CHEMISTRY
A EUROPEAN JOURNAL

Synthesis of Enantiomerically Pure Cyclohex-2-en-1-ols: Development of Novel Multicomponent Reactions

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Abstract: Multicomponent reactions of aldehydes, dienophiles, and alcohols or carboxylic acid anhydrides have been developed for the first time. In situ generation of 1-acyloxy- and 1-alkoxy-1,3-butadiene derivatives in toluene in the presence of electron-deficient dienophiles provides selective and efficient access to functionalized cyclohex-2-ene-1-ols in good yields. Subsequent enzyme-catalyzed kinetic resolution gave the corresponding enantiomers with high enantioselectivity.

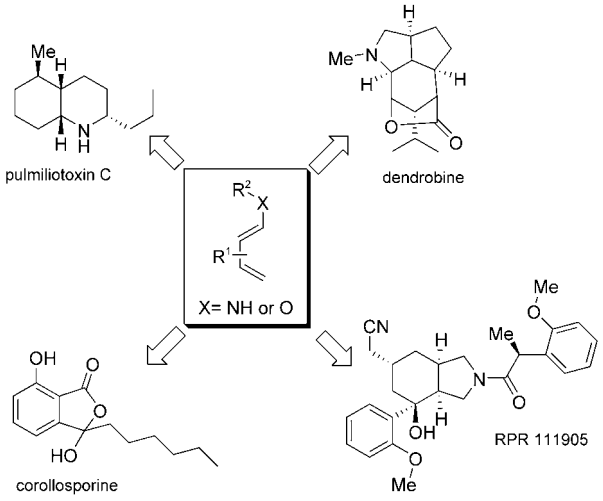
Keywords: cyclohexenes · enzymes · kinetic resolution · multicomponent reactions

Introduction

The development and exploration of new domino[1] and multicomponent reactions (MCR)[2] constitutes an important field of activity in current organic synthesis. Unlike the usual stepwise formation of individual bonds in the target molecule, the most attractive attribute of MCRs is the inherent formation of several bonds in one operation without isolating the intermediates, changing the reaction conditions, or adding further reagents. Thus, the adoption of MCRs instead of stepwise procedures allows for minimization of waste production and energy usage as well as expenditure of human labour.

In the past, some of us have developed a new three-component coupling reaction for the synthesis of substituted 1-amido-cyclohexenes and 1-amido-3,4-cylohexadienes, starting from readily available substrates like **a**mides, **a**ldehydes and **d**ienophiles (AAD reaction).[3] Our method involves condensation reactions of amides and aldehydes to generate 1-(*N*-acylamino)-1,3-butadiene species, which are converted in situ with electron-deficient dienophiles in Diels–Alder reactions to the desired products. Selected examples of the obtained 1-amido-cyclohex-2-ene derivatives have been successfully applied in the synthesis of anilines,[4] phthalic acid esters,[5] and cyclohexenylamines.[6] Moreover, this type of MCR product is of interest for the synthesis of pharmaceutically attractive molecules like dendrobine,[7] pumiliotoxin C,[8] phenanthridones,[9] and nonpeptide NK1 P-antagonists, for example, RPR 111905[10] (Scheme 1).

So far, the scope of the AAD reaction has been limited to the use of 1-(*N*-acylamino)-1,3-butadienes as key intermedi-



Scheme 1. AAD intermediates as potential precursors for biologically active compounds.

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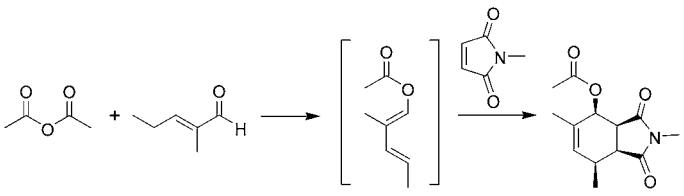
DOI: 10.1002/chem.200401258

ates. To broaden the applicability of our method we became interested in the in situ generation of 1-(*O*-acyloxy)- and 1-alkoxy-1,3-butadiene derivatives, and subsequent trapping by electron-deficient dienophiles. The synthesis of 1-acyloxy-1,3-butadiene derivatives has been investigated by several research groups in the past.[11] In general, this class of compounds is prepared by conversion of carboxylic acid anhydrides and α,β-unsaturated aldehydes in the presence of catalytic amounts of acid or base at elevated temperatures. 1-Acyloxy-1,3-butadienes have also been obtained by a copper acetate mediated reaction of isopropenyl esters with α,β-unsaturated aldehydes. However, to the best of our knowledge, no example of the in situ usage of 1-acyloxy-1,3-butadienes in multicomponent reactions has been described in the literature before. Herein, for the first time, we report on the preparation of various substituted racemic 3-cyclohexene-1-ol derivatives, which were obtained in one step from commercially available substrates with high selectivity. In addition, we demonstrate that the new MCR products can be easily transformed to enantiomerically pure cyclohex-2-en-1-ols, which constitute interesting chiral building blocks for the synthesis of various natural products and their analogues.[12]

Results and Discussion

As a model system for the development of the novel MCR the reaction of acetic acid anhydride, 2-methyl-2-pentenal and *N*-methyl-maleimide was studied (Scheme 2).



Scheme 2. A new multicomponent reaction of **an**hydrides, **a**ldehydes, and **d**ienophiles (ANAD reaction).

Using the typical conditions known from the AAD reaction (2 mol% *p*-toluenesulfonic acid (TSA), *N*-methylpyrrolidone (NMP), 16 h) only minor formation of the desired cycloaddition product was observed (15%; Table 1, entry 1). However, changing the solvent from NMP to toluene[13] enhanced the product yield to 71% (Table 1, entry 2). Due to the better stabilization of polar intermediates in NMP, aldol-like oligomerization reactions took place to a large extent and decreased the yield of the desired product. Apparently, these side reactions are supressed in less polar solvents, for example, toluene. Further attempts to vary the reaction time, temperature, solvents, and concentration of the acid did not lead to improved product yields.

To demonstrate the general applicability of the **an**hydrides, **a**ldehydes, and **d**ienophiles (ANAD) reaction, different aldehydes, anhydrides and dienophiles were used. As shown in Table 1 (entries 1–11), a variety of substituted isoindol derivatives were obtained from α,β-unsaturated aldehydes, carboxylic acid anhydrides, and *N*-methyl maleimide. Except for the reaction of 4-methyl-2-pentenal (Table 1, entry 9), the corresponding products were isolated in 60–67% yield. The desired cycloaddition adducts were also observed in 67–68% yield when propionic acid anhydride or hexanoic acid anhydride, instead of acetic acid anhydride, was applied in the presence of 2-methyl-2-pentenal and *N*-methyl maleimide (Table 1, entries 10, 11).

Applying acrylonitrile, fumaric acid dinitrile, tetracyanoethylene, and maleic anhydride as dienophiles, the expected MCR products were obtained in 70%, 61%, 58% and 98% yield, respectively (Table 1, entries 12–14, 17). Because of the high 1,4-elimination tendency of aromatic ester residues within the cyclohexene scaffold, the use of aromatic anhydrides like benzoic acid anhydride and phenyl acetic acid anhydride afforded the desired products in trace amounts only. Nevertheless, we were able to prepare 1-phenacyloxy-1,3-butadiene-derivatives in situ by using phenyl acetyl chloride, α,β-unsaturated aldehydes, and one equivalent of potassium butoxide at −78°C in THF. After adding the dienophile, reactions were allowed to stir at 60°C and the desired products isolated in 96 and 55% yield (Table 1, entries 15, 16).

One- and two-dimensional NMR experiments unambiguously established the stereochemical structure of all new MCR products. Except for fumaric acid dinitrile, which produced a diastereomeric mixture, we observed the selective *endo*-addition of the dienophile during the Diels–Alder step. Thus, analyses of the ^{1}H–^{1}H coupling constants of the alkyl substituents on the cyclohexene ring revealed the exclusive formation of the all-*syn* products.

To extend the versatility of this type of domino reaction sequence further, we also tried to combine the in situ formation of 1-alkoxy-1,3-butadienes with subsequent Diels–Alder reactions. 1-Alkoxy-1,3-butadienes are generally synthesized by alcohol elimination from α,β-unsatured acetals at elevated temperatures or by acid-catalyzed condensation of alcohols and α,β-unsaturated aldehydes.[14] Again, 2-methyl-2-pentenal and *N*-methyl maleimide were used as part of the model system. A disappointing yield of 10% of the appropiate product was obtained when the previously optimized set of conditions using methanol, instead of the carboxylic acid anhydride, was applied (Table 2, entry 1).

