65 (m, 1H, NCH), 4.95–5.14 (m, 2H, CH_2), 5.40 (s, 1H, CH), 5.60–5.71 (m, 1H, CH), 6.92 (s, 5H, Ar–H), 7.15–7.88 (m, 4H, Ar–H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 26.8$ (CH_2), 42.5 (CH_2), 63.6 (CH), 117.6 (CH_2), 123.1, 123.3, 127.5, 128.0, 128.4, 131.6 (C–Ar), 132.9 (CH), 141.1, 146.5 (C–Ar), 168.0 (CO) ppm.

2,3-Diallyl-1-isoindolinone (**20**, $C_{14}H_{15}NO$)
Colorless oil; yield 0.27 g (88 %); $R_f = 0.33$ (petroleum ether/ethylacetate, 4/1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 2.38$–2.55 (m, 2H, CH_2), 3.50–3.60 (m, 1H, CH), 4.41–4.50 (m, 2H, NCH, CH), 4.81–4.90 (m, 2H, CH_2), 5.09–5.15 (m, 3H, CH_2, CH), 5.66–5.70 (m, 1H, CH), 7.24–7.70 (m, 4H, Ar–H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 34.8$, 42.3 (2 CH_2), 57.9 (CH), 118.7, 117.4 (2 CH_2), 127.7 (CH), 122.0, 123.0 (C–Ar), 132.8 (CH), 130.9, 131.0, 131.2 (C–Ar), 144.4 (C–Ar), 167.6 (CO) ppm.

2-Allyl-3-(propa-1,2-dienyl)isoindolin-1-one (**22**, $C_{14}H_{13}NO$)
Colorless oil; yield 0.21 g (81 %); $R_f = 0.36$ (petroleum ether/ethylacetate, 4/1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 3.71$–3.80 (m, 1H, NCH), 4.56–4.65 (m, 1H, NCH), 4.79–4.88 (m, 2H, CH_2), 4.97 (d, $J = 6.1$ Hz, 1H, CH), 5.12–5.29 (m, 3H, CH_2), 5.72–5.87 (m, 1H, CH), 7.41–7.79 (m, 3H, Ar–H), 7.80–7.85 (m, 1H, Ar–H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 42.7$ (CH_2), 57.6 (CH), 77.4 (CH_2), 88.5 (CH), 117.4 (CH_2), 123.4, 131.3, 131.5, 131.7 (C–Ar), 132.8 (CH), 133.1, 144.7 (C–Ar), 167.4 (CO), 210.0 (=C=) ppm.

2-Allyl-3-hydroxyhexahydro-1-isoindolone (**27**, $C_{11}H_{15}NO_2$)
Sodium borohydride (0.88 g, 23 mmol) was added in one portion to a stirred solution of 2-allylhexahydro-1,3-isoindoledione (**26**, 4.5 mmol) [26] in 120 cm^3 methanol, cooled to −5 °C in an ice-salt bath, and the resulting solution was stirred for 30 min. The reaction mixture was partitioned between 200 cm^3 of CH_2Cl_2 and 100 cm^3 of saturated aqueous sodium bicarbonate. The layers were separated and the aqueous phase was extracted with three 150-cm^3 portions of CH_2Cl_2. The combined organic phase was dried with $MgSO_4$ and concentrated in vacuo to give **27** as a white solid. Yield 0.59 g (65 %); $R_f = 0.34$ (petroleum ether/ethylacetate, 3/1); m.p.: 79 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.20$–1.41 (m, 4H, 2 CH_2), 1.55–1.70 (m, 4H, 2 CH_2), 2.43–2.57 (m, 2H, 2 CH), 3.73 (d, $J = 7.0$ Hz, 1H, NCH), 3.77 (d, $J = 7.0$ Hz, 1H, CHOH), 4.13–4.22 (m, 1H, NCH), 5.06–5.32 (m, 3H, CH_2, OH), 5.64–5.85 (m, 1H, CH) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 22.2$, 23.1, 23.2, 24.3 (4 CH_2), 37.0, 41.0 (2CH), 41.9 (CH_2), 83.9 (CH), 117.4 (CH_2), 132.9 (CH), 176.1 (CO) ppm.

