Tetrahedron 75 (2019) 1315–1321

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Diastereoselective multicomponent Amine-Aldehyde-Dienophile (AAD) process for the synthesis of polysubstituted cyclohex-2-enylamines

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ARTICLE INFO

Article history:
Received 30 October 2018
Received in revised form
20 January 2019
Accepted 25 January 2019
Available online 30 January 2019

Keywords:
Multicomponent
AAD
Cyclohex-2-enylamine
Diels-Alder
Primary amines

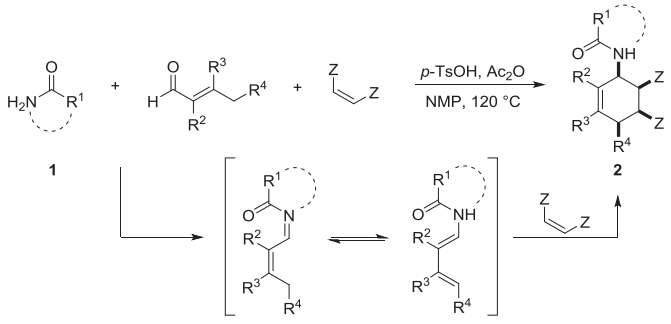
ABSTRACT

The multicomponent Amine-Aldehyde-Dienophile reaction is optimized employing benzyl or 4-methoxybenzylamine. The interest of the transformation consist in the synthesis of polysubstituted cyclohex-2-enylamines. The study of the scope of this AAD process is carried out, as well as the diastereoselective version, employing commercially available chiral benzylic amines and a maleimide with the chiral information at the *N*-substituent. VCD spectroscopy is a very useful tool for the determination of the absolute configuration of the isolated enantiomerically enriched compounds.

1. Introduction

Amide-Aldehyde-Dienophile (AAD) reaction is a well-known multicomponent reaction introduced by Beller and co-workers in 2001 (Scheme 1) [1]. Since then, Beller's group have been expanding the scope of this multicomponent AAD reaction using different dienophiles, several substituted α,β-unsaturated aldehydes and different lineal or cyclic amides **1**, obtaining in all cases only the *endo*-approach of the Diels-Alder reaction in the racemic version (Scheme 1) [2]. The same group performed the chiral version of the same reaction introducing a stereocenter in the amide **1**, using for that purpose substituted lactams. This reagent, in combination with different aldehydes and dienophiles yield enantioenriched *endo*-products **2** as major diastereoisomer in the AAD reaction [3].

The *N*-cyclohex-2-en-1-amide scaffold **2** is a unit present in the somatostatin analogues and the group of Kessler applied conveniently this reaction to achieve the desired product [4]. Beller's group also applied this reaction to synthetize corollosporine analogues to test their antimicrobial activity [5]. The employment of an amine instead of the amide in this reaction is less known and less favoured, being necessary the use of quite reactive reagents to carry out the reaction. Few works have been reported using a multicomponent Amine-Aldehyde-Dienophile (AAD) reaction to obtain a



Scheme 1. Multicomponent reaction of the general Amide-Aldehyde-Dienophile (AAD).

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https://doi.org/10.1016/j.tet.2019.01.063
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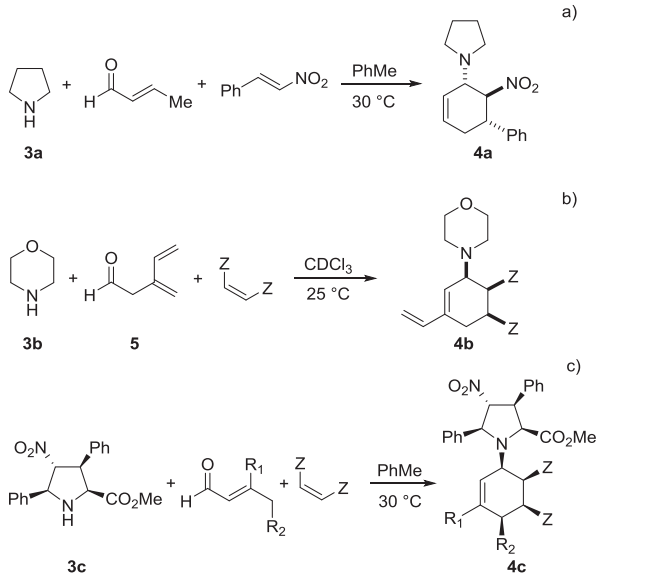


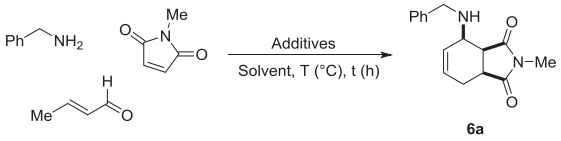
Scheme 2. a) Multicomponent AAD sequence employing the secondary amine **3a**. b) Multicomponent AAD process employing the aldehyde **5**. c) Full diasteresoselective AAD reaction employing enantiomerically enriched nitroprolinate **3c**.

cyclohex-2-en-1-amine skeleton **4**. Thus, in 2014, Weber and co-workers [6] performed the AAD reaction with pyrrolidine **3a**, different substituted α,β-unsaturated aldehydes and only nitrostyrenes as dienophiles (Scheme 2a). In contrast, the group of Sherburn [7] introduce different dienophiles, morpholine, but just working with one aldehyde **5**, which is a very reactive aldehyde obtaining high to excellent yields (Scheme 2b). In this work, one example with benzylamine was reported. More recently, our group introduced an AAD reaction with chiral nitroprolinate **3c** obtaining the enantiopure *endo*-diastereoisomers **4c** as exclusive product in the crude mixture with excellent yields after purification (Scheme 2c) [8]. In this multicomponent reaction, it was possible to induce the absolute configuration of three new stereogenic centers in a single reaction step. In fact, this mechanism is the basic interaction of similar organocatalytic Diels-Alder reactions [9].

According to these precedents, pyrrolidine derivatives and morpholines cannot be transformed in amines whilst sulfonamides and amides required so hard hydrolysis conditions that many functional groups of the molecule (for example, succinimides) can be hydrolysed too [10]. So, the evaluation of primary amines, such as benzylamine and *p*-methoxybenzylamine, which can be easily transformed in the corresponding primary amines, using alternative methodologies to the classical hydrolysis, is the main goal of this work. Also, the publication of a family of antibacterial agents 3-aminocyclohexenes [11] encourage us to study the scope this multicomponent AmineAD.