We thought that the initially generated water prevents the efficient formation of the required 1-methoxy-1,3-butadiene derivative. We therefore studied the effect of water-removal agents on the target reaction. No improvement was observed in the presence of commonly applied dehydration reagents like anhydrides, molecular sieves, and anhydrous salts (Table 2, entries 2–4). However, using trimethoxymethane, which acts both as water detracting reagent and alcohol donor, the desired MCR product was obtained in 73% yield (Table 2, entry 5). Finally, the scope and limitation of this new MCR variant (reaction of **al**cohols, **a**ldehydes, and **d**ien-

Table 1. The ANAD reaction.[a]

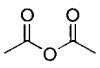
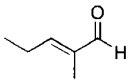
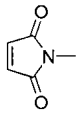
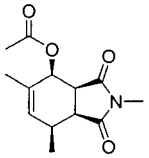
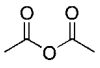
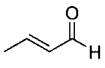
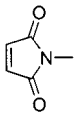
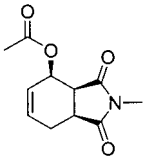
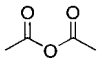
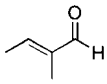
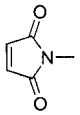
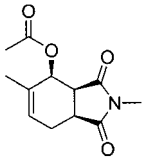
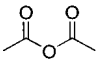
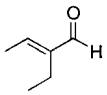
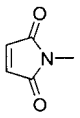
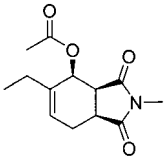
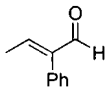
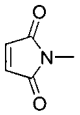
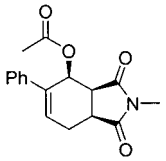
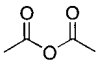
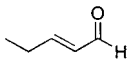
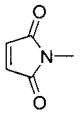
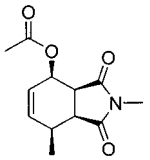
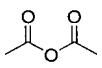
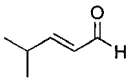
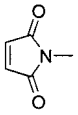
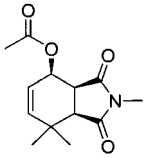
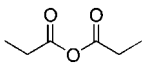
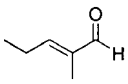
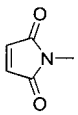
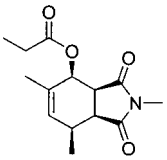
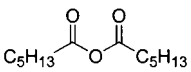
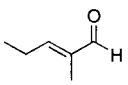
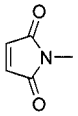
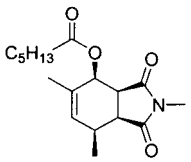
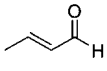
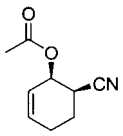
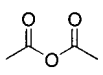
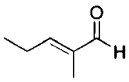
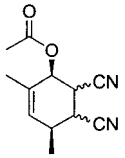
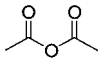
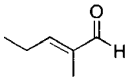
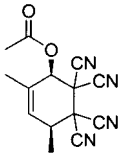
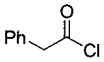
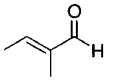
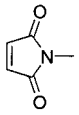
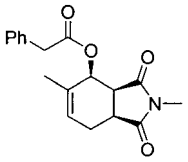
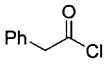
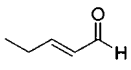
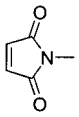
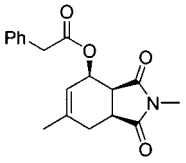
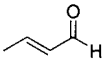
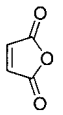
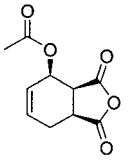
Entry	Anhydride	Aldehyde	Dienophile	Product		Yield [%]
1[b]					**1**	15
2						71
3[c]						51
4					**2**	61
5					**3**	62
6					**4**	67
7					**5**	60
8					**6**	64
9					**7**	13
10					**8**	67
11					**9**	68
12[d]					**10**	70

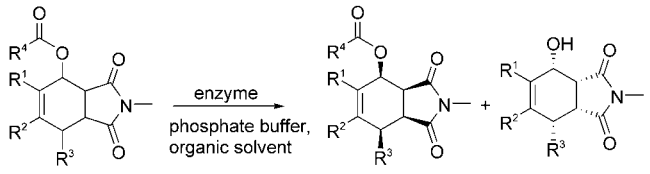
Table 1. (Continued)

Entry	Anhydride	Aldehyde	Dienophile	Product		Yield [%]
13					**11**	61
14[e]					**12**	58
15[f]					**13**	96
16[f]					**14**	55
17					**14a**	98

[a] Reaction conditions: 11.25 mmol anhydride, 7.5 mmol aldehyde, 11.25 mmol dienophile (or 60 mmol acrylonitrile), 30 mL toluene, 2 mol% *p*-TSA, 110°C; 16 h. [b] NMP instead of toluene. [c] 90°C. [d] 5 d. [e] The diene was formed first, tetracyanoethylene was added after 4 h and the reaction was allowed to stir at room temperature for an additional 16 h. [f] Phenyl acetyl chloride (10 mmol) was added to a freshly prepared solution of α,β-unsaturated aldehyde (10 mmol) and potassium butoxide (10 mmol) at −78°C in 30 mL THF. After stirring at −78°C for 30 min, dienophile (5 mmol) was added. The reaction mixture was then stirred for 16 h at 60°C.

ophiles (ALAD reaction)) was also investigated. Apart from trimethoxymethane, triethoxymethane and benzyl alcohol were also used with differently substituted α,β-unsaturated aldehydes. Except for crotonaldehyde, the yields of the MCR products were around 70% (Table 2, entries 8–12).

Clearly, the novel three-component coupling reactions based on aldehydes, dienophiles, and carboxylic acid anhydrides or alcohols allow for an efficient one-pot preparation of either *O*-acyl-substituted cyclohexenes. Although up to four stereogenic centers are created, typically one diastereomer is formed in a highly selective way. Unfortunately, the development of enantioselective variants of our methodology may be difficult due to the comparably high reaction temperature. Hence, we were interested in the synthesis of enantiomerically pure MCR compounds by means of kinetic resolution processes. The most easy and general kinetic resolution of alcohol derivatives (esters) is achieved by using enzymes.[15] Thus, the kinetic resolution of the racemic esters **1**–**4**, **7**, **13**, and **14** (Scheme 3) and **10** (Scheme 4) was investigated in the presence of different lipases and esterases.[16]



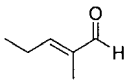
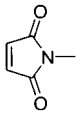
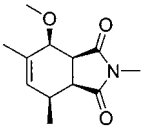
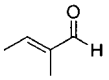
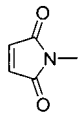
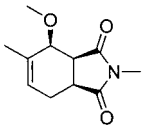
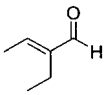
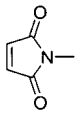
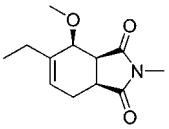
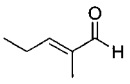
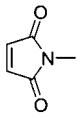
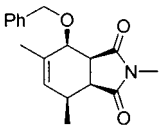
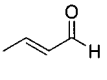
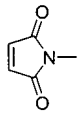
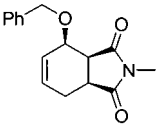
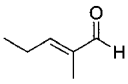
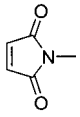
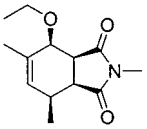
1, 2, 4, 7, 13-14

1: R^2 = H, R^1 = R^3 = R^4 = Me
2: R^1 = R^2 = R^3 = H, R^4 = Me
4: R^1 = Et, R^2 = R^3 = H, R^4 = Me
7: R^1 = Ph, R^2 = R^3 = H, R^4 = Me
13: R^1 = Me, R^2 = R^3 = H, R^4 = Bn
14: R^1 = R^3 = H, R^2 = Me, R^4 = Bn

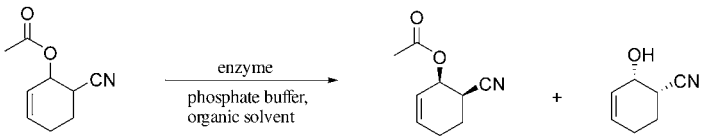
Scheme 3. Enzyme-catalyzed kinetic resolution of racemic esters **1**, **2**, **4**, **7**, **13**, and **14**.