2-Allyl-3-oxohexahydroisoindol-1-yl acetate (**28**, $C_{13}H_{19}NO_3$)
Preparation was performed as described for **4**, furnishing a colorless oil which was chromatographed on silica gel

(petroleum ether/ethyl acetate) as eluent to give **28**. Colorless oil; yield 0.79 g (63 %); $R_f = 0.42$ (petroleum ether/ethylacetate, 4/1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.02$–1.85 (m, 8H, 4 CH_2), 1.94 (s, 3H, CH_3), 2.00–2.15 (m, 1H, CH), 2.67–2.58 (m, 1H, CH), 3.53 (dd, $J = 7.1$ Hz, 15.2 Hz, 1H, NCH), 4.13 (dd, $J = 5.3$ Hz, 15.2 Hz, 1H, NCH), 5.02–5.20 (m, 2H, CH_2), 5.57 (s, 1H, CH), 5.63 (m, 1H, CH) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 20.3$, 21.8, 22.0 (3 CH_2), 22.6 (CH_3), 24.9 (CH_2), 33.9, 39.6 (2 CH), 42.5 (CH_2), 84.8 (*CH*OAc), 116.7 (CH_2), 131.8 (CH), 169.7, 176.8 (2 CO) ppm.

2,3-Diallylhexahydro-1-isoindolone (**29**, $C_{14}H_{21}NO$)
Preparation was performed as described for **6**–**22**, furnishing a colorless oil which was chromatographed on silica gel (petroleum ether/ethyl acetate) as eluent to give **29**. Colorless oil; yield 0.22 g (71 %); $R_f = 0.45$ (petroleum ether/ethylacetate, 4/1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.91$–1.60 (m, 8H, 4 CH_2), 1.85–2.05 (m, 2H, CH), 2.10–2.29 (m, 1H, CH), 2.38–2.50 (m, 1H, CH), 2.87–3.00 (m, 1H, CH), 3.33 (d, $J = 7.8$ Hz, 1H, NCH), 4.24 (d, $J = 4.4$ Hz, 1H, NCH), 4.88–5.17 (m, 4H, 2 CH_2), 5.47–5.70 (m, 2H, 2 CH) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 22.8$, 23.1, 23.6, 28.5, 34.6, 36.2 (6 CH_2), 39.3 (CH), 43.4 (CH), 61.2 (CH), 117.8, 118.0 (2 CH_2), 132.8, 133.8 (2CH), 174.9 (CO) ppm.

General procedure for olefin metathesis

A solution of 0.003 g [bis(tricyclohexylphosphane)-benzylidene)]-ruthenium(IV) dichloride (Grubbs' catalyst, 0.004 mmol) in 5 cm^3 CH_2Cl_2 was added to a solution of diallyl derivatives **20** or **29** (1 mmol) in 10 cm^3 CH_2Cl_2 under an argon atmosphere. The mixture was refluxed for 12 h. The solvent was removed under reduced pressure and the oily residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 5:1) to give **23** or **30**, respectively.

1,4,6,10b-Tetrahydropyrido[2,1-a]isoindol-6-one
(**23**, $C_{12}H_{11}NO$)
Colorless soild; yield 0.12 g (64 %); $R_f = 0.43$ (petroleum ether/ethylacetate, 3/1); m.p.: 85–88 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.82$–2.00 (m, 1H, CH_b), 2.68–2.73 (m, 1H, CH_b), 3.78–3.85 (m, 1H, CH_f), 4.37 (dd, $J = 5.0$ Hz, 10.9 Hz, 1H, CH_f), 4.58 (m, 1H, CH_d), 5.76–5.90 (m, 2H, CH_c, CH_g), 7.35–7.57 (m, 3H, Ar–H), 7.74–7.85 (m, 1H, Ar–H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 29.8$ (CH_b), 39.4 (CH_F), 54.3 (CH_d), 121.6, 122.6 (C–Ar), 123.3 (CH_c), 123.5 (CH_g), 127.9, 131.0, 132.1, 145.7 (C–Ar), 166.6 (CO) ppm; MS (MALDI, positive mode, matrix: DHB): $m/z = 186.1$ ($[M + H]^+$).

