Tetrahedron 64 (2008) 5435–5441

Contents lists available at ScienceDirect

Tetrahedron

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

Improved preparation of alkyl 2-(3-indolyl)-3-nitroalkanoates under fully heterogeneous conditions: stereoselective synthesis of alkyl (*E*)-2-(3-indolyl)-2-alkenoates

Roberto Ballini, Serena Gabrielli, Alessandro Palmieri *, Marino Petrini *

Dipartimento di Scienze Chimiche, Università di Camerino, via S. Agostino, 1. I-62032 Camerino, Italy

ARTICLE INFO

Article history:
Received 29 January 2008
Received in revised form 19 March 2008
Accepted 3 April 2008
Available online 8 April 2008

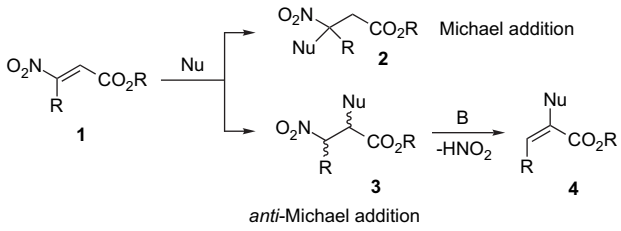
Keywords:
Conjugate addition
Heterogeneous catalysis
Indoles
Nitroaldol reaction
Nitroalkenes

ABSTRACT

Ethyl 3-nitro-2-alkenoates can be generated starting from nitroalkanes and ethyl 2-oxoacetate under heterogeneous conditions that minimize work-up procedures, avoid any purification step and direct manipulation of the nitroalkene system. Reaction of ethyl 3-nitro-2-alkenoates, formed in situ from their acetoxy precursors, with indoles in the presence of basic alumina affords ethyl 2-(3-indolyl)-3-nitroalkanoates that are central intermediates for the preparation of tryptamines and carboline alkaloids. A base promoted elimination of nitrous acid from these nitroindolyl derivatives readily produces ethyl 2-(3-indolyl)-2-alkenoates with high *E* stereoselectivity. The latter compounds can be used as Michael acceptors in intra- and intermolecular reactions with nucleophilic reagents.

1. Introduction

The addition reaction of indole derivatives to electron-poor olefins represents a useful procedure to introduce functionalized substituents at the 3-position of this heterocyclic ring. Activation of the alkene moiety toward this addition can be realized using Brønsted or Lewis acid catalysts, in a process that can be regarded as a Friedel–Crafts reaction.[1] Conversely, deprotonation of the nitrogen atom in indoles by basic reagents, affords the corresponding anion that is nucleophilic enough to undergo a conjugate addition to Michael acceptors.[2] The latter option is particularly effective when strong electrophilic olefins such as nitroalkenes are used in the conjugate addition.[3] The interest in such adducts is widely justified by their role as central intermediates for the synthesis of many pharmacologically active compounds.[4] Among different nitroalkenes, 3-nitro-2-alkenoates **1** occupy an intriguing position since the nitro and the carboxylic groups activate both termini of the carbon–carbon double bond. The superior electron-withdrawing aptitude exerted by the nitro group usually leads to an *anti*-Michael addition of nucleophiles to these derivatives (resulting in **3**).[5] The obtained products, besides the usual transformations of the nitro and ester groups, may enjoy an additional synthetic option involving a base promoted elimination of nitrous acid leading to α,β-unsaturated esters **4** (Scheme 1).[6]



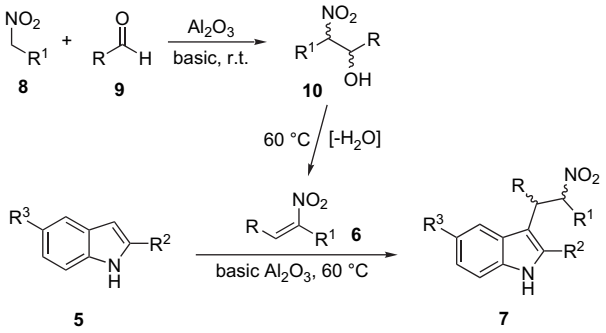
Scheme 1.

Recently, we have devised a new procedure for the conjugate addition of indoles **5** to nitroalkenes **6** in the presence of basic alumina under solventless conditions (Scheme 2).[7] Basic alumina is also able to promote the nitroaldol condensation[8] between a nitroalkane **8** and an aldehyde **9** leading to the corresponding nitro alcohol **10**, which upon heating under the same conditions dehydrates to the parent nitroalkene **6**.[9]

Therefore, using basic alumina as the single promoter, it is possible to avoid direct manipulation of nitroalkenes **6** that often are toxic and lachrymatory compounds, generating them directly in the reaction vessel from their remote precursors.[10] This appealing procedure is not applicable to 3-nitro-2-alkenoates **1** since their nitro alcohol precursors are not efficiently dehydrated under the

* Corresponding authors. Tel.: +39 0737 402253; fax: +39 0737 402297.
E-mail addresses: alessandro.palmieri@unicam.it (A. Palmieri), marino.petrini@unicam.it (M. Petrini).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.04.014



Scheme 2.

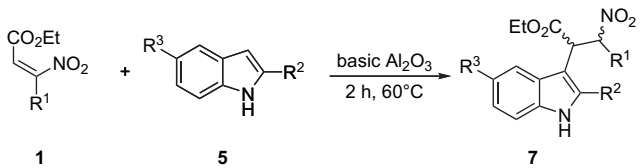
usual reaction conditions. Keeping in mind that organic reactions on solid supports represent a crucial feature for the development of environmentally friendly chemical processes,[11] a study has been undertaken with the aim to realize an efficient conjugate addition of indole derivatives to 3-nitro-2-alkenoates produced in situ from their forerunners. In this paper, we present the results of our synthetic efforts and, in addition, we demonstrate that a base-induced elimination of nitrous acid from 2-(3-indolyl)-3-nitroalkanoates provides a rapid entry into the corresponding α,β-unsaturated esters.

2. Results and discussion

Direct utilization of 3-nitro-2-alkenoates in the reaction with indoles in the presence of basic alumina has been previously tested only for a single example,[7] and therefore we decided to verify its applicability for a selected combination of substrates. As shown in Table 1, conjugate addition of indoles **5** to 3-nitro-2-alkenoates **1**[12] occurs with a satisfactory degree of efficiency to give excellent yields of the obtained adducts **7**.

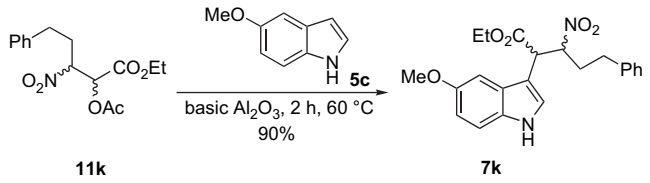
The observed failure in direct dehydration of nitro alcohols **10** often stems from a retro aldol reaction that shifts the equilibrium toward the starting materials.[13] Acylation of the hydroxy group in compound **10** would represent a doubly favorable issue since it avoids the retro aldol process and makes the ester a better leaving group for the elimination reaction.[14] As a possible acyl moiety for this process, we preferred the acetyl group since it is easily introduced using acetic anhydride under heterogeneous conditions and upon elimination produces non-toxic acetic acid salts.[15] This solution proved to be successful since acetylated nitro alcohol **11k** undergoes addition to indole **5c** via the corresponding nitroalkene leading to 3-substituted indole **7k** (Scheme 3).

Table 1
Basic alumina promoted conjugate addition of indoles **5** to ethyl 3-nitro-2-alkenoates **1**



Entry	R^1	R^2	R^3	Product **7**	Yield[a] (%)
1	Me	H	H	**7a**	90
2	*n*-Pr	H	OMe	**7b**	88
3	$CH_3(CH_2)_3$	H	H	**7c**	94
4	$CH_3(CH_2)_3$	Me	H	**7d**	92
5	$AcO(CH_2)_3$	H	OMe	**7e**	91

[a] Yield of pure isolated product.



Scheme 3.