Small-scale hydrolysis reactions were carried out in sodium phosphate buffer (10 mM, pH 7.5) with 20% (v/v) organic solvent at 37 or 40°C.[17] After specific time intervals samples were withdrawn, were extracted with dichloromethane, and were analyzed by GC and HPLC with chiral col-

Table 2. Multicomponent reaction of **al**cohols, **a**ldehydes, and **d**ienophiles (ALAD reaction).[a]

Entry	Alcohol	Additive	Aldehyde	Dienophile	Product		Yield [%]
1	MeOH	–				**15**	10
2	MeOH	Ac_2O					4
3	MeOH	mol sieve (4 Å)					4
4	MeOH	Na_2SO_4					9
5	$HC(OMe)_3$	–					73
6[b]	$HC(OMe)_3$	–					53
7[c]	$HC(OMe)_3$	–					28
8	$HC(OMe)_3$	–				**16**	67
9	$HC(OMe)_3$	–				**17**	69
10	Bn-OH	–				**18**	68
11	Bn-OH	–				**19**	30
12	$HC(OEt)_3$	–				**20**	70

[a] Reaction conditions: 11.25 mmol anhydride, 7.5 mmol aldehyde, 11.25 mmol dienophile, 30 mL toluene, 2 mol% *p*-TSA, 110°C, 16 h. [b] 90°C. [c] 70°C.



10

Scheme 4. Enzyme-catalyzed kinetic resolution of racemic ester **10**.

Table 3. Enzyme-catalyzed kinetic resolution of racemic esters **1**, **2**, **4**, **7**, **13**, **14**, and **10**.

	Enzyme	Time [h]	Conversion[a] [%]	Enantiomeric excess ee_S[b] [%]	ee_P[b,c] [%]	E[a]
1	pNBE	0.5	50	99	99	>100
2	BCL	24	49	95	>99	>100
4	pNBE	8	50	97	n.d.	>100
7	Chirazyme E-3	25	50	>99	n.d.	>100
13	PGA-450	72	48	91	98	>100
14	Chirazyme E-3	48	51	94	93	79
10	CAL-B	1.5	50	>99	99	>100

[a] Calculated according to Chen et al.[18] [b] Determined by GC or HPLC with chiral columns. [c] Determined for all alcohols.

umns (Table 3). It is worth noting that enzymes exhibiting high enantioselectivity (E[18] = 79 to >100) have been found for all substrates. Reaction rates for phenyl acetic acid esters (**13**–**14**) were significantly longer than for acetic acid esters (0.5–25 h compared to 48–72 h; Table 3). Interestingly, for **4**, **13**, and **14** enzymes showing opposite enantiopreference were also detected, but exhibiting less enantioselectivity.

Preparative-scale experiments with >2 mmol substrate in the presence of *Burkholderia cepacia* lipase (BCL, lipase PS "Amano") were also performed for **2**.[19] After 27 h, 50% conversion was reached and the remaining ester and the newly formed alcohol were isolated from the reaction mixture in 46% and 44% yield, respectively. For both compounds the enantiomeric excess was >99%, which equals an E value >100. So far, crystallization experiments to get suitable X-ray crystals for the determination of the absolute stereochemistry were not successful.

In summary, we have developed two novel multicomponent reactions. Generation of 1-acyloxy- and 1-alkoxy-1,3-butadiene-derivatives in toluene in the presence of electron-deficient dienophiles provides an efficient access to functionalized 3-cyclohexene-1-ol derivatives in good yields. This ANAD and ALAD methodology probably constitutes the

most simple and direct approach to a variety of O-functionalized cyclohexene derivatives. The ubiquitous, off-the-shelf starting materials readily react even in the presence of air. Kinetic resolution of the racemic esters by using hydrolases afforded the corresponding products with high enantioselectivity (>99% *ee*). This two-step sequence allows for a practical and general synthesis of enantiomerically pure cyclohexenols. It is worth noting that the obtained products are of interest as precursors and analogues of biologically active natural products, for example, RPR 111905.

Experimental Section

Procedure A: Carboxylic acid anhydride (11.25 mmol), α,β-unsaturated aldehyde (7.5 mmol), dienophile (11.25 mmol) or acrylonitrile (60 mmol), and *p*-toluenesulfonic acid monohydrate (2 mol%) were combined in a pressure tube, and toluene (30 mL) was added. The reaction mixture was stirred at 110°C for 16 h. After cooling, all volatile compounds were removed under reduced pressure. Silica gel flash chromatography (*n*-heptane/EtOAc) afforded the desired products.

Procedure B: Phenyl acetyl chloride (10 mmol) was added to a freshly prepared solution of α,β-unsaturated aldehyde (10 mmol) and potassium butoxide (10 mmol) at −78°C in THF (30 mL). After stirring at −78°C for 30 min, the dienophile (5 mmol) was added. The reaction mixture was then stirred for 16 h at 60°C. After cooling, all volatile compounds were removed under reduced pressure. Silica gel flash chromatography (*n*-heptane/EtOAc) afforded the desired products.

Procedure C: Trimethoxymethane (5 mmol), α,β-unsaturated aldehyde (5 mmol), dienophile (7.5 mmol), and *p*-toluenesulfonic acid monohydrate (2 mol%) were combined in a pressure tube, and toluene (20 mL) was added. The reaction mixture was stirred at 110°C for 16 h. After cooling, all volatile compounds were removed under reduced pressure. Silica gel flash chromatography (*n*-heptane/EtOAc) afforded the desired products.

Procedure D: All small-scale reactions were carried out in 1.5 mL Eppendorf tubes with phosphate buffer (400 μl, 10 mM, pH 7.5) and organic solvent (100 μl) in a thermoshaker (Eppendorf, Hamburg, Germany) at 1000 rpm. After specific time intervals, samples (100 μl) were taken and the same amount of distilled water was added before extraction of substrate and product with dichloromethane (3×100 μl). The organic phases were dried before GC or HPLC analysis.

Compound ***1***: 4 mg (15.92 μmol) substrate, 5 mg (~100 U) lyophilized pNBE, DMSO, 40°C.

Compound ***2***: 5 mg (22.40 μmol) substrate, 1 mg (~30 U) lyophilized BCL, toluene, 40°C.

Compound ***4***: 5 mg (19.90 μmol) substrate, 3 mg (~60 U) lyophilized pNBE, DMSO, 37°C.

Compound ***7***: 5 mg (16.70 μmol) substrate, 5 mg (~60 U) lyophilized Chirazyme E-3, toluene, 37°C.

Compound ***10***: 3 mg (18.16 μmol) substrate, 5 mg (~600 U) lyophilized CAL-B, toluene, 40°C.

Compound ***13***: 6 mg (19.15 μmol) substrate, 35 mg carrier-fixed PGA, toluene, 37°C.

Compound ***14***: 7 mg (22.34 μmol) substrate, 7 mg (~85 U) lyophilized Chirazyme E-3, toluene, 37°C.

Procedure E: The enzymatic hydrolysis in preparative scale was performed in a 250 mL flask with **2** (2.24 mmol) and BCL (900 U) dissolved in phosphate buffer (40 mL, 10 mM, pH 7.5) and toluene (10 mL). The mixture was stirred in a water bath at 40°C until 50% conversion was reached. For the isolation of substrate and product, 50 mL distilled water was added and the reaction mixture was extracted with dichloromethane (6×20 mL). The organic phase was dried, filtered and excess solvent was removed in vacuo. Ester **2** and alcohol **2a** were separated by silica gel chromatography (column 5×30 cm). Ester **2** was eluted first with 2:1 = dichloromethane/ethyl acetate. The organic mixture was then changed to 1:2 = dichloromethane/ethyl acetate to elute the alcohol **2a**.

Procedure F: Acetic acid anhydride (20 mmol), crotonaldehyde (10 mmol), maleic anhydride (10 mmol), and *p*-toluenesulfonic acid monohydrate (2 mol%) were combined in a pressure tube, and toluene (25 mL) was added. The reaction mixture was stirred at 110°C for 24 h. After cooling, all volatile compounds were removed under reduced pressure and the oily product was dried under vacuum (oil pump) for 24 h. No further work up was necessary.