2. Results and discussion

The model reaction employed for the optimization of this multicomponent AAD involved benzylamine, crotonaldehyde and *N*-methylmaleimide (NMM) as dienophile (Scheme 3). Toluene was selected as solvent due to the good results obtained in our group [8]. Only two parameters, the temperature and the nature of some additives were evaluated (Table 1) for the generation of compound **6a**. When the reaction was carried out without additives at room temperature for 16 h only Michael addition products were observed (Table 1, entry 1). However, the increment of the temperature favoured the AAD reaction (Table 1, entries 2–3) obtaining complex



Scheme 3. Multicomponent AAD synthesis of product **6a**.

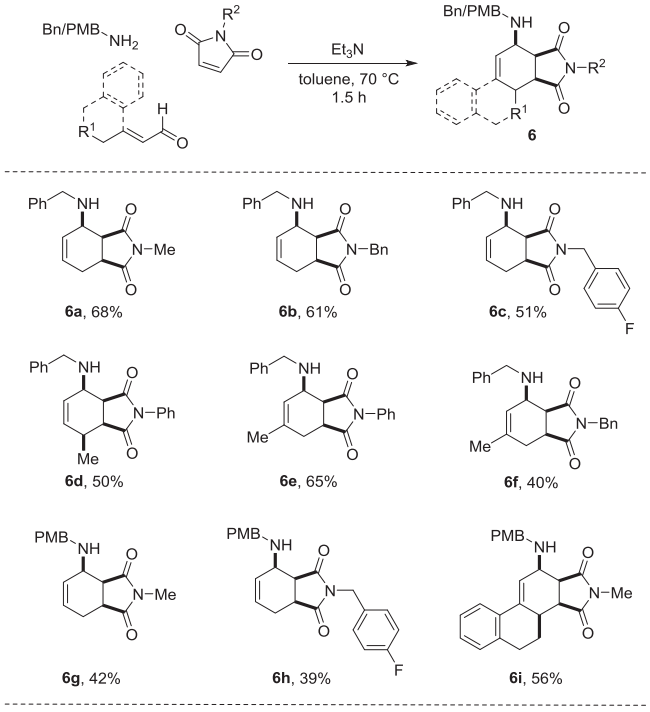
Table 1
Optimization of the reaction conditions to synthetize cyclohex-2-en-1-amine **6a** *via* AAD reaction.

Entry	Additives	Solvent	T (°C)	t (h)	Yield (%)[a]
1	–	$PhCH_3$	25	16	0
2	–	$PhCH_3$	70	16	48
3	–	$PhCH_3$	110	16	72
4	*p*-TsOH (30%)	$PhCH_3$	70	16	0
5	BzOH (30%)	$PhCH_3$	70	16	65
6	$ClSiMe_3$ (30%)	$PhCH_3$	70	16	63
7	$ClSiMe_3$ (30%), Et_3N (30%)	$PhCH_3$	70	16	69
8	$ClSiMe_3$ (100%), Et_3N (100%)	$PhCH_3$	70	16	76
9[b]	$ClSiMe_3$ (100%), Et_3N (100%)	$PhCH_3$	70	16	87
10[b]	$ClSiMe_3$ (100%), Et_3N (100%)	$PhCH_3$	110	16	88
11[b]	$ClSiMe_3$ (100%), Et_3N (100%)	$PhCH_3$	50	16	31
12[b]	$ClSiMe_3$ (100%), Et_3N (100%)	$CHCl_3$	70	16	25
13	Et_3N (100%)	$CHCl_3$	70	16	>95
14	–	$CHCl_3$	70	16	0
15	Et_3N (100%)	$CHCl_3$	70	1.5	>95
16	Et_3N (100%)	PhMe	70	1.5	89

[a] Isolated yields after flash chromatography.
[b] *Sequential reaction*: benzylamine, trimethylsilyl chloride and triethylamine reacted during 30 min at rt, then crotonaldehyde and NMM was added and stirring continued 16 h at the selected temperature.

crude products (^{1}H NMR). Next, the addition of *p*-toluenesulfonic acid as additive was tested obtaining only the Michael-type compounds at the end of the reaction (Table 1, entry 4). On the other hand, benzoic acid at 70 °C gave better results than when the reaction was carry out without additive at the same temperature (Table 1, entry 5). With the idea of working with a masked secondary amine derived from benzylamine, we used trimethylsilyl chloride and trimethylamine in several proportions for the *in situ* generation of trimethylsilylbenzylamine (Table 1, entries 6–12). The use of TMSCl (30% mol) gave a high conversion and a very complex reaction crude for **6a** (Table 1, entry 6). The combination TMSCl/Et_3N (30% mol, each) afforded cleaner crude mixtures (Table 1, entry 7). When 1 equiv of both additives were tested the yield increased to 76% (Table 1, entry 8). Surprisingly, using a sequential mode of the reaction, mixing benzylamine, trimethylsilyl chloride and triethylamine in toluene, and after 30 min adding crotonaldehyde and *N*-methylmaleimide, the best yield was obtained (Table 1, entry 9). No significative differences were observed when the temperature was raised, in contrast, the reaction conversion was lower when the temperature decreased to 50 °C (Table 1, entries 10 and 11, respectively). Taking into consideration the work of Sherburn [7], chloroform was select as solvent obtaining lower chemical yields but with cleaner crude reaction mixture (Table 1, entry 12). Complete conversion was detected when triethylamine was added without trimethylsilyl chloride (Table 1, entry 13), demonstrating that the presence of the base is critical for the reaction to take place (Table 1, entry 14). At this point, the time of the reaction was controlled observing that the reaction was completed in only 1.5 h in chloroform and also in toluene (Table 1, entries 15 and 16).

With this optimal conditions in hand, the amine, the aldehyde and the dipolarophile were mixed in chloroform at 70 °C in the presence of triethylamine to assess the scope of the AAD reaction (Scheme 4). Crotonaldehyde and benzylamine were allowed to react with



Scheme 4. Synthesis of cyclohex-2-en-1-amines **6** *via* AAD reaction.