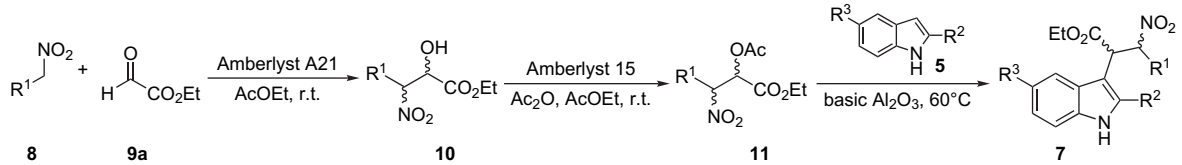
Further studies aimed at optimization of the overall procedure gave the results displayed in Table 2. The nitroaldol condensation of nitroalkanes **8** with ethyl 2-oxoacetate **9a** is carried out under heterogeneous conditions using Amberlyst A21 as basic promoter.[12c,16] After the appropriate time (see Table 2), the solution containing the nitro alcohol **10** is filtered and to this solution are added acetic anhydride and Amberlyst 15, a macroreticular resin endowed with acid character which is able to promote the acetylation process.

Once the esterification is complete, the solvent and excess of acetic anhydride are removed at reduced pressure and compound **11** thus obtained can be used for the next step that simply involves addition of indole **5** and basic alumina and heating the solid mixture at 60 °C. Reaction on solid support avoids any work-up procedure at the end of the process since direct application of the mixture to the head of a chromatographic column and elution with an appropriate solvent system affords pure 3-substituted indoles **7**. The whole procedure is thus effected using a limited amount of ethyl acetate,[17] and executing a single purification step as regards the final product. The yields of the obtained 3-substituted indoles **7** are particularly good given that they refer to four synthetic operations. The diastereomeric ratio for compounds **7** is generally rather modest in most of the prepared products. Ethyl 2-(3-indolyl)-3-nitroalkanoates **7** obtained by this procedure find several applications as pivotal intermediates for the synthesis of tryptamine derivatives **12** easily obtainable by simple reduction of the nitro group (Scheme 4). Tryptamines are, in turn, starting materials for the preparation of tetrahydro β-carbolines **13** exploiting a Pictet–Spengler reaction with carbonyl derivatives.[18] Compounds **13** can be easily conveted into β-carboline alkaloids **14** by a final oxidative aromatization.[7b]

However, we were attracted by the possibility, offered by the presence of the nitro group at the β-position, of introducing a further unsaturation in the alkyl framework thus generating an α,β-unsaturated ester. Elimination of nitrous acid from 3-nitro esters is a common practice in many synthetic processes and can be easily carried out under basic conditions.[19] As testified by the high yields obtained in the conjugate additions of indoles **5** to ethyl 3-nitro-2-alkenoates **1**, basic alumina is practically unable to provide this elimination (Table 1). The basic character of alumina can be enhanced upon addition of KF but this operation provides only a modest result in the elimination of nitrous acid from indole **7h** (Table 3, entry 1).[20]

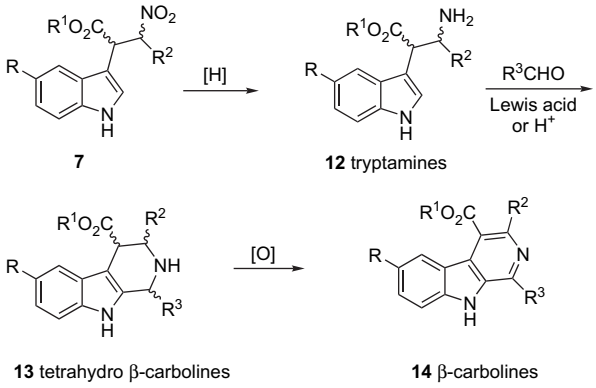
A survey of other base/solvent combinations running under homogeneous conditions, allowed us to identify tetramethylguanidine (TMG) as the best promoter for elimination of nitrous acid from 3-substituted indoles **7h** (Table 3, entry 3). This base gives satisfactory results with most of the nitro esters **7** leading to the corresponding α,β-unsaturated esters **15** in good yields (Table 4). The only disappointing result is obtained using ethyl 2-(3-indolyl)-3-nitropropanoate **7g**. Since it is unsubstituted at the 3-position it probably gives a rather unstable alkenoate **15g** that is difficult to recover in pure form. A considerable level of diastereoselectivity is also observed in compound **15** with the *E* stereoisomer largely prevalent. The *E* stereochemistry of the double bond has been assigned by evaluating the NOE effect by irradiation of the methyl

Table 2
Synthesis of ethyl 2-(3-indolyl)-3-nitroalkanoates **7** by conjugate addition of indoles **5** to ethyl 3-nitro-2-alkenoates obtained from their remote precursors under heterogeneous conditions



Entry	R^1	R^2	R^3	Reaction time (h)				Yield[a] (%)	Diastereomeric ratio[c]
				10	**11**	**7**			
1	Me	H	H	17	1	5.5	**7a**	56	1:1
2	*n*-Pr	H	OMe	16	1	6.5	**7b**	57	3:2
3	$CH_3(CH_2)_3$	H	H	16	1.5	5	**7c**	55	3:1
4	$CH_3(CH_2)_3$	Me	H	16	1.5	2	**7d**	56	3:1
5	$AcO(CH_2)_3$	H	OMe	16	1	3	**7e**	55	1:1
6	Me	H	OMe	18	1	6	**7f**	55	3:1
7	H	H	H	—	—	1.5	**7g**	80[b]	—
8	Et	Me	H	18	1	1.5	**7h**	53	4:1
9	$CH_3(CH_2)_4$	H	H	17	1.5	8	**7i**	51	3:1
10	$Ph(CH_2)_2$	Me	H	17	1	2.5	**7j**	55	3:2
11	$Ph(CH_2)_2$	H	OMe	17	1	5	**7k**	56	3:2

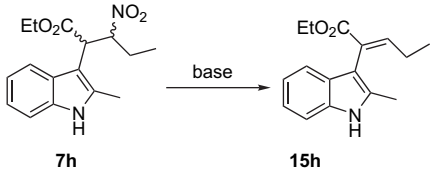
[a] Yield of pure isolated product after three steps.
[b] Yield of pure isolated product **7g** (methyl ester) starting from compound **11g** (methyl ester) and indole.
[c] Diastereomeric ratio was evaluated by ^{1}H NMR spectroscopy.



Scheme 4.

signal in compound **15a**. The enhancement of the peak intensity of protons at C-2 and C-4 of the indole ring reveals a proximity effect with the methyl group that is compatible with the *E* stereochemistry. The chemical shift of the vinyl protons for the *E* stereoisomer is always downfield relative to those of the *Z* in compounds **15** and this correlates with the values reported for a similar derivative bearing a phenyl group instead of the indole ring.[21] Finally, these

Table 3
Screening of different base/solvent combinations for elimination of nitrous acid from ethyl 2-(3-indolyl)-3-nitroalkanoates **7**



Entry	Reaction conditions	Reaction time (h)	Yield[a] (%)
1	KF/basic Al_2O_3, THF, reflux[b]	2.5	44
2	2 equiv DBU, MeCN, rt	1.5	52
3	2 equiv TMG, MeCN, rt	17	84
4	2 equiv Bu_3P, MeCN, rt	No reaction	

[a] Yield of pure isolated product.
[b] 1.2 g of solid base/mmol of substrate was employed.