2,3,3a,4,7,7a-Hexahydro-2,4,6-trimethyl-1,3-dioxo-1*H*-isoindol-7-yl acetate (1): Procedure A; R_f (SiO_2, *n*-heptane/EtOA*c* = 1:1): 0.35; yield: 71%; colorless oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.56 (m, 1H; C=C*H*CH), 5.35 (d, *J* = 6.93 Hz, 1H; COOC*H*), 3.49 and 3.11 (2d, *J* = 1.98 Hz and *J* = 7.13 Hz, both 1H; 2C*H*CON), 2.76 (s, 3H; CONC*H*$_3$), 2.58 (m, 1H; C=CHC*H*CH$_3$), 2.02 (s, 3H; C*H*$_3$COO), 1.66 (s, 3H; C*H*$_3$C=C), 1.22 ppm (d, *J* = 7.53 Hz, 3H; C*H*$_3$CHC=C); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ = 177.4 and 175.4 (CH*C*ON), 169.8 (CH$_3$*C*OO), 134.0 (CH$_3$*C*=C), 129.7 (C=*C*CHCH$_3$), 68.4 (*C*HOCO), 43.0 and 42.5 (2*C*HCON), 28.6 (CON*C*H$_3$), 24.3 (CH$_3$*C*HCH=C), 20.7 (*C*H$_3$COO), 18.6 (*C*H$_3$C=CH), 17.2 ppm (*C*H$_3$CHCH=C); MS (EI, 70 eV): *m/z* (%): 251 (19) [*M*]$^+$, 208 (100) [*M*−Ac]$^+$, 191 (19), 123 (66), 112 (26), 106 (48), 98 (33), 91 (30), 43 (79) [*M*]$^+$, no other peaks >10%; IR (KBr): $\tilde{\nu}$ = 3456 (m), 2976 (m), 2732 (w), 1699 (s), 1135 (m), 851 cm^{-1} (w); HR-MS (EI): calcd for $C_{13}H_{17}NO_4$: 251.11521; found: 251.11352 [*M*]$^+$.

2,3,3a,4,7,7a-Hexahydro-2-methyl-1,3-dioxo-1*H*-isoindol-7-yl acetate (2): Procedure A; R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.41; yield: 61%; colorless solid; m.p.: 91°C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.03 and 5.93 (2m, both 1H; C*H*=C*H*), 5.33 (m, 1H; CHC*H*O), 3.45 (dd, *J* = 2.57 Hz and *J* = 6.74 Hz, 1H; OCHC*H*CON), 3.23 (m, 1H; CH$_2$C*H*CON), 2.81 (s, 3H; CONC*H*$_3$), 2.39 (m, 2H; C*H*$_2$), 1.95 ppm (s, 3H; C*H*$_3$COO); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ = 179.5 and 175.7 (2*C*ONCH$_3$), 169.6 (CH$_3$*C*OO), 130.6 (OCH*C*H=CH), 127.5 (CH$_2$*C*H=CH), 65.9 (O*C*HCH), 42.1 (CH*C*HCO), 36.8 (CH$_2$*C*HCO), 24.4 (CON*C*H$_3$), 21.9 (*C*H$_2$), 20.5 ppm (*C*H$_3$COO); MS (EI, 70 eV): *m/z* (%): 223 (4) [*M*]$^+$, 181 (80), 112 (39), 95 (62), 78 (76), 43 (100), no other peaks >10%; IR (KBr): $\tilde{\nu}$ = 3443 (m), 3056 (m), 2971 (m), 2892 (m), 2861 (w), 1698 (s), 1238 (s), 793 cm^{-1} (w); HR-MS (EI): calcd for $C_{11}H_{13}NO_4$: 223.08446; found; 223.08311 [*M*]$^+$.

(+)-2,3,3a,4,7,7a-Hexahydro-2-methyl-1,3-dioxo-1*H*-isoindol-7-yl acetate: Procedure E; yield: 92%; >99% *ee*; $[\alpha]_D^{21}$ = +104 (*c* = 1 in methanol); ^{1}H NMR ([D$_6$]DMSO): δ = 6.03 and 5.93 (2m, both 1H; C*H*=C*H*), 5.33 (m, 1H; CHC*H*O), 3.45 (dd, *J* = 2.57, 6.74 Hz, 1H; OCHC*H*CON), 3.23 (m, 1H; CH$_2$C*H*CON), 2.81 (s, 3H; CONC*H*$_3$), 2.39 (m, 2H; C*H*$_2$), 1.95 ppm (s, 3H; CH$_3$COO).

4-Hydroxy-3a,4,7,7a-tetrahydro-2-methyl-2*H*-isoindole-1,3-dione (2a): Procedure E; R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.23; yield: 88%, >99% *ee*; $[\alpha]_D^{21}$ = −150 (*c* = 1 in methanol); colorless solid; m.p.: 96–97°C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.96 (m, 1H; CHC*H*=CH), 5.84 (m, 1H; CH$_2$C*H*=CH), 4.97 (m, 1H; CHO*H*), 4.33 (m, 1H; C*H*-OH), 3.09 (m, 1H; CHC*H*CO), 2.94 (m, 1H; CH$_2$C*H*CO), 2.76 (s, 3H; CONC*H*$_3$), 2.42–2.18 ppm (m, 2H; C*H*$_2$); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ = 180.3 and 177.3 (2*C*ONCH$_3$), 131.7 (CH*C*H=CH), 128.5 (CH$_2$*C*H=CH), 62.3 (HO*C*HCH), 45.5 (CH*C*HCO), 36.4 (CH$_2$*C*HCO), 24.1 (CON*C*H$_3$), 21.5 ppm (CH$_2$), MS (EI, 70 eV): *m/z* (%): 181 (14) [*M*]$^+$, 153 (100), 125 (30), 113 (52), 95 (43), 78 (35), 70 (67), 55 (24), 39 (57), 27 (28), no other peaks >10%. IR (KBr): $\tilde{\nu}$ = 3408 (s), 3051 (m), 2995 (w), 2945 (m), 2905 (m), 2857 (m), 1757 (m), 1686 (s), 1438 (s), 1281 (s), 1046 (s), 807 (m), 611 (m), 407 cm^{-1} (w); HR-MS (EI): calcd for $C_9H_{11}NO_3$: 181.07389; found: 182.08118 [*M*+H]$^+$.

2,3,3a,4,7,7a-Hexahydro-2,5-dimethyl-1,3-dioxo-1*H*-isoindol-7-yl acetate (3): Procedure A; R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.43; yield: 62%; colorless solid; m.p.: 71–72°C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.74 (m, 1H; C=C*H*CH$_2$), 5.36 (d, *J* = 5.5 Hz, 1H; COOC*H*C=CH), 3.37 (dd, *J* = 3.96, 5.55 Hz, 1H; COOCHC*H*CO), 3.15 (m, 1H; CH$_2$C*H*CON), 2.82 (s, 3H; CONC*H*$_3$), 2.40 and 2.25 (2m, both 1H; C=CHC*H*$_2$CH), 1.92 ppm (s, 3H; C*H*$_3$COO); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ =

179.6 and 175.9 (2 CHCON), 169.6 (CH_3COO), 135.0 (CH_3C=CH), 125.0 (CH_3C=CH), 68.7 (COOCHCH), 43.3 (CHCHCON), 36.2 (CH_2CHCON), 24.2 (CONCH_3), 22.0 (CH_2CH_2CH=C), 20.4 (CH_3C=CH) 20.1 ppm (CH_3COO); MS (EI, 70 eV): *m/z* (%): 237 (6) $[M]^+$, 195 (73), 109 (54), 92 (75), 43 (100), no other peaks >10%; IR (KBr): $\tilde{\nu}$=3428 (m), 3001 (m), 2985 (m), 2946 (m), 2823 (m), 2713 (m) 1770 (s), 1385 (s), 988 (m), 867 (m), 716 cm^{-1} (m); HR-MS (EI): calcd for $C_{12}H_{15}NO_4$: 237.10011; found: 237.09985 $[M]^+$.

5-Ethyl-2,3,3a,4,7,7a-hexahydro-2-methyl-1,3-dioxo-1*H*-isoindol-7-yl acetate (4): Procedure A; R_f (SiO_2, *n*-heptane/EtOAc=1:1): 0.41; yield: 67%; colorless oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=6.17 (m, 1H; C*H*=C(Et)), 5.90 (d, *J*=5.35 Hz, 1H; COOC*H*C(Et)=CH), 3.76 (m, 1H; OCHC*H*CON), 3.60 (m, 1H; CH_2C*H*CON), 3.27 (s, 3H; CONCH_3), 2.90 and 2.73 (2m, both 1H; EtC=CHCH_2CH), 2.56 (m, 2H; CH_3CH_2CH=C), 2.34 (s, 3H; CH_3COO), 1.36 ppm (t, *J*=7.62 Hz, 3H; CH_3CH_2); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ=179.6 and 175.9 (2 CHCON), 169.5 (CH_3COO), 140.4 (CH=*C*(Et)CH), 123.6 (CH_2*C*H=C(Et)), 68.0 (CH*C*HO), 43.8 (CH*C*HCO), 36.6 (CH_2*C*HCO), 26.4 (CON*C*H_3), 24.2 (CHCH_2*C*=C), 21.9 (*C*H_3COO), 20.4 (*C*H_3CH_2C=C), 11.8 ppm (*C*H_3CH_2); MS (EI, 70 eV): *m/z* (%): 251 (7) $[M]^+$, 208 (100) $[M-Ac]^+$, 191 (70), 180 (18), 123 (43), 106 (95), 91 (87), 79 (32), 43 (97) $[Ac]^+$, 29 (16), no other peaks >10%; IR (KBr): $\tilde{\nu}$=3448 (m), 2995 (m), 2981 (m), 2954 (m), 2837 (m), 1710 (s), 1233 (s), 1188 (m), 716 cm^{-1} (m); HR-MS (EI): calcd for $C_{13}H_{17}NO_4$: 251.11576; found: 251.11530 $[M]^+$.