1,4,6,6a,7,8,9,10,10a,10b-Decahydropyrido[2,1-a]isoindol-6-one (**30**, $C_{12}H_{17}NO$)
Colorless oil; yield 0.14 g (72 %); $R_f = 0.51$ (petroleum ether/ethylacetate, 3/1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.13$–1.45 (m, 4H, 2 cyclo-CH_2), 1.50–1.70 (m, 4H, 2 cyclo-CH_2), 1.75–1.90 (m, 2H, cyclo-CH), 2.01–2.14 (m, 1H, CH_b), 2.20–2.41 (m, 1H, H_b), 3.05–3.21 (m, 1H, H_a), 3.45 (dm, $J = 18.6$ Hz, H_e), 4.20 (dm, 1H, $J = 18.6$ Hz, H_e), 5.50–5.77 (m, 2H, H_d, H_c) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 22.7$, 22.9, 23.7, 26.3, 28.6 (C-cyclo), 38.1 (C_b), 40.1 (C_e), 40.2 (C-cyclo), 55.7 (C_a), 123.6 (C_c), 123.9 (C_d), 175.3 (CO) ppm; EI-MS: $m/z = 192.0$.

1,2,3,4,6,10b-Hexahydropyrido[2,1-a]isoindol-6-one
(**24**, $C_{12}H_{13}NO$)
Formic acid (four drops) was added to a solution of **23** (1.3 mmol) in 10 cm^3 methanol and the mixture was hydrogenated under hydrogen (0.14 g of 10 % Pd on carbon). TLC monitoring indicated the reaction was complete after 14 h. Filtration through Celite and column chromatography (CH_2Cl_2/MeOH, 20:1) gave **24** as colorless oil. Yield 0.18 g (77 %); $R_f = 0.49$ (petroleum ether/ethylacetate, 3/1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.98$ (dd, 1H, $J = 3.5$ Hz, 12.8 Hz, CH_d), 1.13–1.69 (m, 3H, CH_d, 2 CH_c), 1.71–1.87 (m, 1H, CH_b), 2.22 (dm, 1H, $J = 2.8$ Hz, 12.9 Hz, CH_b), 2.83 (dd, 1H, $J = 3.6$ Hz, 12.9 Hz, H_e), 4.14 (dd, 1H, $J = 3.8$ Hz, 11.8 Hz, H_a), 4.35 (dm, 1H, $J = 4.9$ Hz, 13.2 Hz, H_e), 7.31–7.55 (m, 3H, Ar–H), 7.68–7.78 (d, $J = 7.3$ Hz, 1H, Ar–H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 23.3$ (C_d), 25.0 (C_c), 31.5 (C_b), 39.3 (C_e), 58.6 (C_a), 121.4, 123.2, 127.7, 130.8, 132.1, 145.5 (C–Ar), 165.8 (CO) ppm; MS (MALDI, positive mode, matrix: DHB): $m/z = 188.2$ ($[M + H]^+$), 210.2 ($[M + Na]^+$), 226.2 ($[M + K]^+$).