Table 4
Synthesis of ethyl 2-(3-indolyl)-2-alkenoates **15** by TMG promoted elimination of nitrous acid from ethyl 2-(3-indolyl)-3-nitroalkanoates **7**

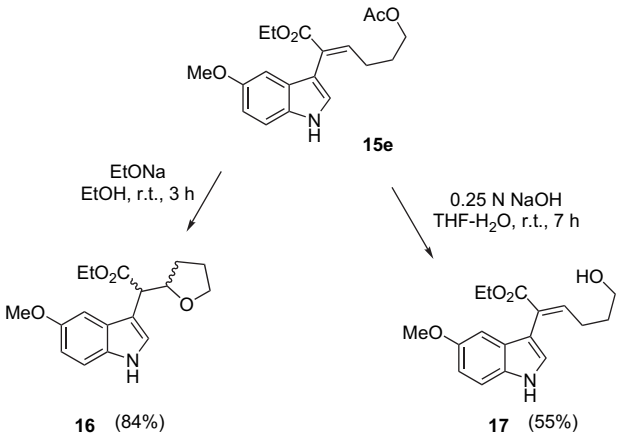
Entry	Nitro ester **7**	Product **15**	Reaction time (h)	Yield[a] (%)	*E*:*Z*[c]
1	**7a**	**15a**	4	85	94:6
2	**7b**	**15b**	4.5	93	94:6
3	**7c**	**15c**	6	97	92:8
4	**7d**	**15d**	14	80	95:5
5	**7e**	**15e**	2	91	95:5
6	**7f**	**15f**	2	95	96:4
7	**7g**	**15g**	2	20[b]	—
8	**7h**	**15h**	17	84	96:4
9	**7i**	**15i**	12	76	93:7
10	**7j**	**15j**	7	90	93:7
11	**7k**	**15k**	2	96	95:5

[a] Yield of pure isolated product.
[b] Extensive product decomposition is observed soon after isolation.
[c] Diastereomeric ratio was evaluated by ^{1}H NMR spectroscopy.

results are consistent with those obtained in a related process involving a tandem conjugate addition of nitroalkanes to dialkyl 2-butenedioates followed by elimination of nitrous acid.[19] Unsaturated esters of type **15** are rather uncommon, but according to their structural features these derivatives are possible candidates for conjugate additions with external nucleophiles or involved in intramolecular processes.

As a matter of fact, ethanolysis of the acetoxy group in compound **15e** is followed by a ring closure leading to the formation of a tetrahydrofuran derivative **16** by an oxy-Michael process (Scheme 5).

Alternatively, chemoselective hydrolysis of the acetoxy group in compound **15e** leads to ester **17** in which the free hydroxy group is amenable to further synthetic transformations. A further synthetic option concerning compounds **15** could involve their utilization as dienes in Diels–Alder reactions. Indeed, the modest aromaticity



Scheme 5.

level of the pyrrole nucleus in the indole system usually makes 3-vinylindole derivatives suitable substrates in the inter- or intramolecular reaction with reactive dienophiles.[22]

3. Conclusions

Organic reactions working under heterogeneous conditions are usually featured by reduced solvent consumption, simplified work-up procedures, and waste minimization. Application of these principles to the preparation of ethyl 2-(3-indolyl)-3-nitroalkanoates involves a three-step procedure in which two macroreticular resins and a solid base are employed to produce four synthetic transformations. The same solvent is used for the first two synthetic operations, while the third one is carried out under solventless conditions. Filtrations and solvent evaporation are the only work-up procedures required until column chromatography leading to pure ethyl 2-(3-indolyl)-3-nitroalkanoates that are important intermediates for the synthesis of tryptamines and carboline alkaloids. A stereoselective base promoted elimination of nitrous acid from these nitro esters allows a direct access to ethyl (*E*)-2-(3-indolyl)-2-alkenoates that are amenable to further synthetic transformations.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at 400 MHz on a Varian Mercury Plus 400 in $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ as solvent. Microanalyses were performed with a CHNS-O analyzer Model EA 1108 from Fisons Instruments. IR spectra were recorded with a Perkin–Elmer Paragon 500 FT-IR. All chemicals used are commercial. β-Nitroacrylates **1**[12] and 4-nitrobutyl acetate **8j**[23] were prepared as previously reported. Commercial basic alumina (Fluka) was activated by heating at 150 °C/1 mmHg for 5 h before utilization. Potassium fluoride on basic alumina was prepared using commercial basic alumina (Baker) following the Bergbreiter's procedure.[24]

4.2. General procedure for the preparation of ethyl 2-(3-indolyl)-3-nitroalkanoates 7

To a stirred solution of ethyl oxoacetate **9a** (50% in toluene, 3 mmol, 0.6 mL) and nitroalkane **8** (3.3 mmol) in EtOAc (1 mL), Amberlyst A21 (0.825 g) was added at room temperature. The heterogeneous solution was stirred for the appropriate time (see Table 2) and the catalyst was then filtered off and washed with EtOAc (3×4 mL). The combined organic solutions were treated with Ac_2O (5 mmol, 0.51 g, 0.47 mL) and Amberlyst 15 (1.5 g). The resulting mixture was stirred at room temperature for the appropriate time (see Table 2) and the resin was filtered off and washed with EtOAc (3×6 mL). The crude product **11** obtained after removal of the solvent and excess of Ac_2O was mixed with indole **5** (2.5 mmol) and activated basic alumina (3 g) and then vigorously stirred at 60 °C. After the reaction was complete (see Table 2), the solid mixture upon cooling was directly charged on a chromatography column and eluted (hexanes/ethyl acetate 9:1) to afford pure product **7**.

4.2.1. Ethyl 2-(1H-3-indolyl)-3-nitrobutanoate, ***7a***

Yield: 56% (diastereomeric ratio 1:1). Viscous red oil. IR (cm^{-1}, neat): 1360, 1557, 1732, 3410. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.17 (t, 1.5H, J=7.3 Hz), 1.21 (t, 1.5H, J=7.3 Hz), 1.40 (d, 1.5H, J=6.8 Hz), 1.73 (d, 1.5H, J=6.4 Hz), 4.01–4.27 (m, 2H), 4.45–4.53 (m, 1H), 5.29–5.40 (m, 1H), 7.09–7.27 (m, 3H), 7.28–7.32 (m, 0.5H), 7.34–7.38 (m, 0.5H), 7.66–7.74 (m, 1H), 8.68 (br s, 0.5H), 8.82 (br s, 0.5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.2, 14.3, 18.4, 18.6, 47.4, 48.0, 61.9, 62.0, 83.7, 85.0, 107.8, 108.2, 111.8, 112.0, 119.0, 119.1, 120.3, 120.5, 122.7, 122.9, 124.0, 124.1, 126.1, 126.2, 136.3, 136.6, 170.7, 171.8. GC–MS (70 eV): m/z: 276 (M^+), 229, 202, 174, 157 (100), 130. Anal. Calcd for $C_{14}H_{16}N_2O_4$ (276.29): C, 60.86; H, 5.84; N, 10.14. Found: C, 61.04; H, 5.89; N, 10.12.

4.2.2. Ethyl 2-(5-methoxy-1H-3-indolyl)-3-nitrohexanoate, ***7b***

Yield: 57% (diastereomeric ratio 3:2). Yellow solid; mp 87–91 °C. IR (cm^{-1}, Nujol): 1377, 1556, 1728, 3402. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.77 (t, 1.8H, J=7.3 Hz), 0.98 (t, 1.2H, J=7.3 Hz), 1.12–1.51 (m, 5H), 1.58–1.78 (m, 1H), 1.83–1.94 (m, 0.4H), 2.03–2.19 (m, 0.6H), 3.86 (s, 1.8H), 3.87 (s, 1.2H), 4.00–4.26 (m, 2H), 4.39 (d, 0.4H, J=10.7 Hz), 4.47 (d, 0.6H, J=11.5 Hz), 5.21–5.32 (m, 1H), 6.84 (dd, 0.4H, J=2.2, 8.6 Hz), 6.89 (dd, 0.6H, J=2.2, 8.6 Hz), 7.10–7.17 (m, 2H), 7.19 (d, 0.4H, J=9.0 Hz), 7.27 (d, 0.6H, J=8.6 Hz), 8.32 (br s, 0.4H), 8.46 (br s, 0.6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.4, 13.5, 14.1, 14.2, 18.6, 19.5, 33.8, 34.9, 46.4, 47.4, 56.0, 56.1, 61.8, 88.0, 89.9, 100.6, 100.8, 107.9, 108.1, 112.3, 112.6, 113.0, 113.3, 124.3, 126.6, 126.7, 131.3, 131.5, 154.6, 154.7, 170.7, 171.5. GC–MS (70 eV): m/z: 334 (M^+), 287, 232 (100), 214, 186, 160, 115, 29. Anal. Calcd for $C_{17}H_{22}N_2O_5$ (334.37): C, 61.07; H, 6.63; N, 8.38. Found: C, 60.93; H, 6.80; N, 8.16.