2,3,3a,4,7,7a-Hexahydro-2-methyl-1,3-dioxo-5-phenyl-1*H*-isoindol-7-yl acetate (5): Procedure A; R_f (SiO_2, *n*-heptane/EtOAc=1:1): 0.49; yield: 60%; colorless solid; m.p.: 134–137 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=7.35 (m, 5H; *H*-Ar), 6.52 (dd, *J*=4.0 Hz, *J*=3.2 Hz, 1H; CH_2C*H*=C(Ph)), 6.19 (d, *J*=4.56 Hz, 1H; OC*H*), 3.44 (m, 1H; OCHC*H*CO), 3.26 (m, 1H; CH_2C*H*CON), 2.85 (s, 3H; CONCH_3), 2.75 and 2.44 (2m, both 1H; CHCH_2CH=C), 1.83 ppm (s, 3H; CH_3COO); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ=179.5 and 176.0 (2 CH*C*ON), 168.9 (CH_3COO), 138.1 (Ph*C*=CH), 137.9 (*p*-*C*H-Ar), 129.7 and 128.5 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 127.4 (*i*-*C*-Ar), 125.4 (PhC=*C*HCH$_2$), 66.4 (O*C*H), 44.9 (CH*C*HCON), 35.9 (CH_2*C*HCON), 24.3 (CON*C*H_3), 22.8 (CHCH_2CH), 20.8 ppm (*C*H_3COO); MS (EI, 70 eV): *m/z* (%): 299 (1) $[M]^+$, 239 (65), 154 (100), 43 (20), no other peaks >10%; IR (KBr): $\tilde{\nu}$=3453 (m), 3035 (w), 2945 (m), 2911 (w), 2856 (w), 1744 (s), 1700 (s), 1230 (s), 762 cm^{-1} (w); HR-MS (EI): calcd for $C_{17}H_{17}NO_4$: 299.11576; found 299.11420 $[M]^+$.

2,3,3a,4,7,7a-Hexahydro-2,4-dimethyl-1,3-dioxo-1*H*-isoindol-7-yl acetate (6): Procedure A; R_f (SiO_2, *n*-heptane/EtOAc=1:1): 0.33; yield: 64%; colorless solid; m.p.: 142–145 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=5.82 (m, 2H; C*H*=C*H*), 3.56 (m, 1H; OC*H*CH), 3.31 (m, 1H; CHC*H*CON), 2.81 (m, 1H; CH(CH_3)C*H*CON), 2.76 (s, 3H; CONCH_3), 2.55 (m, 1H; CH_3C*H*CH), 2.01 (s, 3H; CH_3COO), 1.31 ppm (d, *J*=7.33 Hz, 3H; CH_3CHCH); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ=177.4 and 175.0 (CH*C*ON), 169.7 (CH_3COO), 135.8 and 127.0 (*C*H=*C*H), 66.7 (COO*C*HCH), 42.6 and 42.2 (CO*C*HCH), 28.9 (CON*C*H_3), 24.3 (CH_3*C*HCH), 20.8 (*C*H_3COO), 17.0 ppm (*C*H_3CHCH); MS (EI, 70 eV): *m/z* (%)=237 (5) $[M]^+$, 195 (79), 109 (48), 92 (93), 43 (100), no other peaks >10%. IR (KBr): $\tilde{\nu}$=3437 (m), 2990 (m), 2972 (m), 2935 (m), 2855 (m), 1700 (s), 1237 (s), 716 cm^{-1} (m); HR-MS (EI): calcd for $C_{12}H_{15}NO_4$: 237.10011; found: 237.09920 $[M]^+$.

2,3,3a,4,7,7a-Hexahydro-2,4,4-trimethyl-1,3-dioxo-1*H*-isoindol-7-yl acetate (7): Procedure A; R_f (SiO_2, *n*-heptane/EtOAc=1:1): 0.39; yield: 13%; colorless oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=5.96 (m, 1H; CH=C*H*CH), 5.89 (m, 1H; C*H*=CHCH), 5.51 (dd, *J*=1.2 Hz und *J*=5.74 Hz, 1H; COOC*H*CH), 3.46 (dd, *J*=3.17 Hz and *J*=6.93 Hz, 1H; COOCHC*H*CO), 2.96 (s, 3H; CONCH_3); 2.83 (m, 1H; C-(CH_3)$_2$C*H*CON), 1.86 (m, 3H; CH_3COO), 1.26 and 1.08 ppm (2s, both 3H; (CH_3CCH_3). ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ=177.5 and 175.4 (2 CH*C*ON), 169.6 (CH_3COO), 144.9 (CH=*C*HCH), 123.3 (*C*H=CHCH), 62.7 (*C*HOCO), 47.6 (CH*C*HCON), 42.4 (C(CH_3)$_2$*C*HCON), 32.7 and 31.0 (*C*H_3CCH_3), 25.7 (CH_3*C*CH_3), 24.3 (CON*C*H_3), 20.6 ppm (*C*H_3COO); MS (EI, 70 eV): *m/z* (%): 251 (4) $[M]^+$, 208 (85), 191 (38), 123 (37), 113 (47), 112 (34), 98 (29), 91 (49), 83 (21), 69 (16), 43 (100), no other peaks >10%; IR (KBr): $\tilde{\nu}$=3423 (m), 3391 (w), 2157 (w), 2243 (w), 1776 (s) 1232 (s), 706 cm^{-1} (m); HR-MS (EI): calcd for $C_{13}H_{17}NO_4$: 251.11576; found: 251.11624 $[M]^+$.

2,3,3a,4,7,7a-Hexahydro-2,4,6-trimethyl-1,3-dioxo-1*H*-isoindol-7-yl propionate (8): Procedure A. R_f (SiO_2, *n*-heptane/EtOAc=2/1): 0.67. Yield: 67%. Colorless oil. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=5.37 (d, *J*=7.13 Hz, 1H; CH(CH_3)C*H*=C), 3.48 (dd, 1H; *J*=1.98, 7.13 Hz, 1H; OC*H*CH), 3.10 (m, 1H; CHC*H*CON), 2.81 (m, 1H; CH(CH_3)C*H*CON), 2.76 (s, 3H; CONCH_3), 2.55 (m, 1H; CH_3C*H*CH), 2.31 (m, 2H; CH_3CH_2CO), 1.65 (s, 3H; CH_3C=CH), 1.19 (d, *J*=7.33 Hz, 3H; CH_3CHCH), 1.02 ppm (t, *J*=7.53 Hz, 3H; CH_3CH_2CO); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ=177.5 and 175.4 (2 CH*C*ON), 172.9 (CH_2*C*OO), 134.0 (*C*H_3C=CH), 129.9 (CH(CH_3)*C*H=C), 68.2 (COO*C*HCH), 43.0 (CH(CH_3)*C*HCO), 42.4 (CH*C*HCO), 28.5 (CH_3CH_2*C*O), 27.1 (CON*C*H_3), 24.2 (CH_3*C*HCH), 18.8 (*C*H_3C=CH), 17.2 (*C*H_3CHCH), 8.9 ppm (*C*H_3CH_2CO); MS (EI, 70 eV): *m/z* (%): 265 (5) $[M]^+$, 208 (100), 191 (16), 123 (44), 106 (39), 91 (25), 57 (76), 29 (31), no other peaks >10%; IR (KBr): $\tilde{\nu}$=3448 (s), 2942 (s), 2882 (s), 2738 (w), 2362 (w), 1700 (s), 1559 (w), 1457 (s), 1436 (s), 1384 (m), 1285 (m), 1194 (m), 1074 (m), 1024 (m), 798 (m), 726 (w), 663 (w), 608 (w), 571 (w), 506 cm^{-1} (w); HR-MS (EI): calcd for $C_{14}H_{19}NO_4$: 265.13141; found: 265.13392 $[M]^+$.