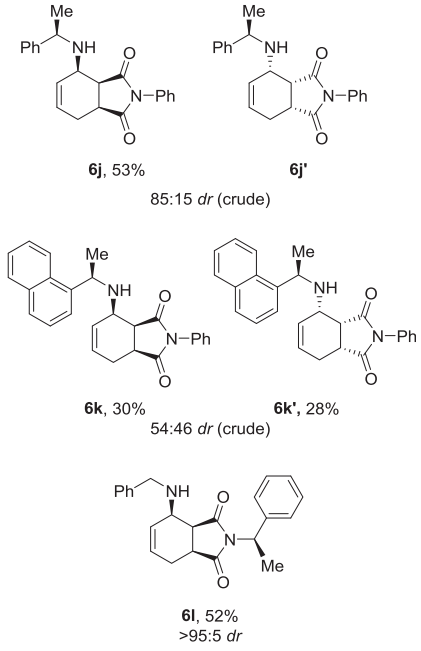


Fig. 1. Synthesis of enantiomerically enriched cyclohex-2-en-1-amines **6j-l** *via* AAD reaction.

maleimides (NMM and NBM) obtaining only one stereoisomer (**6a** and **6b**, respectively) in the crude mixture in good isolated yields after purification (68% and 61%, respectively, Scheme 4). Fluorinated maleimide [12] was also employed in this reaction obtaining the corresponding products **6c** in 51% yield (Scheme 4). Other aldehyde such as *E*-2-pentenal was assayed with *N*-phenylmaleimide (NPM) yielding product **6d** in 50%. 3-Methylcrotonaldehyde was also tried in this reaction with NPM and NBM obtaining, in both cases, almost only one diastereoisomer of **6e** and **6f**, in moderate isolated yields after purification (65% and 40%, respectively, Scheme 4). Apart from benzylamine, aliphatic primary amines such as butylamine or allylamine failed in this reaction, however other benzylamine derivative as *p*-methoxybenzylamine was well tolerated. For example, $PMBNH_2$ was allowed to react with crotonaldehyde and two different maleimides obtaining **6g** and **6h** with moderate to good isolated yields (42% and 39%, respectively). Interestingly, the pseudo-steroidal tetracyclic product **6i** was isolated, from the corresponding aldehyde [13], in 56% yield. The relative configuration of all molecules **6** was confirmed by nOe experiments and by comparison of chemical shifts (^{1}H NMR). Compounds **6b**, **6c**, **6d**, **6e**, **6f** and **6h** were isolated with very small amounts of other diastereoisomer, which was very difficult to separate by column chromatography (see SI). The AAD reaction with fumarates, maleic anhydride, acrylates, vinylic sulfones, chalcone derivatives, nitroalkenes, etc., completely failed. In some examples, complex crude reaction mixtures were obtained isolating the expected product in low yields.

The diastereoselective version of this AAD transformation was also examined (Scheme 4 and Fig. 1). Using the lowest temperature (70 °C) and shorter reaction times (1.5 h), chiral benzylamines were first tried in order to obtain enantiopure diastereoisomers. (*R*)-α-Methylbenzylamine was reacted with crotonaldehyde and NPM giving a 85:15 mixture of two diastereoisomers in the crude of the reaction (^{1}H NMR) isolating only the major product **6j** after purification in good yield (53%). (*R*)-1-(1-Naphthyl)ethylamine was also attempted obtaining in this example an almost equimolar diastereomeric ratio for products **6k** and **6k**′ was identified. In both cases, nOe results indicated the general *all-cis* arrangement observed in this survey. When the chiral information was anchored to the maleimide, the diastereoselectivity was higher than in the two previous examples run with chrial benzylic amines. Molecule **6l** was generated in 52% yield as a 95:5 diastereomeric ratio when (*R*)-*N*-(1-phenylethyl)maleimide was employed as enantiomerically enriched dienophile (Fig. 1).

The proposed absolute configuration of compound **6j**, drawn in Fig. 1, was confirmed by vibrational circular dichroism (VCD) analysis (Fig. 2). Fortunately, both diastereoisomers **6j** and **6j**′ exhibited opposite theoretical VCD patterns, which was more relevant in the carbonyl absorption area. The experimental VCD (dots) and the resulting fitting line matched perfectly (Fig. 2) with the theoretical data provided for diastereoisomer **6j**. Every maximum of the experimental absorption plot (1720 and

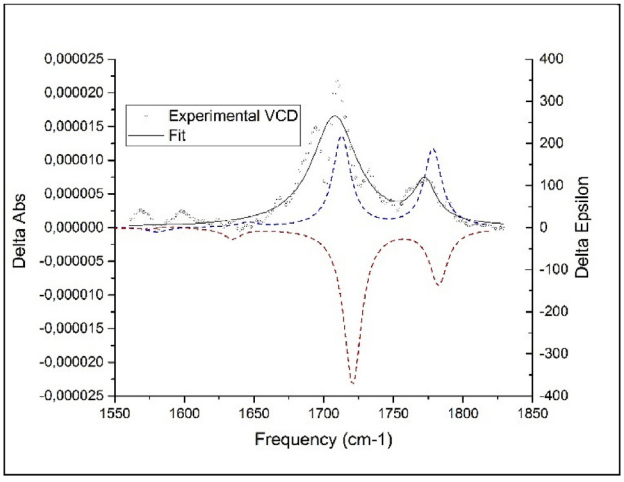


Fig. 2. VCD analysis of product **6j**. Blue dashed line corresponds to theoretical VCD calculated with a B3LYP/6-311G+(2d, 2p) level for configuration **6j**. Red dashed line corresponds to theoretical VCD calculated with a B3LYP/6-311G+(2d, 2p) level for the minor diastereoisomer **6j'**. Black curve corresponds to experimental VCD.

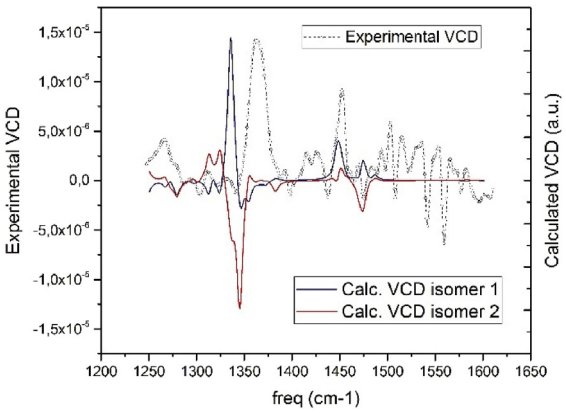


Fig. 3. VCD analysis of product **6l**. Blue line corresponds to theoretical VCD calculated with a B3LYP/6-311G+(2d, 2p) level for configuration **6l**. Red dashed line corresponds to theoretical VCD calculated with a B3LYP/6-311G+(2d, 2p) level for the minor diastereoisomer **6l'**. Black curve corresponds to experimental VCD.

1785 cm^{-1}) is composed by the sum of two closed bands, possibly due to the formation of intramolecular hydrogen bonds between the NH and the closer carbonyl group [14]. This interaction was also supported by the *all-cis* relative configuration of this fused ring.