4.2.3. Ethyl 2-(1H-3-indolyl)-3-nitroheptanoate, ***7c***

Yield: 55% (diastereomeric ratio 3:1). Yellow solid; mp 70–75 °C. IR (cm^{-1}, Nujol): 1365, 1552, 1733, 3405. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.74 (t, 2.4H, J=7.3 Hz), 0.92 (t, 0.6H, J=7.3 Hz), 1.00–1.49 (m, 7H), 1.61–1.78 (m, 1.8H), 1.89–2.01 (m, 0.1H), 2.06–2.21 (m, 0.1H), 3.99–4.27 (m, 2H), 4.44 (d, 0.2H, J=10.7 Hz), 4.53 (d, 0.8H, J=11.1 Hz), 5.24–5.34 (m, 1H), 7.10–7.28 (m, 3H), 7.33 (d, 0.2H, J=8.1 Hz), 7.40 (d, 0.8H, J=8.1 Hz), 7.68–7.76 (m, 1H), 8.26 (br s, 0.2H), 8.36 (br s, 0.8H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.8, 13.9, 14.1, 14.2, 22.0, 22.1, 27.2, 28.2, 31.6, 32.6, 46.4, 47.5, 61.8, 88.2, 90.2, 108.3, 108.6, 111.6, 111.8, 119.1, 119.2, 120.4, 120.6, 122.8, 123.0, 123.7, 123.8, 126.1, 136.2, 136.4, 170.7, 171.5. GC–MS (70 eV): m/z: 318 (M^+), 271, 242, 225, 202 (100), 156, 130. Anal. Calcd for $C_{17}H_{22}N_2O_4$ (318.37): C, 64.14; H, 6.96; N, 8.80. Found: C, 64.20; H, 7.02; N, 8.74.

4.2.4. Ethyl 2-(2-methyl-1H-3-indolyl)-3-nitroheptanoate, ***7d***

Yield: 56% (diastereomeric ratio 3:1). Yellow oil. IR (cm^{-1}, neat): 1369, 1554, 1730, 3399. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.77 (t, 2.25H, J=6.8 Hz), 0.93 (t, 0.75H, J=6.8 Hz), 1.00–1.51 (m, 7H), 1.56–1.68 (m, 1.75H), 1.97–2.16 (m, 0.25H), 2.36 (s, 0.75H), 2.48 (s, 2.25H), 3.97–4.25 (m, 2H), 4.31 (d, 0.25H, J=11.1 Hz), 4.49 (d, 0.75H, J=11.1 Hz), 5.42–5.53 (m, 1H), 7.05–7.32 (m, 3H), 7.61 (d, 0.75H, J=7.7 Hz), 7.70–

7.74 (m, 0.25H), 7.94 (br s, 0.25H), 8.07 (br s, 0.75H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 11.9, 12.3, 13.8, 14.0, 14.2, 14.3, 22.1, 22.2, 27.3, 28.3, 31.6, 33.1, 46.1, 47.4, 61.7, 87.0, 88.9, 103.9, 104.0, 110.7, 110.9, 118.8, 119.0, 120.2, 120.4, 121.7, 122.0, 126.7, 134.1, 134.4, 135.3, 135.5, 170.5, 171.2. GC–MS (70 eV): *m*/*z*: 332 (M^+), 286, 216 (100), 170, 146. Anal. Calcd for $C_{18}H_{24}N_2O_4$ (332.39): C, 65.04; H, 7.28; N, 8.43. Found: C, 65.00; H, 7.25; N, 8.47.

4.2.5. Ethyl 6-(acetyloxy)-2-(5-methoxy-1H-3-indolyl)-3-nitrohexanoate, **7e**

Yield: 55% (diastereomeric ratio 1:1). Yellow viscous oil. IR (cm^{-1}, neat): 1370, 1551, 1727, 3416. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.17 (t, 1.65H, *J*=7.3 Hz), 1.22 (t, 1.35H, *J*=7.3 Hz), 1.48–1.61 (m, 0.55H), 1.63–1.86 (m, 2.45H), 1.83 (s, 1.65H), 1.97–2.10 (m, 0.45H), 2.06 (s, 1.35H), 2.13–2.26 (m, 0.55H), 3.86 (s, 1.65H), 3.87 (s, 1.35H), 3.91 (t, 1.10H, *J*=6.4 Hz), 4.00–4.26 (m, 2.90H), 4.40 (d, 0.45H, *J*=10.7 Hz), 4.47 (d, 0.55H, *J*=11.1 Hz), 5.21–5.32 (m, 1H), 6.85 (dd, 0.45H, *J*=2.6, 9.0 Hz), 6.89 (dd, 0.55H, *J*=2.4, 8.8 Hz), 7.09 (d, 0.55H, *J*=2.2 Hz), 7.12–7.17 (m, 1.45H), 7.21 (d, 0.45H, *J*=8.5 Hz), 7.27 (d, 0.55H, *J*=9.0 Hz), 8.22 (br s, 0.45H), 8.32 (br s, 0.55H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1, 14.2, 20.8, 21.1, 24.5, 25.4, 28.3, 29.5, 46.2, 47.3, 56.0, 61.9, 62.9, 63.2, 87.4, 89.6, 100.5, 100.7, 107.6, 107.9, 112.3, 112.6, 113.1, 113.5, 124.3, 124.4, 126.5, 131.3, 131.5, 154.6, 154.8, 170.5, 171.1, 171.2. GC–MS (70 eV): *m*/*z*: 392 (M^+), 345, 273, 232 (100), 212, 186, 160, 43. Anal. Calcd for $C_{19}H_{24}N_2O_7$ (392.40): C, 58.16; H, 6.16; N, 7.14. Found: C, 58.34; H, 6.20; N, 7.12.

4.2.6. Ethyl 2-(5-methoxy-1H-3-indolyl)-3-nitrobutanoate, **7f**

Yield: 55% (diastereomeric ratio 3:1). Viscous yellow oil. IR (cm^{-1}, neat): 1372, 1550, 1733, 3409. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.18 (t, 1.05H, *J*=7.3 Hz), 1.23 (t, 1.95H, *J*=7.3 Hz), 1.42 (d, 1.05H, *J*=6.8 Hz), 1.73 (d, 1.95H, *J*=6.8 Hz), 3.86 (s, 1.05H), 3.87 (s, 1.95H), 4.02–4.27 (m, 2H), 4.41–4.46 (m, 1H), 5.25–5.35 (m, 1H), 6.82–6.93 (m, 1H), 7.09–7.28 (m, 3H), 8.29 (br s, 0.65H), 8.39 (br s, 0.35H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1, 14.2, 18.3, 18.5, 47.3, 47.9, 56.0, 56.1, 61.8, 61.9, 83.5, 84.9, 100.6, 107.7, 108.2, 112.4, 112.6, 113.1, 113.3, 124.3, 124.4, 126.6, 131.3, 131.5, 154.6, 154.7, 170.6, 171.5. GC–MS (70 eV): *m*/*z*: 306 (M^+), 259, 232, 204, 187 (100), 172, 160, 144, 115, 29. Anal. Calcd for $C_{15}H_{18}N_2O_5$ (306.31): C, 58.82; H, 5.92; N, 9.15. Found: C, 58.63; H, 5.86; N, 9.07.

4.2.7. Methyl 2-(1H-3-indolyl)-3-nitropropanoate, **7g**

Yield: 80%. Yellow oil. IR (cm^{-1}, neat): 1368, 1554, 1733, 3401. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.74 (s, 3H), 4.65 (dd, 1H, *J*=5.1, 14.5 Hz), 4.74–4.80 (m, 1H), 5.21 (dd, 1H, *J*=9.8, 14.5 Hz), 7.13 (d, 1H, *J*=3.0 Hz), 7.16–7.21 (m, 1H), 7.23–7.28 (m, 1H), 7.36–7.40 (m, 1H), 7.65 (dd, 1H, *J*=0.9, 7.7 Hz), 8.32 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 40.8, 53.0, 75.4, 108.0, 111.8, 118.7, 120.7, 123.1, 123.2, 125.8, 136.4, 171.9. GC–MS (70 eV): *m*/*z*: 248 (M^+), 201, 160, 143 (100), 115. Anal. Calcd for $C_{12}H_{12}N_2O_4$ (248.23): C, 58.06; H, 4.87; N, 11.29. Found: C, 58.21; H, 4.95; N, 11.24.