2,3,3a,4,7,7a-Hexahydro-2,4,6-trimethyl-1,3-dioxo-1*H*-isoindol-7-yl hexanoate (9): Procedure A. R_f (SiO_2, *n*-heptane/EtOAc=1:2): 0.39; yield: 68%; colorless oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=5.58 (m, 1H; C*H*=C(CH_3), 5.37 (m, 1H; C*H*OCO), 3.47 (dd, *J*=6.93, 2.18 Hz, 1H; OCHC*H*CO), 3.11 (dd, *J*=7.33, 1.98 Hz, 1H; CH(CH_3)C*H*CO), 2.75 (s, 3H; CONCH_3), 2.57 (m, 1H; CH_3C*H*CH), 2.27 (m, 2H; CH_2COO), 1.65 (m, 3H; CH_3C=CH), 1.52 (m, 2H; CH_2), 1.25 (m, 4H; 2 CH_2), 1.19 (d, *J*=7.13 Hz, 3H; CH_3CHCH), 0.83 ppm (m, 3H; CH_3CH_2); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ=177.5 and 175.4 (2 *C*ONCH_3), 172.2 (*C*OOCH), 133.9 (CH_3C=CH), 129.9 (CH(CH_3)*C*H=C), 68.1 (O*C*HCH), 43.1 and 42.2 (2 *C*HCON), 33.7, 30.5, 24.0, and 21.8 (4 CH_2), 28.5 (CON*C*H_3) 24.2 (CH_3*C*HCH), 18.9 (*C*H_3C=CH), 17.2 (*C*H_3CHCH), 13.7 ppm (*C*H_3CH_2); MS (EI, 70 eV): *m/z* (%): 307 (2) $[M]^+$, 209 (24), 208 (100), 191 (14), 123 (25), 106 (24), 99 (57), 91 (15), 71 (41), 60 (20), 43 (61), no other peaks >10%; IR (KBr): $\tilde{\nu}$=3465 (m), 2958 (m), 2934 (m), 2873 (m), 1705 (s), 1437 (m), 1383 (m), 1289 (m), 1243 (m), 1164 (m), 1099 (m), 1007 (m), 808 (w), 616 cm^{-1} (w); HR-MS (EI): calcd for $C_{17}H_{25}NO_4$: 307.17836; found: 307.17803 $[M]^+$.

6-Cyanocyclohex-2-enyl acetate (10): Procedure A; 120 h; R_f (SiO_2, *n*-heptane/EtOAc=1:1): 0.32; yield: 70%; colorless oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=5.97 and 5.63 (2m, both 1H; C*H*=C*H*), 5.34 (m, 1H; OC*H*CH), 3.40 (m, 1H; CHC*H*CN), 2.13 (m, 2H; CH(CN)CH_2CH_2), 2.06 (s, 3H; CH_3COO), 1.92 ppm (m, 2H; CH=CHCH_2CH_2); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ=169.3 (CH_3COO), 131.9 and 123.6 (2 *C*H=*C*H), 119.6 (*C*N), 65.4 (O*C*HCH), 29.3 (CH*C*HCN), 22.3 (CH_2CH_2CHCN), 21.8 (CH=CH*C*H_2CH_2), 20.7 ppm (*C*H_3COO); MS (EI, 70 eV): *m/z* (%): 165 (1) $[M]^+$, 138 (21), 96 (13), 70 (12), 43 (100) $[Ac]^+$, no other peaks >10%. IR (KBr): $\tilde{\nu}$=3456 (w), 3042 (w), 2941 (m), 2844 (w), 2244 (m), 1744 (s), 1653 (w), 1434 (m), 1373 (s), 1234 (s), 1153 (w), 1092 (m), 1045 (s), 962 (m), 916 (m), 874 (w), 771 (w), 730 (w), 696 (w), 660 (w), 622 (w), 604 (w), 491 (w), 438 cm^{-1} (w); HR-MS (ESI): calcd for [$C_{12}H_{15}NO_4Na$]: 188.06875; found: 188.06730 $[M+Na]^+$.

5,6-Dicyano-2,4-dimethylcyclohex-2-enyl acetate (11): Procedure A. R_f (SiO_2, *n*-heptane/EtOAc=2/1): 0.35; yield: 61%; colorless oil; m.p.: 126–128 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=5.55 (m, 1H; C*H*=CHCH$_3$), 3.93–3.83 (m, 1H; OC*H*CH), 3.02 (m, 1H; OCHC*H*CN), 2.54 (m,1H; CH(CH_3)C*H*CN), 2.11 (s, 3H; CH_3COO), 2.09 (m, 1H; CH_3C*H*CH), 1.62 (s, 3H; CH_3C=CH), 1.15 ppm (d, *J*=7.13 Hz, 3H; CH_3CHCH). ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ=169.6 (*C*H_3COO), 130.7 (CH_3*C*=CH), 129.0 (CH_3C=*C*H), 119.3 and 117.4 (both *C*N), 64.9 (O*C*HCH), 33.9 and 33.1 (both *C*HCN), 31.9 (CH_3*C*HCH), 20.3 (*C*H_3COO), 19.8 (*C*H_3C=CH), 18.8 ppm (*C*H_3CHCH); MS (EI, 70 eV): *m/z* (%)=218 (2) $[M]^+$, 191 (15), 149 (57), 98 (16), 43 (100), $[Ac]^+$, no other peaks >10%; IR (KBr): $\tilde{\nu}$=3464 (m), 2969 (s), 2933 (s), 2881 (w), 2246 (m), 1752 (s), 1741 (s), 1453 (m), 1375 (s), 1224 (s), 1109 (m), 1033 (m), 1016 (m), 1001 (m), 818 (w), 698 (w), 578 (w), 503 (w), 439 cm^{-1}

(w); HR-MS (EI): calcd for $C_{12}H_{14}N_2O_2$: 218.10553; found: 218.09969 $[M]^+$.

5,5,6,6-Tetracyano-2,4-dimethylcyclohex-2-enyl acetate (12): Procedure A. R_f (SiO_2, *n*-heptane/EtOAc = 2:1): 0.43; yield: 58%; colorless oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.28 (m, 1H; C*H*=CCH$_3$), 5.83 (m, 1H; OC*H*C(CN)$_2$), 3.49 (m, 1H; CH$_3$C*H*C(CN)$_2$), 2.20 (s, 3H; C*H*$_3$COO), 1.78 (m, 3H; C*H*$_3$C=CH), 1.46 ppm (d, J = 6.93 Hz, 3H; C*H*$_3$CHC(CN)$_2$); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ = 168.5 (CH$_3$*C*OO), 128.6 (CH$_3$*C*=CH), 126.8 (CH$_3$C=*C*HCH), 112.0, 110.2, 108.9, and 108.6 (4 *C*N), 65.7 (O*C*HC(CN)$_2$), 43.9 (OCH-*C*(CN)$_2$), 42.1 (CH*C*(CN)$_2$), 35.7 (CH$_3$*C*HC(CN)$_2$), 20.0 (*C*H$_3$COO), 19.6 (*C*H$_3$C=CH), 17.3 ppm (*C*H$_3$CHC(CN)$_2$); MS (EI, 70 eV): *m/z* (%): 268 (2) $[M]^+$, 98 (12), 43 (100) $[Ac]^+$, no other peaks >10%; IR (KBr): $\tilde{\nu}$ = 3436 (m), 2986 (m), 2956 (m), 2884 (m), 1771 (s), 1372 (m), 1208 (s), 1029 cm^{-1} (s); HR-MS (EI): calcd for $C_{14}H_{12}N_4O_2$: 268.09603; found 268.09541 $[M]^+$.

2,3,3a,4,7,7a-Hexahydro-2,5-dimethyl-1,3-dioxo-1*H*-isoindol-7-yl 2-phenylacetate (13): Procedure B. R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.15; yield: 96%; colorless oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.31–7.17 (m, 5H; *H*-Ar), 5.72 (m, 1H; CH$_2$C*H*=CCH$_3$), 5.36 (d, J = 5.15 Hz, 1H; OC*H*), 3.57 (d, J = 4.16 Hz, 2H; PhC*H*$_2$CO), 3.31 (m, 1H; OCHC*H*CO), 3.10 (m, 1H; CH$_2$C*H*CO), 2.73 (s, 3H; CONC*H*$_3$), 2.36 and 2.07 (m, 1H; C*H*$_2$), 1.75 ppm (s, 3H; C*H*$_3$C=CH); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ = 179.3 and 175.8 (2CHCON), 170.1 (CH$_2$*C*OO), 135.3 (CH$_3$*C*=CH), 134.0 (*i*-*C*-Ar), 129.2 and 128.3 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 126.8 (*p*-*C*H-Ar), 125.6 (CH$_2$*C*H=*C*CH$_3$), 69.3 (O*C*H), 43.5 (OCH*C*HCO), 40.4 (Ph*C*H$_2$CO), 36.5 (CH$_2$*C*HCO), 24.2 (CON*C*H$_3$), 21.9 (*C*H$_2$), 20.3 ppm (*C*H$_3$C=CH); MS (EI, 70 eV): *m/z* (%): 313 (1) $[M]^+$, 194 (49), 178 (70), 118 (22), 109 (16), 93 (100), 77 (23), 65 (23), 39 (13), no other peaks >10%; IR (KBr): $\tilde{\nu}$ = 3462 (w), 3031 (m), 2951 (m), 1736 (s), 1705 (s), 1435 (m), 1131 (s), 705 cm^{-1} (m); HR-MS (EI): calcd for $C_{18}H_{19}NO_4$: 313.13141; found: 313.13172 $[M]^+$.