The assignment of the absolute configuration for compound **6l** was more complicated. The initial X-ray diffraction analysis of a monocrystal revealed that the two enantiomers of **6l** were symmetrically arranged in the unit cell together with two molecules of hydrogen chloride [15]. This crystallization occurred in the solution of the sample prepared for the analysis of its VCD experiment (Fig. 3). Despite of a displacement of the experimental carbonyl band with respect to the calculated ones, the small absorbance at around 1450 cm^{-1} (C-N absorbance) also confirmed the drawn stereochemistry of **6l** in Fig. 1. It is important to remark that calculated conformations for both cycloadducts **6j** and **6l** revealed the presence of strong hydrogen bonds (2.53–2.56 Å in solid state of both enantiomers) between a carbonyl group of the succinimide moiety and the hydrogen atom of the amino group. These interactions can modify the normal absorbance wavelength of the carbonyls in solution and even avoid the detection of the NH band in ^{1}H NMR spectroscopy (see SI).

3. Conclusions

The preparation of polysubstituted *N*-benzyl and *N*-PMB-cyclohex-2-eneamines has been optimized. Many aldehydes and maleimides can be combined with benzylamine or 4-methoxybenzylamine in a diastereoselective multicomponent process namely Amine-Aldehyde-Dienophile (AAD). Chemical yields are moderate to good and allow to generate *all-cis* relative configuration in the resulting final products. This sequence offers the possibility to remove the protecting group to achieve the free amino group which could not be accomplished yet. The introduction of a chiral information at the benzylic group of the benzylic amine or in the *N*-substituent of the maleimide gave also enantiomerically enriched compounds after separation by column chromatography. The absolute configuration of a representative example was determined by VCD spectroscopy.

4. Experimental section

4.1. General

All commercially available reagents and solvents were used without further purification, only aldehydes were also distilled prior to use. Only the aldehyde precursor of compound **6i** was prepared according to the literature [13]. Analytical TLC was performed on Schleicher & Schuell F1400/LS 254 silica gel plates, and the spots were visualized under UV light ($\lambda = 254$ nm). Flash chromatography was carried out on handpacked columns of Merck silica gel 60 (0.040–0.063 mm). Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. The structurally most important peaks of the IR spectra (recorded using a Nicolet 510 P-FT) are listed and wave numbers are given in cm^{-1}. NMR spectra were obtained using a Bruker AC-300 or AC-400 and were recorded at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR, using $CDCl_3$ as solvent and TMS as internal standard (0.00 ppm). The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved and br s = broad signal. All coupling constants (*J*) are given in Hz and chemical shifts in ppm. ^{13}C NMR spectra were referenced to $CDCl_3$ at 77.16 ppm. DEPT-135 experiments were performed to assign CH, CH_2 and CH_3. ^{19}F NMR were recorded at 282 MHz using CDCl3 as solvent. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV using a Shimadzu QP-5000 by injection or DIP; fragment ions in *m*/*z* are given with relative intensities (%) in parentheses. High-resolution mass spectra (HRMS) were measured on an instrument using a quadrupole time-of-flight mass spectrometer (QTOF) and also through the electron impact mode (EI) at 70 eV using a Finnigan VG Platform or a Finnigan MAT 95S. VCD analysis was recorded in a Jasco FVS-6000.

4.2. General procedure for the synthesis of products **6**

To a stirred solution of benzylamine derivative (0.25 mmol) and Et_3N (1 equiv., 0.25 mmol) in 1 mL of toluene was added the aldehyde (1 equiv., 0.25 mmol), the dienophile (1 equiv., 0.25 mmol) and 0.5 mL more of chloroform. The solution was stirred at 70 °C during 1.5 h, and after the solvent was removed under vacuum. The crude of the reaction was purified with flash chromatography to give the desired compound.

4.2.1. (3aS*,4R*,7aS*)-4-(Benzylamino)-2-methyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6a**)

Brown sticky oil (45.9 mg, 68% yield). IR (neat) ν_{max}: 1695, 1438, 1385, 1283, 1266, 1119, 993, 732, 700 cm^{-1}. ^{1}H NMR δ: 2.07–2.17 (m, 1H, =CHC*H*$_2$), 2.68 (ddd, *J* = 15.5, 6.7, 2.0 Hz, 1H, =CHC*H*$_2$), 2.94 (s, 3H, NC*H*$_3$), 3.11 (td, *J* = 8.2, 2.0 Hz, 1H, CH$_2$C*H*C=O), 3.12 (br s, 1H, N*H*), 3.38–3.51 (m, 2H, NCHC*H*C=O and NC*H*CH=), 3.93 (d, *J* = 13.0 Hz, 1H, NC*H*$_2$Ph), 4.07 (d, *J* = 13.0 Hz, 1H, NC*H*$_2$Ph), 5.81–5.90 (m, 1H, =C*H*CH$_2$), 5.92–5.99 (m, 1H, NCHC*H*=), 7.26–7.45 (m, 5H, Ar*H*). ^{13}C NMR δ: 24.1 (=CHCH$_2$), 24.9 (NCH$_3$), 39.3, 42.0 (2xCHC=O), 51.4 (NCH$_2$Ph), 53.5 (NCHCH=), 126.0, 127.5, 128.7, 132.9, 138.7 (Ar*C*, C=*C*), 178.4, 179.9 (2x*C*=O). MS (EI) *m*/*z*: 270 (M^+, <1%), 159 (21), 144 (35), 106 (100), 91 (71), 79 (11). HRMS calculated for $C_{16}H_{18}N_2O_2$: 270.1368; found: 270.1360.