4.2.8. Ethyl 2-(2-methyl-1H-3-indolyl)-3-nitropentanoate, **7h**

Yield: 53% (diastereomeric ratio 4:1). Yellow oil. IR (cm^{-1}, neat): 1375, 1340, 1551, 1731, 3400. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.87 (t, 2.4H, *J*=7.3 Hz), 1.04–1.24 (m, 3.6H), 1.56–1.89 (m, 1H), 2.02–2.26 (m, 1H), 2.32 (s, 0.6H), 2.45 (s, 2.4H), 3.93–4.30 (m, 2H), 4.36 (d, 0.2H, *J*=11.7 Hz), 4.55 (d, 0.8H, *J*=10.6 Hz), 5.39–5.56 (m, 1H), 7.05–7.34 (m, 3H), 7.57–7.69 (m, 0.8H), 7.72–7.82 (m, 0.2H), 8.18 (br s, 0.2H), 8.38 (br s, 0.8H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 9.7, 10.6, 11.5, 11.9, 14.0, 14.1, 25.2, 26.7, 45.6, 47.1, 61.6, 88.2, 90.4, 103.5, 103.6, 110.8, 110.9, 118.5, 118.8, 119.9, 120.2, 121.4, 121.8, 126.5, 126.6, 134.3, 134.5, 135.3, 135.4, 170.4, 171.3. GC–MS (70 eV): *m*/*z*: 304 (M^+), 216, 185, 170, 146 (100), 128, 115. Anal. Calcd for $C_{16}H_{20}N_2O_4$ (304.34): C, 63.14; H, 6.62; N, 9.20. Found: C, 63.41; H, 6.72; N, 9.16.

4.2.9. Ethyl 2-(1H-3-indolyl)-3-nitrooctanoate, **7i**

Yield: 51% (diastereomeric ratio 3:1). White solid; mp 98–104 °C. IR (cm^{-1}, Nujol): 1362, 1557, 1729, 3417. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.77 (t, 2.1H, *J*=6.8 Hz), 0.90 (t, 0.9H, *J*=6.8 Hz), 0.98–1.50 (m, 9H), 1.60–1.78 (m, 1.7H), 1.89–2.01 (m, 0.15H), 2.07–2.22 (m, 0.15H), 4.00–4.26 (m, 2H), 4.44 (d, 0.3H, *J*=10.7 Hz), 4.54 (d, 0.7H, *J*=11.1 Hz), 5.25–5.35 (m, 1H), 7.11–7.29 (m, 3H), 7.32 (d, 0.3H, *J*=8.1 Hz), 7.39 (d, 0.7H, *J*=8.1 Hz), 7.68–7.77 (m, 1H), 8.30 (br s, 0.3H), 8.40 (br s, 0.7H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.0, 14.1, 14.2, 14.3, 22.4, 22.5, 24.9, 25.8, 31.0, 31.2, 31.9, 33.0, 46.5, 47.6, 61.9, 88.3, 90.3, 108.3, 108.5, 111.7, 111.9, 119.2, 120.4, 120.6, 122.8, 123.0, 123.8, 123.9, 126.2, 136.2, 136.5, 170.8, 171.6. GC–MS (70 eV): *m*/*z*: 332 (M^+), 285, 239, 212, 202 (100), 156, 130, 29. Anal. Calcd for $C_{18}H_{24}N_2O_4$ (332.39): C, 65.04; H, 7.28; N, 8.43. Found: C, 64.88; H, 7.21; N, 8.32.

4.2.10. Ethyl 2-(2-methyl-1H-3-indolyl)-3-nitro-5-phenylpentanoate, **7j**

Yield: 55% (diastereomeric ratio 3:2). Viscous yellow oil. IR (cm^{-1}, neat): 1372, 1552, 1727, 3402. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.11–1.17 (m, 3H), 1.88–2.03 (m, 1H), 2.29–2.83 (m, 3H), 2.36 (s, 1.8H), 2.37 (s, 1.2H), 3.97–4.08 (m, 1H), 4.10–4.21 (m, 1H), 4.34 (d, 0.4H, *J*=11.1 Hz), 4.55 (d, 0.6H, *J*=11.1 Hz), 5.44–5.58 (m, 1H), 6.89–6.94 (m, 1H), 7.03–7.38 (m, 7H), 7.52 (d, 0.6H, *J*=7.7 Hz), 7.62–7.67 (m, 0.4H), 7.96 (br s, 0.4H), 8.06 (br s, 0.6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 11.8, 12.2, 14.1, 14.2, 31.4, 32.4, 33.4, 35.0, 45.9, 47.3, 61.7, 86.2, 88.3, 103.6, 103.7, 110.7, 110.8, 118.6, 118.9, 120.2, 120.4, 121.7, 122.0, 126.5, 126.6, 126.7, 128.5, 128.6, 128.8, 134.0, 134.4, 135.3, 135.4, 139.6, 139.9, 170.3, 171.1. GC–MS (70 eV): *m*/*z*: 380 (M^+), 260, 216, 170 (100), 146, 129, 91. Anal. Calcd for $C_{22}H_{24}N_2O_4$ (380.44): C, 69.46; H, 6.36; N, 7.36. Found: C, 69.79; H, 6.46; N, 7.38.

4.2.11. Ethyl 2-(5-methoxy-1H-3-indolyl)-3-nitro-5-phenylpentanoate, **7k**

Yield: 56% (diastereomeric ratio 3:2). Yellow waxy solid. IR (cm^{-1}, Nujol): 1372, 1548, 1731, 3414. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.14–1.21 (m, 3H), 1.96–2.11 (m, 1H), 2.20–2.31 (m, 0.6H), 2.38–2.57 (m, 1H), 2.62–2.78 (m, 1.4H), 3.83 (s, 1.8H), 3.85 (s, 1.2H), 3.99–4.23 (m, 2H), 4.42 (d, 0.4H, *J*=10.7 Hz), 4.51 (d, 0.6H, *J*=11.1 Hz), 5.23–5.31 (m, 1H), 6.82–7.35 (m, 9H), 8.17 (br s, 0.4H), 8.22 (br s, 0.6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.2, 14.3, 31.5, 32.3, 33.5, 34.5, 46.4, 47.5, 56.0, 56.1, 61.9, 87.1, 89.4, 100.6, 100.7, 107.7, 108.1, 112.4, 112.6, 113.3, 113.6, 124.2, 124.3, 126.6, 126.7, 128.6, 128.7, 128.8, 128.9, 131.3, 131.5, 139.6, 139.7, 154.7, 154.8, 170.5, 171.3. GC–MS (70 eV): *m*/*z*: 396 (M^+), 349, 276, 258, 232 (100), 186, 154, 117, 91. Anal. Calcd for $C_{22}H_{24}N_2O_5$ (396.44): C, 66.65; H, 6.10; N, 7.07. Found: C, 66.91; H, 6.19; N, 7.01.

4.3. Ethyl 2-(acetyloxy)-3-nitro-5-phenylpentanoate, 11k

To a stirred solution of nitro alcohol **10k**[12c] (1 mmol, 0.25 g) in ethyl acetate (4 mL), Ac_2O (1.5 mmol, 0.15 g, 0.14 mL) and Amberlyst 15 (0.45 g) were successively added at room temperature. The resulting mixture was stirred at the same temperature for 1 h and then the resin was filtered off and washed with EtOAc (3×3 mL). The crude product obtained after removal of the solvent and excess of Ac_2O was purified by column chromatography (hexanes/ethyl acetate 8:2) leading to 0.3 g of acetoxy derivative **11k** as a yellow oil (yield 97%). IR (cm^{-1}, neat): 1369, 1553, 1621, 1726. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.96 (t, 1.5H, *J*=7.3 Hz), 1.96 (t, 1.5H, *J*=7.3 Hz), 2.00–2.15 (m, 1H), 2.12 (s, 1.5H), 2.13 (s, 1.5H), 2.40–2.52 (m, 0.5H), 2.54–2.87 (m, 2.5H), 4.10–4.29 (m, 2H), 4.75–4.82 (m, 0.5H), 4.83–4.90 (m, 0.5H), 5.37 (d, 0.5H, *J*=6.0 Hz), 5.59 (d, 0.5H, *J*=3.4 Hz), 7.11–7.18 (m, 2H), 7.19–7.33 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.0, 14.1, 20.4, 20.5, 30.3, 31.0, 31.8, 32.0, 62.6, 62.7, 71.6, 71.7, 85.3, 85.5,

126.8, 126.9, 128.5, 128.6, 128.9, 129.0, 139.1, 139.3, 166.0, 166.4, 169.5, 169.7.