2,3,3a,4,7,7a-Hexahydro-2,5-dimethyl-1,3-dioxo-1*H*-isoindol-7-yl 2-phenylacetate (14): Procedure B; R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.15; yield: 55%; colorless oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.32–7.11 (m, 5H; *H*-Ar), 5.71 (m, 1H; C*H*=CCH$_3$), 5.35 (m, 1H; OC*H*), 3.54 (d, J = 4.16 Hz, 2H; PhC*H*$_2$CO), 3.23 (m, 2H; 2 C*H*CONCH$_3$), 2.74 (s, 3H; CONC*H*$_3$), 2.27 and 2.15 (2m, both 1H; C*H*$_2$), 1.71 ppm (s, 3H; C*H*$_3$C=CH); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ = 179.3 and 175.7 (2CHCON), 169.9 (CH$_2$*C*OO), 141.1 (CH$_3$*C*=CH), 134.0 (*i*-*C*-Ar), 129.2 and 128.2 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 126.7 (*p*-*C*H-Ar), 120.2 (OCH*C*H=C), 66.5 (O*C*H), 42.4 (OCH*C*HCO), 40.4 (Ph*C*H$_2$CO), 36.6 (CH$_2$*C*HCO), 26.6 (*C*H$_2$), 24.3 (CON*C*H$_3$), 23.0 ppm (CH$_3$*C*=CH); MS (EI, 70 eV): *m/z* (%): 313 (1) $[M]^+$, 194 (28), 178 (57), 93 (100), 77 (17), 65 (15), no other peaks >10%; IR (KBr): $\tilde{\nu}$ = 3447 (m), 3033 (m), 2964 (m), 2936 (m), 2907 (m), 1736 (s), 1700 (s), 1435 (s), 1154 (s), 1009 (m), 722 cm^{-1} (m); HR-MS (EI): calcd for $C_{18}H_{19}NO_4$: 313.13141; found: 313.13344 $[M]^+$.

1,3,3a,4,7,7a-Hexahydro-1,3-dioxoisobenzofuran-4-yl acetate (14a): Procedure F; yield: 98%; yellowish oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.14–6.05 (m, 1H; *H*C=), 6.04–6.00 (m, 1H; *H*C=), 5.37 (m, 1H; OC*H*), 3.75–3.70 (m, 2H; CH$_2$C*H*C*H*), 2.48–2.43 (m, 2H; C*H*$_2$), 1.97 (s, 3H; C*H*$_3$); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ = 174.9, 170.6, and 169.3 (3*C*O), 131.0 and 126.5 (H*C*=*C*H), 64.7 (*C*HO), 43.3 and 37.0 (2*C*H), 21.5 (*C*H$_2$), 20.4 ppm (*C*H$_3$); MS (EI, 70 eV): *m/z* (%): 210 (0.2) $[M]^+$, 122 (18), 95 (18), 78 (32), 43 (100) $[Ac]^+$, no other peaks >10%; IR (KBr): $\tilde{\nu}$ = 2968 (s), 1858 (m), 1786 (s), 1743 (s), 1372 (m), 1228 (s), 1101 (m), 1050 (s), 922 (s), 787 cm^{-1} (s); HR-MS (EI): calcd for $C_{10}H_{10}O_5$: 210.05283; found: 210.05169 $[M]^+$.

3a,4,7,7a-Tetrahydro-4-methoxy-2,5,7-trimethyl-2*H*-isoindole-1,3-dione (15): Procedure C; R_f (SiO_2, *n*-heptane/EtOAc = 1/1): 0.39; yield: 73%; colorless oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.51 (m, 1H; (CH$_3$)C*H*=C), 3.99 (d, J = 5.74 Hz, 1H; OC*H*CH), 3.40 (dd, J = 2.77, 6.14 Hz, 1H; OCHC*H*CON), 3.32 (s, 3H; OC*H*$_3$), 3.04 (m, 1H; CH-(CH$_3$)C*H*CON), 2.75 (s, 3H; CONCH$_3$), 2.48 (m, 1H; CH$_3$C*H*CH), 1.70 (s, 3H; C*H*$_3$C=CH), 1.20 ppm (d, J = 7.33 Hz, 3H; C*H*$_3$CHCH); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ = 177.8 and 175.8 (2CHCON), 136.4 (CH$_3$*C*=CH), 128.5 (CH(CH$_3$)*C*H=C), 76.0 (O*C*HCH), 56.3 (*C*H$_3$O), 43.5 (OCH*C*HCON), 42.2 (CH(CH$_3$)*C*HCON), 28.5 (CON*C*H$_3$), 24.1 (CH$_3$*C*HCH), 19.8 (*C*H$_3$C=CH), 17.2 ppm (*C*H$_3$CH); MS (EI, 70 eV): *m/z* (%): 223 (45) $[M]^+$, 208 (36), 191 (24), 123 (56), 112 (100), 106 (47), 97 (48), 91 (56), 79 (24), 43 (36), no other peaks >10%. IR (KBr): $\tilde{\nu}$ = 3452 (s), 2937 (s), 2834 (m), 1699 (s), 1541 (m), 1436 (s), 1383 (s), 1287 (s), 1204 (s), 1110 (s), 1000 (s), 903 (m), 809 (m), 729 (m), 616 (m), 576 (m), 460 cm^{-1} (m); HR-MS (EI): calcd for $C_{12}H_{17}NO_3$: 223.12084; found: 223.11810 $[M]^+$.

3a,4,7,7a-Tetrahydro-4-methoxy-2,5-dimethyl-2*H*-isoindole-1,3-dione (16): Procedure C; R_f (SiO_2, *n*-heptane/EtOAc = 2:1): 0.26; yield: 67%; colorless oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.81 (m, 1H; CH$_2$C*H*=CH$_3$), 4.11 (m, 1H; OC*H*CH), 3.21 (s, 3H; OC*H*$_3$), 3.01 (m, 1H; OCHC*H*CO), 2.97 (s, 3H; CONC*H*$_3$), 2.92 (m, 1H; CH$_2$C*H*CO), 2.51–2.44 (m, 2H; C*H*$_2$), 1.86 ppm (s, 3H; C*H*$_3$C=CH); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ = 180.3 and 177.2 (2CH*C*ON), 136.3 (CH$_3$*C*=CH), 124.8 (CH$_2$*C*H=C), 76.2 (O*C*H), 56.6 (O*C*H$_3$), 46.0 (OCH*C*HCO), 37.1 (CH$_2$*C*HCO), 24.5 (CON*C*H$_3$), 22.6 (*C*H$_3$C=CH), 22.2 ppm (*C*H$_2$); MS (EI, 70 eV): *m/z* (%): 209 (54) $[M]^+$, 194 (42), 177 (26), 121 (30), 109 (46), 98 (100), 92 (90), 83 (36), 77 (37), 65 (18), 58 (21), 43 (15), 39 (26), 29 (18), no other peaks >10%; IR (KBr): $\tilde{\nu}$ = 3457 (w), 2934 (m), 2824 (m), 1775 (m), 1700 (s), 1435 (s), 1384 (s), 1280 (s), 1130 (m), 1093 (m), 1023 (m), 977 (m), 849 (w), 793 (w), 732 (w), 670 (w), 621 (w), 520 cm^{-1} (w); HR-MS (EI): calcd for $C_{11}H_{15}NO_3$: 209.10519; found: 209.10515 $[M]^+$.