1,2,3,4,6,10b-Hexahydropyrido[2,1-a]isoindole
(**25**, $C_{12}H_{15}N$)
A solution of **24** (1.13 mmol) dissolved in 10 cm^3 THF was added to a suspension of 0.12 g $LiAlH_4$ (2.3 mmol) in 5 cm^3 THF and refluxed for 4 h. Excess hydride was destroyed at 0 °C with 0.5 cm^3 10 % aq. NH_4Cl; the solid was filtered and washed with 30 cm^3 ethyl acetate. The organic phase was dried ($MgSO_4$) and evaporated, and the crude material was purified by column chromatography on silica gel to give **25** as a colorless oil. Yield 0.13 g (66 %); $R_f = 0.52$ (petroleum ether/ethylacetate, 3/1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.96$–1.75 (m, 4H, 4 CH_{2c}, CH_{2c}), 1.85–2.00 (m, 1H, CH_b), 2.30 (dm, 1H, $J = 2.9$ Hz, 10.1 Hz, CH_b), 2.90 (dd, 1H, $J = 3.6$ Hz, 12.9 Hz, H_e), 3.38–3.50 (m, 1H, H_e), 3.61–3.70 (m, 1H, CH_a), 4.20 (dd, 1H, $J = 3.6$ Hz, 11.9 Hz, H_g), 4.44 (dd, 1H, $J = 5.0$ Hz, 13.9 Hz, H_g), 7.12–7.48 (m, 3H, Ar–H), 7.77–7.79 (d, $J = 7.2$ Hz, 1H, Ar–H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 23.5$ (C_d), 23.95 (C_e), 25.2 (C_c), 31.6 (C_b),

39.3 (C_a), 58.8 (C_g), 121.5, 123.5, 128.0, 131.0, 132.3, 145.6 (C–Ar) ppm; MS (MALDI, positive mode, matrix: DHB): $m/z = 174.4$ ($[M + H]^+$).

References

1. Scherlach K, Schuemann J, Dahse HM, Hertweck C (2010) J Antibiot 63:375
2. Chen J, Huang PQ, Queneau Y (2009) J Org Chem 74:7457
3. Lamblin M, Couture A, Deniau E, Grandclaudon P (2007) Org Biomol Chem 5:1466
4. Rys V, Couture A, Deniau E, Grandclaudon P (2003) Tetrahedron 59:6615
5. Ishihara Y, Kiyota Y, Goto G (1990) Chem Pharm Bull 38:3024
6. Sorbera LA, Leeson PA, Silvestre J, Castaner P (2001) J Drugs Fut 26:651
7. Li S, Wang X, Guo H, Chen L (1985) Yiyano Gongye 16:543. Chem Abstr. 105:3788.
8. Ferland JM, Demerson CA, Humber LG (1985) Can J Chem 63:361
9. Norman MH, Minick DJ, Rigdon GC (1996) J Med Chem 39:149
10. Achinami K, Ashizawa N, Kobayasui F (1991) Japanese patent 03:133,955. Chem Abstr 115:255977
11. Taylor EC, Zhou P, Jennings LD, Mao Z, Hu B, Jun JG (1997) Tetrahedron Lett 38:521
12. Shen L, Hsung RP (2005) Org Lett 7:775
13. Comins DL, Schiling S, Zhang Y (2005) Org Lett 7:95
14. Boger DL, Lee JK, Goldberg J, Jin Q (2000) J Org Chem 65:1467
15. Fuwa H, Sasaki M (2007) Org Biomol Chem 5:1849
16. Ali IAI, El-Ashry ESH, Schmidt RR (2003) Eur J Org Chem 4121
17. Ali IAI, Abdel Rahman AAH, El-Ashry ESH, Schmidt RR (2003) Synthesis 1065
18. Ali IAI, El-Ashry ESH, Schmidt RR (2004) Tetrahedron 60:4773
19. Ali IAI, Fathalla W (2013) Curr Org Chem 17:1903
20. Maity AK, Roy S (2012) J Org Chem 77:2935
21. Michael JP (2007) Nat Prod Rep 24:191
22. Ben-Othman R, Othman M, Ciamala K, Knorr M, Strohmann C, Decroix B (2009) Tetrahedron 65:4846
23. Ben-Othman R, Othman M, Coste S, Decroix B (2008) Tetrahedron 64:559
24. Miller B, Mao S, Kara M, Rosenker G, Pierce GJ, Wipf P (2012) Beilstein J Org Chem 8:1091
25. Abe Y, Ohsawa A, Igeta H (1982) Heterocycles 19:49
26. Baldwin BW, Hirose T, Wang Z-H (1996) J Chem Soc Chem Commun 23:2669