4.4. General procedure for the preparation of ethyl 2-(3-indolyl)-2-alkenoates 15

To a stirred solution of product **7** (2 mmol) in acetonitrile (10 mL), TMG (4 mmol) was added and the solution was stirred at room temperature for the appropriate time (see Table 4). After removal of the solvent at reduced pressure, the crude product was purified by flash chromatography (hexanes/ethyl acetate 95:5) affording the pure product **15**.

4.4.1. Ethyl (E)-2-(1H-3-indolyl)-2-butenoate, ***15a***

Yield: 85%. Yellow oil. IR (cm^{-1}, neat): 1628, 1695, 3401. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.28 (t, 3H, J=7.3 Hz), 1.81 (d, 3H, J=6.9 Hz), 4.25 (q, 2H, J=7.3 Hz), 7.03 (d, 1H, J=2.6 Hz), 7.09–7.22 (m, 2H), 7.26 (q, 1H, J=7.3 Hz), 7.32 (d, 1H, J=7.7 Hz), 7.40 (d, 1H, J=7.7 Hz), 8.38 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.5, 16.3, 61.0, 110.0, 111.5, 119.8, 120.2, 122.0, 124.7, 127.2, 127.7, 135.9, 140.5, 168.2. GC–MS (70 eV): m/z: 229 (M^+), 200, 183, 155 (100), 154, 129, 77. Anal. Calcd for $C_{14}H_{15}NO_2$ (229.27): C, 73.34; H, 6.59; N, 6.11. Found: C, 73.56; H, 6.51; N, 6.16.

4.4.2. Ethyl (E)-2-(5-methoxy-1H-3-indolyl)-2-hexenoate, ***15b***

Yield: 93%. Yellow oil. IR (cm^{-1}, neat): 1626, 1700, 3402. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.87 (t, 3H, J=7.7 Hz), 1.23 (t, 3H, J=7.3 Hz), 1.39–1.52 (m, 2H), 2.15 (q, 2H, J=7.3 Hz), 3.81 (s, 3H), 4.23 (q, 2H, J=7.3 Hz), 6.79–6.87 (m, 2H), 7.03 (d, 1H, J=2.6 Hz), 7.14 (t, 1H, J=7.7 Hz), 7.21 (d, 1H, J=8.5 Hz), 8.40 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1, 14.6, 22.5, 32.3, 56.0, 61.0, 101.7, 110.3, 112.2, 112.5, 125.3, 126.8, 127.9, 131.1, 145.9, 154.4, 168.4. GC–MS (70 eV): m/z: 287 (M^+), 258, 212 (100), 198, 184, 172, 154, 142, 128, 115, 29. Anal. Calcd for $C_{17}H_{21}NO_3$ (287.35): C, 71.06; H, 7.37; N, 4.87. Found: C, 71.15; H, 7.41; N, 4.90.

4.4.3. Ethyl (E)-2-(1H-3-indolyl)-2-heptenoate, ***15c***

Yield: 97%. Yellow oil. IR (cm^{-1}, neat): 1633, 1694, 3404. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.82 (t, 3H, J=7.3 Hz), 1.21–1.48 (m, 4H), 1.27 (t, 3H, J=7.3 Hz), 2.18 (q, 2H, J=7.3 Hz), 4.24 (q, 2H, J=7.3 Hz), 7.04 (d, 1H, J=2.6 Hz), 7.09–7.23 (m, 3H), 7.33 (d, 1H, J=8.1 Hz), 7.40 (d, 1H, J=8.1 Hz), 8.30 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1, 14.5, 22.6, 30.0, 31.4, 61.0, 110.6, 111.4, 119.9, 120.2, 122.1, 124.4, 126.5, 127.5, 135.9, 146.1, 168.3. GC–MS (70 eV): m/z: 271 (M^+, 100), 242, 225, 196, 182, 168, 154, 142, 127, 115, 29. Anal. Calcd for $C_{17}H_{21}NO_2$ (271.35): C, 75.25; H, 7.80; N, 5.16. Found: C, 75.54; H, 7.89; N, 5.11.

4.4.4. Ethyl (E)-2-(2-methyl-1H-3-indolyl)-2-heptenoate, ***15d***

Yield: 80%. Yellow solid; mp 55–57 °C. IR (cm^{-1}, Nujol): 1624, 1688, 3347. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.80 (t, 3H, J=7.3 Hz), 1.17–1.30 (m, 2H), 1.24 (t, 3H, J=7.3 Hz), 1.33–1.46 (m, 2H), 1.97–2.11 (m, 2H), 2.21 (s, 3H), 4.20 (q, 2H, J=7.3 Hz), 7.03–7.14 (m, 2H), 7.19–7.30 (m, 3H), 8.04 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.6, 14.0, 14.5, 22.5, 29.8, 30.9, 60.8, 107.7, 110.5, 119.1, 119.6, 121.1, 126.3, 128.8, 133.3, 135.4, 147.7, 168.1. GC–MS (70 eV): m/z: 285 (M^+), 212, 196 (100), 168, 154, 29. Anal. Calcd for $C_{18}H_{23}NO_2$ (285.38): C, 75.76; H, 8.12; N, 4.91. Found: C, 75.61; H, 8.41; N, 4.91.

4.4.5. Ethyl (E)-6-(acetyloxy)-2-(5-methoxy-1H-3-indolyl)-2-hexenoate, ***15e***

Yield: 91%. Yellow oil. IR (cm^{-1}, neat): 1622, 1701, 1730, 3422. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.27 (t, 3H, J=7.3 Hz), 1.72–1.81 (m, 2H), 1.91 (s, 3H), 2.26 (q, 2H, J=7.3 Hz), 3.81 (s, 3H), 3.99 (t, 2H, J=6.4 Hz), 4.23 (q, 2H, J=7.3 Hz), 6.77 (d, 1H, J=2.6 Hz), 6.84 (dd, 1H, J=2.6, 9.0 Hz), 7.03 (d, 1H, J=2.6 Hz), 7.11 (t, 1H, J=7.7 Hz), 7.22 (d, 1H, J=8.6 Hz), 8.37 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.6, 21.0, 26.8, 28.1, 56.0, 61.2, 64.0, 101.5, 110.0, 112.2, 112.6, 125.2, 127.7, 127.8, 131.0, 144.0, 154.4, 168.1, 171.4. GC–MS (70 eV): m/z: 345 (M^+), 299, 272, 257, 228, 212 (100), 198, 184, 154, 128, 43. Anal. Calcd for $C_{19}H_{23}NO_5$ (345.39): C, 66.07; H, 6.71; N, 4.06. Found: C, 66.27; H, 6.69; N, 4.10.

4.4.6. Ethyl (E)-2-(5-methoxy-1H-3-indolyl)-2-butenoate, ***15f***

Yield: 95%. Yellow oil. IR (cm^{-1}, neat): 1624, 1697, 3400. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.13 (t, 3H, J=7.3 Hz), 1.68 (d, 3H, J=7.3 Hz), 3.66 (s, 3H), 4.08 (q, 2H, J=7.3 Hz), 6.61 (d, 1H, J=2.6 Hz), 6.67 (dd, 1H, J=2.6, 8.6 Hz), 6.97 (d, 1H, J=2.6 Hz), 7.06 (q, 1H, J=7.3 Hz), 7.14 (d, 1H, J=8.9 Hz), 9.68 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.2, 16.0, 55.5, 60.4, 101.3, 108.8, 111.6, 112.1, 125.5, 127.2, 127.7, 130.9, 139.4, 153.6, 167.8. GC–MS (70 eV): m/z: 259 (M^+), 185, 170, 154, 142, 128, 115, 29. Anal. Calcd for $C_{15}H_{17}NO_3$ (259.30): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.33; H, 6.53; N, 5.36.

4.4.7. Ethyl 2-(1H-3-indolyl)acrylate, ***15g***

Yield: 20%. GC–MS (70 eV): m/z: 201 (M^+), 142 (100), 115, 88, 70.