4.2.2. (3aS*,4R*,7aS*)-2-Benzyl-4-(benzylamino)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6b**)

Yellow prisms (52.8 mg, 61% yield), mp 75–77 °C. IR (neat) ν_{max}: 1684, 1475, 1428, 1399, 1344, 1173, 1145, 1071, 915, 741, 699 cm^{-1}. ^{1}H NMR δ: 2.05–2.18 (m, 1H, =CHC*H*$_2$), 2.66 (ddd, *J* = 15.6, 6.7, 2.1 Hz, 1H, =CHC*H*$_2$), 3.02 (br s, 1H, N*H*), 3.09 (td, *J* = 8.3, 2.1 Hz, 1H, CH$_2$C*H*C=O), 3.40 (dd, *J* = 8.8, 6.0 Hz, 1H, NCHC*H*C=O), 3.45–3.48 (m, 1H, NC*H*CH=), 3.89 (d, *J* = 13.0 Hz, 1H, CHNC*H*$_2$Ph), 4.03 (d, *J* = 13.0 Hz, 1H, CHNC*H*$_2$Ph), 4.60 (s, 2H, O=CNC*H*$_2$Ph), 5.78–5.85 (m, 1H, =C*H*CH$_2$), 5.93 (dt, *J* = 9.5, 3.1 Hz, 1H, NCHC*H*=), 7.23–7.41 (m, 10H, Ar*H*). ^{13}C NMR δ: 24.2 (=CHCH$_2$), 39.3, 42.0 (2x*C*HC=O),

42.4 (O=CNCH$_2$Ph), 51.3 (CHNCH$_2$Ph), 53.5 (NCHCH=), 127.3, 127.9, 128.4, 128.5, 128.6, 128.7, 128.9, 133.6, 135.7, 139.4 (Ar*C*, C=*C*), 178.0, 179.6 (2x*C*=O). MS (EI) *m/z*: 346 (M^+, 1%), 159 (24), 144 (26), 106 (100), 91 (66). HRMS calculated for $C_{22}H_{22}N_2O_2$: 346.1681; found: 346.1661.

4.2.3. (3aS*,4R*,7aS*)-4-(Benzylamino)-2-(4-fluorobenzyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6c**)

Dark yellow sticky oil (46.5 mg, 51% yield). IR (neat) ν_{max}: 1691, 1509, 1397, 1342, 1222, 1158, 1098, 910, 737, 699 cm^{-1}. ^{1}H NMR δ: 2.05–2.19 (m, 1H, =CHC*H*$_2$), 2.58 (br s, 1H, N*H*), 2.65 (ddd, *J* = 15.7, 6.6, 2.2 Hz, 1H, =CHC*H*$_2$), 3.08 (td, *J* = 8.3, 2.2 Hz, 1H, CH$_2$C*H*C=O), 3.36 (dd, *J* = 8.4, 6.0 Hz, 1H, NCHC*H*C=O), 3.40–3.49 (m, 1H, NC*H*CH=), 3.86 (d, *J* = 13.0 Hz, 1H, CHNC*H*$_2$Ph), 4.01 (d, *J* = 13.0 Hz, 1H, CHNC*H*$_2$Ph), 4.56 (s, 2H, O=CNC*H*$_2$Ar), 5.74–5.85 (m, 1H, =C*H*CH$_2$), 5.90 (dt, *J* = 9.5, 3.0 Hz, 1H, NCHC*H*=), 6.90–6.98 (m, 2H, Ar*H*), 7.24–7.39 (m, 7H, Ar*H*). ^{13}C NMR δ: 24.1 (=CHCH$_2$), 39.3, 41.7 (2x*C*HC=O), 42.1 (O=CNCH$_2$Ar), 51.4 (CHNCH$_2$Ph), 53.5 (NCHCH=), 115.5 (d, $^2J_{C\text{-}F}$ = 21.5 Hz, *C*HCF), 127.1, 127.2, 128.3, 128.5, 128.7 (Ar*C*, *C*=*C*), 130.3 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, *C*HCHCF), 131.6 (d, $^4J_{C\text{-}F}$ = 3.4 Hz, *C*CHCHCF), 133.9, 139.8 (Ar*C*), 162.3 (d, $^1J_{C\text{-}F}$ = 246.3 Hz, *C*F), 177.9, 179.6 (2x*C*=O). ^{19}F NMR δ: 114.2. MS (EI) *m/z*: 364 (M^+, 1%), 159 (25), 144 (27), 109 (18), 106 (100), 91 (59). HRMS calculated for $C_{22}H_{21}FN_2O_2$: 364.1587; found: 364.1569.

4.2.4. (3aS*,4R*,7S*,7aS*)-4-(Benzylamino)-7-methyl-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6d**)

Brown sticky oil (43.5 mg, 50% yield). IR (neat) ν_{max}: 1704, 1598, 1498, 1455, 1383, 1266, 1179, 733, 695 cm^{-1}. ^{1}H NMR δ: 1.44 (d, *J* = 7.4 Hz, 3H, CHC*H*$_3$), 2.43–2.50 (m, 1H, C*H*CH$_3$), 3.14 (dd, *J* = 8.5, 7.1 Hz, 1H, CH$_3$CHC*H*C=O), 3.36 (br s, 1H, N*H*), 3.49–3.53 (m, 1H, NC*H*CH=), 3.59 (dd, *J* = 8.5, 6.0 Hz, 1H, NCHC*H*C=O), 3.92 (d, *J* = 12.8 Hz, 1H, NC*H*$_2$Ph), 4.10 (d, *J* = 12.8 Hz, 1H, NC*H*$_2$Ph), 5.74 (dt, *J* = 9.3, 3.2 Hz, 1H, =C*H*CHCH$_3$), 5.99 (dt, *J* = 9.0, 2.7 Hz, 1H, NCHC*H*=), 7.14–7.49 (m, 10H, Ar*H*). ^{13}C NMR δ: 16.8 (CH*C*H$_3$), 30.9 (*C*HCH$_3$), 42.6, 44.5 (2x*C*HC=O), 51.4 (NCH$_2$Ph), 54.5 (NCHCH=), 126.1, 126.6, 127.3, 128.5, 128.6, 128.7, 129.2, 129.3, 131.7, 133.1, 133.6, 139.4 (Ar*C*, *C*=*C*), 176.3, 177.2 (2x*C*=O). MS (EI) *m/z*: 346 (M^+, 2%), 174 (11), 173 (66), 144 (29), 106 (95), 91 (100), 82 (16), 77 (12). HRMS calculated for $C_{22}H_{22}N_2O_2$: 346.1681; found: 346.1681.