5-Ethyl-3a,4,7,7a-tetrahydro-4-methoxy-2-methyl-2*H*-isoindole-1,3-dione (17): Procedure A; R_f (SiO_2, *n*-heptane/EtOAc = 2:1): 0.32; yield: 69%; colorless oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.69 (m, 1H; C*H*=CEt), 4.02 (m, 1H; OC*H*CH), 3.64 (m, 1H; OCHC*H*CON), 3.15 (m, 1H; CH$_2$C*H*CON), 3.06 (s, 3H; C*H*$_3$OCH), 2.77 (s, 3H; CONC*H*$_3$), 2.10 (m, 2H; CH$_3$C*H*$_2$CH=CEt), 1.81 (m, 2H; CHC*H*$_2$C=CH), 0.94 ppm (t, J = 7.43 Hz, 3H; C*H*$_3$CH$_2$C=CH); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ = 180.2 and 176.8 (2CH*C*ON), 122.4 (Et*C*=CH), 116.1 (EtC=*C*HCH), 75.4 (*C*HOCH$_3$), 56.0 (CHO*C*H$_3$), 45.6 (OCH*C*HCON), 36.6 (CH$_2$*C*HCON), 28.4 (CON*C*H$_3$), 24.0 (*C*H$_2$C=CH), 21.9 (CH*C*H$_2$CH), 11.8 ppm (*C*H$_3$CH$_2$); MS (EI, 70 eV): *m/z* (%): 223 (13) $[M]^+$, 194 (14), 191 (14), 128 (12), 123 (31), 112 (100), 91 (22), 79 (16), 28 (27), no other peaks >10%; IR (KBr): $\tilde{\nu}$ = 3458 (s), 2940 (s), 1776 (s), 1699 (s), 1541 (m), 1436 (s), 1385 (s), 1284 (s), 1134 (s), 1094 (s), 966 (s), 931 (s), 900 (m), 553 (m), 764 (m), 619 (m), 564 cm^{-1} (m); HR-MS (EI): calcd for $C_{12}H_{17}NO_3$: 223.12084; found: 223.12070 $[M]^+$.

4-Benzyloxy-2,5,7-trimethyl-3a,4,7,7a-tetrahydro-2*H*-isoindole-1,3-dione (18): Procedure A; R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.37; yield: 68%; colorless oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.43 (m, 5H; *H*-Ar), 5.62 (m, 1H; CH(CH$_3$)C*H*=CCH$_3$), 4.79 (d, J = 11.9 Hz, 1H; CH=C-(CH$_3$)C*H*O), 4.57 (m, 2H; PhC*H*$_2$O), 4.29 (d, J = 6.14 Hz, 1H; CHC*H*CON), 3.54 (dd, J = 2.97, 6.34 Hz, 1H; CH(CH$_3$)C*H*CON), 3.15 (dd, J = 1.39, 7.72 Hz, 1H; CHC*H*CH$_3$), 2.96 (s, 3H; CONC*H*$_3$), 1.81 (s, 3H; C*H*$_3$C=CH), 1.27 ppm (d, J = 7.3 Hz, 3H; CHCHC*H*$_3$); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ = 177.8 and 175.9 (2CH*C*ON), 138.5 (CH$_3$*C*=CH), 136.2 (*i*-*C*-Ar), 128.8 and 128.1 (2 *o*-*C*H-Ar und 2 *m*-*C*H-Ar), 127.0 (*p*-*C*H-Ar), 124.1 CH(CH$_3$)*C*H=C), 74.2 (O*C*HCH), 70.3 (Ph*C*H$_2$O), 43.9 (CH(CH$_3$)*C*HCON), 42.1 (CH*C*HCON), 28.5 (CON*C*H$_3$), 24.2 (CH*C*HCH$_3$), 19.8 (CH=C*C*H$_3$), 17.3 ppm (CH*C*H$_3$); MS (EI, 70 eV): *m/z* (%) = 193 (64), 178 (10), 107 (24), 91 (100) $[Bn]^+$, 65 (11), no other peaks >10%; IR (KBr): $\tilde{\nu}$ = 3443 (m), 3056 (w), 2970 (m), 2949 (m), 2892 (m), 2861 (w), 1764 (s), 1742 (s), 1698 (s), 1435 (s), 1384 (s), 1371 (s), 1345 (m), 1288 (s), 1253 (s), 1238 (s), 1202 (m), 1172 (m), 1129 (m), 1061 (s), 1010 (m), 793 (m), 694 (m), 553 cm^{-1} (m); HR-MS (EI): calcd for $[C_{18}H_{21}NO_3]$: 299.15214; found: 322.14178 $[M+Na]^+$.

4-Benzyloxy-2-methyl-3a,4,7,7a-tetrahydro-2*H*-isoindole-1,3-dione (19): Procedure A; R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.34; yield: 30%; colorless oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.27–7.04 (m, 5H; *H*-Ar), 5.65 (m, 2H; C*H*=C*H*), 4.30 (m, 2H; PhC*H*$_2$O), 4.09 (m, 1H; C*H*OBn), 2.76 (s, 3H; CONC*H*$_3$), 2.53 (m, 1H; C*H*CON), 2.45 (m, 1H; CH$_2$C*H*CON), 2.27 and 2.06 ppm (2m, both 1H; C*H*$_2$CHCON); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ = 179.2 and 175.9 (2CH*C*ON), 138.7 (*i*-*C*-Ar), 131.9 and 128.6 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 128.5 (*i*-*C*H-Ar), 127.4 and 127.3 (2*C*H=*C*H), 70.3 (Ph*C*H$_2$O), 69.5 (O*C*HCH), 45.0 (OCH*C*HCO), 36.9 (CH$_2$CHCON), 24.3 (CON*C*H$_3$), 22.5 ppm

(CH_2CH=CH); MS (EI, 70 eV): *m/z* (%): 165 (98), 107 (13), 91 (100) $[Bn]^+$, 80 (59), 79 (38), 65 (19), 51 (11), 39 (15), no other peaks >10%; IR (KBr): $\tilde{\nu}$ = 3459 (m), 3033 (m), 2946 (m), 1775 (m), 1701 (s), 1496 (m), 1436 (s), 1384 (m), 1282 (m), 1205 (m), 1072 (s), 986 (m), 930 (m), 853 (w), 802 (m), 741 (m), 699 (m), 673 (w), 613 (w), 466 cm^{-1} (w); HR-MS (EI): calcd for $C_{16}H_{17}NO_3$: 271.12084; found: 294.11048 $[M+Na]^+$.

4-Ethoxy-2,5,7-trimethyl-3a,4,7,7a-tetrahydro-2*H*-isoindole-1,3-dione (20): Procedure A; R_f (SiO_2, *n*-heptane/EtOAc = 2:1): 0.35; yield: 70%; colorless oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.49 (m, 1H; CH-(CH_3)C*H*=CCH$_3$), 4.07 (d, J = 6.14 Hz, 1H; C*H*OCH$_2$), 3.62–3.42 (m, 2H; CH_3CH_2O), 3.32 (m, 1H; OCHC*H*CO), 3.03 (m, 1H; CH-(CH_3)C*H*CON), 2.74 (s, 3H; CONC*H*$_3$), 2.65 (m, 1H; CH_3C=CHC*H*CH$_3$), 1.68 (s, 3H; C*H*$_3$-C=CH), 1.20 (d, J = 7.33 Hz, 3H; CHCHC*H*$_3$), 1.07 ppm (t, J = 7.03 Hz, 3H; C*H*$_3$CH$_2$O); ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]DMSO): δ = 177.8 and 175.7 (2*C*ONCH$_3$), 136.6 (CH_3C=CH), 128.3 (CH_3CH*C*H=C), 74.3 (O*C*HCH), 64.2 (O*C*H$_2$CH$_3$), 43.9 (OCH*C*HCON), 42.1 ($CH_3CHCHCON$), 28.3 (CON*C*H$_3$), 24.1 (CH_3CHCH), 23.2 (*C*H$_3$C=CH), 19.5 (*C*H$_3$CHCH), 17.3 ppm (CH_3CH_2O); MS (EI, 70 eV): *m/z* (%): 237 (23) $[M]^+$, 222 (36), 191 (19), 123 (52), 112 (100), 106 (53), 97 (45), 79 (15), 43 (19), no other peaks >10%; IR (KBr): $\tilde{\nu}$ = 3436 (s), 2942 (s), 1708 (s), 1528 (m), 1477 (s), 1336 (s), 1218 (s), 996 (s), 823 (m), 749 (m), 562 (m), 473 cm^{-1} (m); HR-MS (EI): calcd for $C_{13}H_{19}NO_3$: 237.13649; found: 237.13628 $[M]^+$.

Acknowledgements

The authors thank S. Giertz, S. Buchholz, Dr. C. Fischer, Dr. W. Baumann, and H. Baudisch (all IfOK) for excellent technical and analytical assistance. Generous financial support from the State of Mecklenburg-Vorpommern (Landesforschungsschwerpunkt), the BMBF (Biokatalyse in ionischen Flüssigkeiten), and the "Fonds der Chemischen Industrie" is gratefully acknowledged.

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Received: December 7, 2004
Published online: April 29, 2005