4.4.8. Ethyl (E)-2-(2-methyl-1H-3-indolyl)-2-pentenoate, ***15h***

Yield: 84%. Red waxy solid. IR (cm^{-1}, Nujol): 1622, 1686, 3340. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.99 (t, 3H, J=7.7 Hz), 1.25 (t, 3H, J=7.3 Hz), 1.98–2.12 (m, 2H), 2.18 (s, 3H), 4.22 (q, 2H, J=7.3 Hz), 7.03–7.14 (m, 2H), 7.16–7.31 (m, 3H), 8.14 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.5, 13.3, 14.4, 23.5, 60.8, 107.5, 110.5, 118.9, 119.5, 121.1, 125.9, 128.7, 133.4, 135.4, 148.8, 168.2. GC–MS (70 eV): m/z: 257 (M^+), 182, 168 (100), 154. Anal. Calcd for $C_{16}H_{19}NO_2$ (257.33): C, 74.68; H, 7.44; N, 5.44. Found: C, 74.64; H, 7.46; N, 5.46.

4.4.9. Ethyl (E)-2-(1H-3-indolyl)-2-octenoate, ***15i***

Yield: 76%. Yellow oil. IR (cm^{-1}, neat): 1628, 1700, 3410. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.84 (t, 3H, J=7.3 Hz), 1.16–1.30 (m, 4H), 1.27 (t, 3H, J=7.3 Hz), 1.37–1.49 (m, 2H), 2.17 (q, 2H, J=7.3 Hz), 4.24 (q, 2H, J=7.3 Hz), 7.03 (d, 1H, J=2.6 Hz), 7.09–7.22 (m, 3H), 7.33 (d, 1H, J=8.1 Hz), 7.40 (d, 1H, J=7.7 Hz), 8.31 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.2, 14.5, 22.7, 29.0, 30.3, 31.7, 61.0, 110.6, 111.5, 119.9, 120.2, 122.1, 124.5, 126.5, 127.5, 135.9, 146.3, 168.4. GC–MS (70 eV): m/z: 285 (M^+, 100), 256, 239, 228, 212, 196, 182, 168, 154, 142, 130, 115, 41, 29. Anal. Calcd for $C_{18}H_{23}NO_2$ (285.38): C, 75.76; H, 8.12; N, 4.91. Found: C, 75.77; H, 8.20; N, 4.96.

4.4.10. Ethyl (E)-2-(2-methyl-1H-3-indolyl)-5-phenyl-2-pentenoate, ***15j***

Yield: 90%. Yellow foam. IR (cm^{-1}, neat): 1620, 1683, 3345. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.23 (t, 3H, J=7.7 Hz), 2.16 (s, 3H), 2.28–2.48 (m, 2H), 2.73 (t, 2H, J=7.7 Hz), 4.20 (q, 2H, J=7.3 Hz), 7.00–7.33 (m, 10H), 7.99 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.6, 14.5, 31.8, 35.0, 60.9, 107.6, 110.5, 119.1, 119.7, 121.2, 126.1, 127.0, 128.4, 128.5, 128.6, 133.3, 135.3, 141.3, 146.1, 167.9. GC–MS (70 eV): m/z: 333 (M^+), 242 (100), 214, 168, 154, 91. Anal. Calcd for $C_{22}H_{23}NO_2$ (333.42): C, 79.25; H, 6.95; N, 4.20. Found: C, 79.47; H, 6.99; N, 4.23.

4.4.11. Ethyl (E)-2-(5-methoxy-1H-3-indolyl)-5-phenyl-2-pentenoate, ***15k***

Yield: 96%. Viscous yellow oil. IR (cm^{-1}, neat): 1619, 1702, 3410. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.23 (t, 3H, J=7.3 Hz), 2.47 (q, 2H, J=7.3 Hz), 2.72 (t, 2H, J=7.3 Hz), 3.77 (s, 3H), 4.19 (q, 2H, J=7.3 Hz), 6.73–6.83 (m, 2H), 6.89 (s, 1H), 7.06 (d, 2H, J=7.3 Hz), 7.13 (t, 2H, J=7.3 Hz), 7.17–7.24 (m, 3H), 8.88 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.5, 31.9, 35.3, 55.9, 60.9, 101.5, 109.8, 112.2, 112.3, 125.2, 126.1, 127.4, 127.7, 128.4, 128.5, 131.1, 141.2, 144.1, 154.2, 168.1. GC–MS (70 eV): m/z: 349 (M^+), 258 (100), 184, 91. Anal. Calcd for $C_{22}H_{23}NO_3$ (349.42): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.93; H, 6.69; N, 4.07.

4.5. Ethyl 2-(5-methoxy-1*H*-3-indolyl)-2-tetrahydro-2-furanylacetate 16

Sodium metal (5 mmol, 0.115 g) was dissolved in dry EtOH (7 mL) and then diester **15e** (1 mmol, 0.34 g) dissolved in 2 mL of EtOH was added dropwise at room temperature. After stirring for 3 h at room temperature, 1 M HCl (7 mL) was added and the solution was concentrated under reduced pressure. The resulting aqueous layer was extracted with CH_2Cl_2 (3×15 mL), and the combined organic extracts were dried over Na_2SO_4. The crude product obtained after removal of the solvent at reduced pressure was purified by flash chromatography (hexanes/ethyl acetate 95:5) giving 0.25 g of ester derivative **16** as a white solid (yield 84%), mp 132–135 (d.r=93:7, major diastereomer): IR (cm^{-1}, Nujol): 1217, 1621, 1715, 3350. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.23 (t, 3H, J=7.3 Hz), 1.50–1.62 (m, 1H), 1.74–1.95 (m, 3H), 3.73–3.89 (m, 2H), 3.87 (s, 3H), 3.93–4.00 (m, 1H), 4.08–4.26 (m, 2H), 4.54–4.69 (m, 1H), 6.86 (dd, 1H, J=2.6, 9.0 Hz), 7.16–7.27 (m, 3H), 8.12 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.4, 25.7, 30.1, 49.4, 56.1, 61.1, 68.7, 80.7, 101.2, 110.8, 112.3, 112.8, 123.7, 127.4, 131.4, 154.4, 173.6. GC–MS (70 eV): m/z: 303 (M^+), 233 (100), 204, 187, 160, 71, 43, 29. Anal. Calcd for $C_{17}H_{21}NO_4$ (303.35): C, 67.31; H, 6.98; N, 4.62. Found: C, 67.59; H, 7.05; N, 4.55.

4.6. Ethyl (*E*)-6-hydroxy-2-(5-methoxy-1*H*-3-indolyl)-2-hexenoate 17

A solution of diester **15e** (0.5 mmol, 0.17 g) in THF/water (11 mL, 1:10) was cooled at 0 °C and 0.25 N NaOH (4 mL) was added under stirring. After stirring for 7 h at 0 °C, 1 M HCl was added dropwise until pH=4 and then the solution was extracted with EtOAc (3×20 mL). The combined organic extracts were dried over Na_2SO_4 and the crude product obtained after filtration and removal of the solvent at reduced pressure was purified by flash chromatography (hexanes/ethyl acetate 95:5) giving 0.083 g of hydroxyester derivative **17** as a yellow waxy solid (yield 55%, d.r=94:6, major diastereomer): IR (cm^{-1}, Nujol): 1621, 1701, 3420. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.26 (t, 3H, J=7.3 Hz), 1.59–1.70 (m, 2H), 1.79–1.99 (br s, 1H), 2.23 (q, 2H, J=7.3 Hz), 3.51 (t, 2H, J=6.4 Hz), 3.79 (s, 3H), 4.23 (q, 2H, J=7.3 Hz), 6.78 (d, 1H, J=2.6 Hz), 6.81 (dd, 1H, J=2.6, 9.0 Hz), 6.95 (d, 1H, J=2.6 Hz), 7.11 (t, 1H, J=7.7 Hz), 7.16 (d, 1H, J=9.0 Hz), 8.58 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.5, 26.5, 31.9, 56.0, 61.1, 62.1, 101.5, 109.7, 112.3, 112.4, 125.3, 127.3, 127.6, 131.0, 144.7, 154.2, 168.3. GC–MS (70 eV): m/z: 303 (M^+), 257 (100), 230, 212, 198, 184, 154, 128, 115, 29. Anal. Calcd for $C_{17}H_{21}NO_4$ (303.35): C, 67.31; H, 6.98; N, 4.62. Found: C, 66.98; H, 6.89; N, 4.54.

Acknowledgements

Financial support from University of Camerino and MIUR (National Project "Sintesi organiche ecosostenibili mediate da nuovi sistemi catalitici") is gratefully acknowledged.