4.2.5. (3aS*,4R*,7aS*)-4-(Benzylamino)-6-methyl-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6e**)

Yellow sticky oil (56.2 mg, 65% yield). IR (neat) ν_{max}: 1705, 1499, 1442, 1386, 1265, 1195, 1099, 1057, 732, 700 cm^{-1}. ^{1}H NMR δ: 1.79 (s, 3H, C*H*$_3$), 2.21–2.33 (m, 1H, =CC*H*$_2$), 2.64 (dd, *J* = 15.4, 2.4 Hz, 1H, =CC*H*$_2$), 3.04 (br s, 1H, N*H*), 3.26 (td, *J* = 8.1, 2.4 Hz, 1H, CH$_2$C*H*C=O), 3.45–3.64 (m, 2H, NCHC*H*C=O and NC*H*CH=), 3.92 (d, *J* = 12.9 Hz, 1H, NC*H*$_2$Ph), 4.06 (d, *J* = 12.9 Hz, 1H, NC*H*$_2$Ph), 5.69 (dt, *J* = 3.8, 2.0 Hz, 1H, NCHC*H*=), 7.17–7.48 (m, 10H, Ar*H*). ^{13}C NMR δ: 23.3 (=C*C*H$_3$), 29.7 (=CCH$_2$), 39.1, 41.4 (2x*C*HC=O), 50.7 (NCH$_2$Ph), 53.5 (NCHCH=), 126.6, 128.9, 129.0, 129.1, 129.2, 129.3, 130.3, 131.4, 139.7 (Ar*C*, *C*=*C*), 177.2, 177.9 (2x*C*=O). MS (EI) *m/z*: 346 (M^+, 7%), 345 (26), 255 (32), 241 (12) 239 (16), 173 (17), 158 (24), 106 (49), 93 (29), 92 (15), 91 (100), 77 (18). HRMS calculated for $C_{22}H_{22}N_2O_2$: 346.1681; found: 346.1672.

4.2.6. (3aS*,4R*,7aS*)-2-Benzyl-4-(benzylamino)-6-methyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6f**)

Brown sticky oil (36.0 mg, 40% yield). IR (neat) ν_{max}: 1692, 1431, 1399, 1344, 1181, 1160, 910, 729, 699 cm^{-1}. ^{1}H NMR δ: 1.59 (s, 3H, C*H*$_3$), 2.10–2.21 (m, 1H, =CC*H*$_2$), 2.64 (dd, *J* = 15.4, 2.1 Hz, 1H, =CC*H*$_2$), 3.08 (td, *J* = 8.0, 2.1 Hz, 1H, CH$_2$C*H*C=O), 3.35–3.48 (m, 2H, NCHC*H*C=O and NC*H*CH=), 3.90 (d, *J* = 12.9 Hz, 1H, CHNC*H*$_2$Ph), 4.04 (d, *J* = 12.9 Hz, 1H, CHNC*H*$_2$Ph), 4.57 (d, *J* = 14.2 Hz, 1H, O=CNC*H*$_2$Ph), 4.60 (br s, 1H, N*H*), 4.63 (d, *J* = 14.2 Hz, 1H, O=CNC*H*$_2$Ph), 5.54 (br s, 1H, NCHC*H*=), 7.19–7.44 (m, 10H, Ar*H*). ^{13}C NMR δ: 23.0 (=C*C*H$_3$), 29.4 (=CCH$_2$), 39.3, 41.7 (2x*C*HC=O), 42.5 (O=CNCH$_2$Ph), 51.0 (CHNCH$_2$Ph), 53.9 (NCHCH=), 124.2, 127.7, 127.9, 128.2, 128.5, 128.6, 128.7, 128.8, 128.9, 135.6, 137.2, 137.6 (Ar*C*, *C*=*C*), 178.0, 179.2 (2x*C*=O). MS (EI) *m/z*: 360 (M^+, 2%), 173 (28), 158 (45), 106 (100), 91 (73), 82 (11). HRMS calculated for $C_{23}H_{24}N_2O_2$: 360.1838; found: 360.1828.

4.2.7. (3aS*,4R*,7aS*)-4-[(4-Methoxybenzyl)amino]-2-methyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6g**)

Brown sticky oil (31.7 mg, 42% yield). IR (neat) ν_{max}: 1689, 1510, 1437, 1284, 1245, 1118, 1033, 733, 701 cm^{-1}. ^{1}H NMR δ: 2.08–2.18 (m, 1H, =CHC*H*$_2$), 2.36 (br s, 1H, N*H*), 2.67 (ddd, *J* = 15.5, 6.7, 2.1 Hz, 1H, =CHC*H*$_2$), 2.93 (s, 3H, NC*H*$_3$), 3.09 (td, *J* = 8.3, 2.1 Hz, 1H, CH$_2$C*H*C=O), 3.36 (dd, *J* = 8.7, 6.2 Hz, 1H, NCHC*H*C=O), 3.40–3.47 (m, 1H, NC*H*CH=), 3.80 (s, 3H, OC*H*$_3$), 3.98 (d, *J* = 13.0 Hz, 1H, NC*H*$_2$Ar), 4.07 (d, *J* = 13.0 Hz, 1H, NC*H*$_2$Ar), 5.81–5.87 (m, 1H, =C*H*CH$_2$), 5.92 (dt, *J* = 9.5, 2.9 Hz, 1H, NCHC*H*=), 6.85–6.89 (m, 2H, Ar*H*), 7.29–7.34 (m, 2H, Ar*H*). ^{13}C NMR δ: 24.1 (=CHCH$_2$), 24.9 (NCH$_3$), 39.4, 42.1 (2x*C*HC=O), 50.8 (NCH$_2$Ar), 53.4 (NCHCH=), 55.4 (OCH$_3$), 114.0, 114.1, 127.0, 129.5, 129.6, 132.0, 134.1, 158.8, (Ar*C*, C=*C*), 178.4, 180.1 (2x*C*=O). MS (EI) *m/z*: 300 (M^+, 1%), 136 (100), 121 (96). HRMS calculated for $C_{17}H_{20}N_2O_3$: 300.1474; found: 300.1472.

4.2.8. (3aS*,4R*,7aS*)-2-(4-Fluorobenzyl)-4-[(4-methoxybenzyl) amino]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6h**)

Dark orange sticky oil (38.8 mg, 39% yield). IR (neat) ν_{max}: 1698, 1510, 1433, 1398, 1343, 1247, 1223, 1173, 1033, 733, 699 cm^{-1}. ^{1}H NMR δ: 2.08–2.19 (m, 1H, =CC*H*$_2$), 2.67 (ddd, *J* = 15.6, 6.6, 2.1 Hz, 1H, =CC*H*$_2$), 3.10 (br s, 1H, N*H*), 3.11 (td, *J* = 8.2, 2.1 Hz, 1H, CH$_2$C*H*C=O), 3.41–3.52 (m, 2H, NCHC*H*C=O and NC*H*CH=), 3.80 (s, 3H, OC*H*$_3$), 3.87 (d, *J* = 12.8 Hz, 1H, CHNC*H*$_2$Ar), 3.99 (d, *J* = 12.8 Hz, 1H, CHNC*H*$_2$Ar), 4.56 (s, 2H, O=CNC*H*$_2$Ar), 5.75–5.87 (m, 1H, NCHCH=C*H*), 5.93 (dt, *J* = 9.5, 3.0 Hz, 1H, NCHC*H*=), 6.84–7.00 (m, 4H, Ar*H*), 7.24–7.35 (m, 4H, Ar*H*). ^{13}C NMR δ: 24.2 (=CCH$_2$), 39.3, 41.8 (2x*C*HC=O), 42.0 (O=CNCH$_2$Ar), 51.4 (CHNCH$_2$Ar), 53.3 (NCHCH=), 55.4 (OCH$_3$), 114.1 (Ar*C*), 115.5 (d, $^2J_{C\text{-}F}$ = 21.7 Hz, *C*HCF), 127.5, 129.8 (Ar*C*, *C*=*C*), 130.4 (d, $^3J_{C\text{-}F}$ = 8.2 Hz, *C*HCHCF), 131.6 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, *C*CHCHCF), 133.0, 140.3, 159.1 (Ar*C*), 162.4 (d, $^1J_{C\text{-}F}$ = 246.5 Hz, *C*F), 177.9, 179.5 (2x*C*=O). ^{19}F NMR δ: 114.2. MS (EI) *m/z*: 394 (M^+, 2%), 136 (100), 121 (85), 109 (15). HRMS calculated for $C_{23}H_{23}FN_2O_3$: 394.1693; found: 394.1675.

4.2.9. (3aS*,3bR*,11R*,11aS*)-11-[(4-Methoxybenzyl)amino]-2-methyl-3a,3b,4,5,11,11a-hexahydro-1H-naphtho[2,1-e]isoindole-1,3(2H)-dione (**6i**)

Dark yellow sticky oil (56.6 mg, 56% yield). IR (neat) ν_{max}: 1688, 1611, 1512, 1437, 1384, 1285, 1246, 1177, 1112, 1031, 909, 757, 729 cm^{-1}. ^{1}H NMR δ: 2.07–2.14 (m, 1H, CH$_2$C*H*$_2$CH), 2.22 (qd, *J* = 12.5, 3.5 Hz, 1H, CH$_2$C*H*$_2$CH), 2.56–2.68 (m, 2H, C*H*$_2$CH$_2$CH and CH$_2$CH$_2$C*H*), 2.78 (dt, *J* = 15.1, 4.1 Hz, 1H, C*H*$_2$CH$_2$CH), 2.83 (s, 3H, NC*H*$_3$), 3.21 (t, *J* = 7.7 Hz, 1H, CH$_2$CHC*H*C=O), 3.60–3.67 (m, 2H, NCHC*H*C=O and NC*H*CH=), 3.78 (br s, 1H, N*H*), 3.79 (s, 3H, OC*H*$_3$), 4.05 (d, *J* = 12.8 Hz, 1H, NC*H*$_2$Ar), 4.12 (d, *J* = 12.8 Hz, 1H, NC*H*$_2$Ar), 6.37 (br s, 1H, NCHC*H*=), 6.85–6.90 (m, 2H, Ar*H*), 7.07–7.16 (m, 3H, Ar*H*), 7.21–7.25 (m, 1H, Ar*H*), 7.39–7.44 (m, 2H, Ar*H*). ^{13}C NMR δ: 24.2 (*C*CH$_2$CH$_2$), 24.9 (NCH$_3$), 29.9 (CCH$_2$CH$_2$), 36.5 (CH$_2$*C*HCHC=O), 43.0, 43.4 (2x*C*HC=O), 50.6 (NCH$_2$Ar), 54.3 (NCHCH=), 55.4 (OCH$_3$), 114.2, 123.7, 126.7, 127.8, 128.4, 129.7, 130.1, 130.7, 133.0, 137.4, 138.2, 159.3 (Ar*C*, *C*=*C*), 177.0, 178.3 (2x*C*=O). MS (EI) *m/z*: 402 (M^+, 5%), 291 (10), 170 (42), 136 (57), 121 (100). HRMS calculated for $C_{25}H_{26}N_2O_3$: 402.1943; found: 402.1943.

*4.2.10. (3aS,4R,7aS)-2-Phenyl-4-{[(R)-1-phenylethyl]amino}-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6j**)*

Light brown needles (45.9 mg, 53% yield), mp 135–136 °C (Et_2O), $[\alpha]_D^{25}$ = +96.4 (*c* 1.1, $CHCl_3$), IR (neat) ν_{max}: 1705, 1490, 1447, 1386, 1264, 1173, 1070, 1032, 734, 703 cm^{-1}. ^1H NMR δ: 1.46 (d, *J* = 6.5 Hz, 3H, $CHCH_3$), 2.08 (ddt, *J* = 15.7, 8.1, 2.6 Hz, 1H, =$CHCH_2$), 2.72 (ddd, *J* = 15.7, 6.7, 1.9 Hz, 1H, =$CHCH_2$), 3.21 (td, *J* = 8.1, 1.9 Hz, 1H, CH_2CHC=O), 3.42 (dt, *J* = 6.4, 2.8 Hz, 1H, NCHCH =), 3.62 (dd, *J* = 9.5, 6.3 Hz, 1H, NCHCHC=O), 4.26 (q, *J* = 6.5 Hz, 1H, $CHCH_3$), 5.90 (ddt, *J* = 9.6, 6.5, 2.9 Hz, 1H, =$CHCH_2$), 5.96 (dt, *J* = 9.6, 2.9 Hz, 1H, NCHCH =), 7.18–7.48 (m, 10H, Ar*H*), (NH not observed). ^{13}C NMR δ: 24.3 (CH_2), 24.6 ($NCHCH_3$), 39.3, 40.8 (2x*C*HC = O), 52.0 (NCHCH =), 55.8 ($NCHCH_3$), 126.6, 127.1, 127.3, 127.7, 128.8, 128.9, 129.3, 131.8 (Ar*C*, *C*=*C*), 177.5, 178.9 (2x*C* = O). MS (EI) *m/z*: 346 (M^+, <1%), 331 (14), 173 (43), 120 (100), 106 (27), 105 (72), 79 (28), 77 (20), 69 (26). HRMS calculated for $C_{22}H_{22}N_2O_2$: 346.1681; found: 346.1680.