References and notes

1. (a) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199–1222; For some selected recent examples see: (b) Yang, H.; Hong, Y.-T.; Kim, S. *Org. Lett.* **2007**, *9*, 2281–2284; (c) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029–10041; (d) Kawatsura, M.; Aburatani, S.; Uenishi, J. *Tetrahedron* **2007**, *63*, 4172–4177; (e) Blay, G.; Fernández, I.; Pedro, J. R.; Vila, C. *Org. Lett.* **2007**, *9*, 2601–2604.
2. Adamo, M. F. A.; Konda, V. *Org. Lett.* **2007**, *9*, 303–305.
3. (a) Mahboobi, S.; Wiegrebe, W.; Popp, A. *J. Nat. Prod.* **1999**, *62*, 577–579; (b) Koike, T.; Takeuchi, N.; Hagiwara, M.; Yamazaki, K.; Tobinaga, S. *Heterocycles* **1999**, *51*, 1271–1280; (c) Koike, T.; Hagiwara, M.; Takeuchi, N.; Tobinaga, S. *Heterocycles* **1997**, *45*, 1271–1280.
4. (a) Cao, R.; Peng, W.; Wang, Z.; Xu, A. *Curr. Med. Chem.* **2007**, *14*, 479–500; (b) Czarnocki, Z.; Siwicka, A.; Szawkało, J. *Curr. Org. Synth.* **2005**, *2*, 301–331; (c) Ballini, R.; Marcantoni, E.; Petrini, M. Nitroalkenes as Amination Tools. In *Amino Group Chemistry*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2008; pp 93–148; (d) Sundberg, R. J. *The Chemistry of Indoles*; Academic: New York, NY, 1996; (e) Harada, H.; Hirokawa, Y.; Suzuki, K.; Hiyama, Y.; Oue, M.; Kawashima, H.; Kato, H.; Yoshida, N.; Furutani, Y.; Kato, S. *Chem. Pharm. Bull.* **2005**, *53*, 184–198; (f) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576–6579.
5. Lewandowska, E. *Tetrahedron* **2007**, *63*, 2107–2122.
6. (a) Lewandowska, E. *Tetrahedron* **2006**, *62*, 4879–4883; (b) Ballini, R.; Fiorini, D.; Palmieri, A. *Tetrahedron Lett.* **2005**, *46*, 1245–1246.
7. (a) Ballini, R.; Clemente, R. R.; Palmieri, A.; Petrini, M. *Adv. Synth. Catal.* **2006**, *348*, 191–196; For related processes using acidic activators in the reaction of indoles with methyl β-nitroacrylate see: (b) Bartoli, G.; Bosco, M.; Giuli, S.; Giuliani, A.; Lucarelli, L.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 1941–1944; (c) Murugan, R.; Karthikeyan, M.; Perumal, P. T.; Reddy, B. S. R. *Tetrahedron* **2005**, *61*, 12275–12281.
8. (a) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915–945; (b) Rosini, G. *Comphehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 2, pp 321–340; (c) Rosini, G.; Ballini, R.; Sorrenti, P. *Synthesis* **1983**, 1014–1016; (d) Rosini, G.; Ballini, R.; Petrini, M.; Sorrenti, P. *Synthesis* **1985**, 515–517; For a recent paper see: (e) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A. *Synthesis* **2004**, 1938–1940.
9. Ballini, R.; Castagnani, R.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 2160–2162.
10. (a) Woo, Y.; Lai, D. Y.; Argus, M. F.; Arcos, J. C. *Toxicol. Lett.* **1995**, *79*, 219–228; (b) Talalay, P.; De Long, M. J.; Prochaska, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 8261–8265.
11. (a) Rueck-Braun, K.; Freysoldt, T. H. E.; Wierschem, F. *Chem. Soc. Rev.* **2005**, *34*, 507–516; (b) Sartori, G.; Ballini, R.; Bigi, F.; Bosica, G.; Maggi, R.; Righi, P. *Chem. Rev.* **2004**, *104*, 199–250; (c) Chung, C.; Wan, Y.; Toy, P. H. *Tetrahedron: Asymmetry* **2004**, *15*, 387–399; (d) Valkenberg, M. H.; de Castro, C.; Hoelderich, W. F. *Green Chem.* **2002**, *4*, 88–93; (e) Clark, J. H. *Acc. Chem. Res.* **2002**, *35*, 791–797.
12. (a) Swiderska, M. A.; Stewart, J. D. *Org. Lett.* **2006**, *8*, 6131–6133; (b) Addo, J. K.; Teesdale-Spittle, P.; Hoberg, J. O. *Synthesis* **2005**, 1923–1925; (c) Ballini, R.; Fiorini, D.; Palmieri, A. *Tetrahedron Lett.* **2004**, *45*, 7027–7029.
13. (a) Sohtome, Y.; Takemura, N.; Takada, K.; Takagi, R.; Iguchi, T.; Nagasawa, K. *Chem. Asian J.* **2007**, *2*, 1150–1160; (b) Tosaki, S.; Hara, K.; Gnanadesikan, V.; Morimoto, H.; Harada, S.; Sugita, M.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 11776–11777.
14. (a) Rathgeb, X.; March, S.; Alexakis, A. *J. Org. Chem.* **2006**, *71*, 5737–5742; (b) Woodcock, S. R.; Marwitz, A. J. V.; Bruno, P.; Branchaud, B. P. *Org. Lett.* **2006**, *8*, 3931–3934; (c) Denmark, S. E.; Baiazitov, R. Y. *J. Org. Chem.* **2006**, *71*, 593–605.
15. Pollini, G. P.; Baricordi, N.; Benetti, S.; De Risi, C.; Zanirato, V. *Tetrahedron Lett.* **2005**, *46*, 3699–3701.
16. Ballini, R.; Bosica, G.; Forconi, P. *Tetrahedron* **1996**, *52*, 1677–1684.
17. Ethyl acetate has been recently included among environmentally preferred solvents because of its relatively low volatility and scanty toxicity: (a) Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jennings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C.; Nagy, M. A.; Perry, D. A.; Stefaniak, M. *Green Chem.* **2008**, *10*, 31–36; For a related paper see also: (b) Capello, C.; Fisher, U.; Hungerbühler, K. *Green Chem.* **2007**, *9*, 927–934.
18. (a) Youn, S. W. *Org. Prep. Proc. Int.* **2006**, *38*, 505–591; (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842.
19. (a) Ballini, R.; Rinaldi, A. *Tetrahedron Lett.* **1994**, *35*, 9247–9250; (b) Ballini, R.; Bosica, G. *Tetrahedron* **1995**, *51*, 4213–4222; (c) Ballini, R.; Bosica, G.; Petrelli, L.; Petrini, M. *Synthesis* **1999**, 1236–1240; (d) Ballini, R.; Bosica, G.; Cioci, G.; Fiorini, D.; Petrini, M. *Tetrahedron* **2003**, *59*, 3603–3608.
20. Review: (a) Kabalka, G. W.; Pagni, R. M. *Tetrahedron* **1997**, *53*, 7999–8065; For some recent examples see: (b) Ge, Y.; Hu, L. *Tetrahedron Lett.* **2007**, *48*, 4885–4888; (c) Sharifi, A.; Salimi, R.; Mirzaei, M.; Abaee, M. S. *Synth. Commun.* **2007**, *37*, 1825–1832.
21. Kopinski, R. P.; Pinhey, J. T. *Aust. J. Chem.* **1983**, *36*, 311–316.
22. (a) Joseph, B.; Facompré, M.; Da Costa, H.; Routier, S.; Mérour, J.-Y.; Colson, P.; Houssier, C.; Bailly, C. *Bioorg. Med. Chem.* **2001**, *9*, 1533–1541; (b) Joseph, B.; Da Costa, H.; Mérour, J.-Y.; Léonce, S. *Tetrahedron* **2000**, *56*, 3189–3196; (c) Simoji, Y.; Saito, F.; Tomita, K.; Morisawa, Y. *Heterocycles* **1991**, *32*, 2389–2397.
23. Ballini, R.; Barboni, L.; Giarlo, G. *J. Org. Chem.* **2004**, *69*, 6907–6908.
24. Bergbreiter, D. E.; Lalonde, J. J. *J. Org. Chem.* **1987**, *52*, 1601–1603.