*4.2.11. (3aS,4R,7aS)-4-{[(R)-1-(Naphthalen-1-yl)ethyl]amino}-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6k**)*

Yellow sticky oil (30.1 mg, 30% yield), $[\alpha]_D^{25}$ = +98.6 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}: 1702, 1498, 1380, 1242, 1176, 1045, 749, 692 cm^{-1}. ^1H NMR δ: 1.51 (d, *J* = 6.5 Hz, 3H, $CHCH_3$), 2.00 (ddt, *J* = 15.9, 8.0, 3.0 Hz, 1H, =$CHCH_2$), 2.68 (ddd, *J* = 15.7, 6.9, 2.0 Hz, 1H, =$CHCH_2$), 3.15 (ddd, *J* = 9.3, 8.0, 1.9 Hz, 1H, CH_2CHC=O), 3.39 (dt, *J* = 6.2, 2.6 Hz, 1H, NCHCH =), 3.60 (dd, *J* = 9.1, 6.2 Hz, 1H, NCHCHC=O), 4.42 (q, *J* = 6.5 Hz, 1H, $CHCH_3$), 5.87 (ddt, *J* = 9.6, 6.5, 3.1 Hz, 1H, =$CHCH_2$), 5.96 (dt, *J* = 9.3, 3.1 Hz, 1H, NCHCH =), 7.18–7.89 (m, 12H, Ar*H*) (NH not observed). ^{13}C NMR δ: 24.3 (=$CHCH_2$), 24.9 (CH_3), 39.3, 40.7 (2x*C*HC = O), 52.0 (NCHCH =), 55.7 ($NCHCH_3$), 123.1, 125.1, 125.9, 126.2, 126.6, 127.1, 127.8, 128.7, 128.8, 129.3, 131.8, 133.1, 133.5, 138.9 (Ar*C*, *C*=*C*), 177.4, 179.0 (2x*C* = O). MS (EI) *m/z*: 396 (M^+, 2%), 381 (17), 223 (15), 171 (13), 170 (96), 156 (36), 155 (100), 154 (14), 153 (15), 129 (11), 79 (14). HRMS calculated for $C_{26}H_{24}N_2O_2$: 396.1838; found: 396.1814.

*4.2.12. (3aR,4S,7aR)-4-{[(R)-1-(Naphthalen-1-yl)ethyl]amino}-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6k'**)*

Yellow plates (28.1 mg, 28% yield), mp 113–115 °C, $[\alpha]_D^{26}$ = −34.3 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}: 1702, 1498, 1382, 1180, 861, 822, 750, 692 cm^{-1}. ^1H NMR δ: 1.60 (d, *J* = 6.7 Hz, 3H, $CHCH_3$), 2.01–2.11 (m, 1H, =$CHCH_2$), 2.67 (ddd, *J* = 15.8, 6.8, 1.9 Hz, 1H, =$CHCH_2$), 3.17 (td, *J* = 8.7, 1.9 Hz, 1H, CH_2CHC=O), 3.39–3.44 (m, 1H, NCHCHC=O), 3.52 (br s, 1H, NCHCH =), 4.32 (q, *J* = 6.7 Hz, 1H, $CHCH_3$), 5.93–6.00 (m, 1H, =$CHCH_2$), 6.21 (dt, *J* = 9.7, 3.1 Hz, 1H, NCHCH =), 7.17–7.88 (m, 12H, Ar*H*) (NH not observed). ^{13}C NMR δ: 23.9 (CH_3), 24.4 (=$CHCH_2$), 39.3, 43.4 (2x*C*HC = O), 51.8 (NCHCH =), 56.5 ($NCHCH_3$), 125.3, 126.1, 126.3, 126.6, 126.9, 127.8, 128.0, 128.8, 128.9, 129.3, 131.7, 133.2, 133.5 (Ar*C*, *C*=*C*), 178.1, 178.8 (2x*C* = O). MS (EI) *m/z*: 396 (M^+, 2%), 381 (14), 223 (14), 171 (13), 170 (100), 156 (35), 155 (98), 154 (15), 153 (16), 129 (12), 79 (13). HRMS calculated for $C_{26}H_{24}N_2O_2$: 396.1838; found: 396.1822.

*4.2.13. (3aS,4R,7aS)-4-(Benzylamino)-2-((R)-1-phenylethyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (**6l**)*

Pale brown prisms (47.0 mg, 52% yield), mp 65–67 °C, $[\alpha]_D^{24}$ = +43.3 (*c* 1.0, $CHCl_3$). IR (neat) ν_{max}: 1690, 1496, 1452, 1390, 1362, 1222, 1190, 1106, 1025, 910, 733, 697 cm^{-1}. ^1H NMR δ (mixture of two rotamers): 1.73 (d, *J* = 7.3 Hz, 3H, CH_3), 2.05–2.16 (m, 1H, =$CHCH_2$), 2.61, 2.67 (2ddd, *J* = 15.6, 6.7, 2.1 Hz, 1H, =$CHCH_2$, two rotamers), 3.03 (td, *J* = 8.2, 2.1 Hz, 1H, CH_2CHC=O), 3.37, 3.38 (2dd, *J* = 8.8, 6.0 Hz, 1H, NCHCHC=O, two rotamers), 3.44 (br s, 1H, NH), 3.46–3.50 (m, 1H, NCHCH =), 3.90, 3.93 (2d, *J* = 13.1 Hz, 1H, NCH_2Ph, two rotamers), 4.02, 4.05 (2d, *J* = 13.1 Hz, 1H, NCH_2Ph, two rotamers), 5.36, 5.37 (2q, *J* = 7.3 Hz, 1H, $CHCH_3$, two rotamers), 5.78–5.89 (2m, 1H, =$CHCH_2$, two rotamers), 5.92, 5.98 (dt, *J* = 9.5, 3.0 Hz, 1H, NCHCH = , two rotamers), 7.22–7.43 (m, 10H, Ar*H*). ^{13}C NMR δ: 16.7 (CH_3), 24.3 (=$CHCH_2$), 39.0, 41.6 (2x*C*HC = O), 50.2 ($NCHCH_3$), 51.2 (NCH_2Ph), 53.6 (NCHCH =), 127.2, 127.3, 127.4, 127.7, 128.4, 128.5, 128.6, 133.0, 138.9, 139.5 (Ar*C*, *C*=*C*), 178.0, 179.7 (2x*C* = O). MS (EI) *m/z*: 360 (M^+, 1%), 159 (21), 144 (22), 106 (100), 105 (16), 91 (50). HRMS calculated for $C_{23}H_{24}N_2O_2$: 360.1838; found: 360.1827.

Acknowledgements

We gratefully acknowledge financial support from the Spanish Ministerio de Economia y Competitividad (MINECO), Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER, EU) (Project Nos. CTQ2013-43446-P, CTQ2014-51912-REDC, CTQ2016-76782-P, CTQ2016-81797-REDC, CTQ2016-81893REDT, and CTQ2016-76155-R), the Generalitat Valenciana (PROMETEOII/2014/017) and the University of Alicante.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2019.01.063.

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