Highly Efficient $InBr_3$ Catalyzed Michael Addition of Indoles to α,β-Unsaturated Esters

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A highly efficient synthetic strategy toward Michael addition of indoles to α,β-unsaturated esters has been developed using Lewis acid $InBr_3$ as catalyst. The reactions generated 3-substituted indoles in high yields with excellent regio-selectivity in the presence of catalytic amount of $InBr_3$ under mild reaction conditions. The method is simple, efficient and practical.

Keywords Michael addition, indole, α,β-unsaturated ester, Lewis acid, $InBr_3$

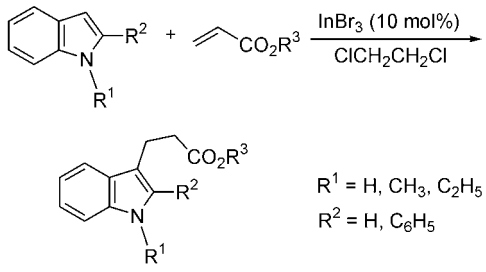
Introduction

Various indole derivatives occur in many pharmacologically and biologically active compounds.[1] Among them, 3-substituted indoles are important building blocks for the synthesis of biologically active compounds and natural products.[2] The Michael addition of indoles to electron-deficient olefins is one of the general and concise routes to 3-substituted indoles. Typically, these conjugate addition reactions are performed under the influence of strong bases, such as alkali metal alkoxides or hydroxides.[3] The strong basic reaction conditions often lead to a number of undesirable side reactions, such as aldol cyclizations, ester solvolysis, and base induced rearrangements such as retro-Claisen or retro-Michael reactions and polymerization reactions. As results, numerous methods have been reported for the conjugate addition of indoles to electron-deficient olefins through the activation of the Michael acceptor in the presence of Lewis acids,[4,5] because Lewis acids have been found to catalyze conjugate addition reactions effectively under mild reaction conditions avoiding undesirable side reaction products along with the 3-substituted indoles.[6,7]

The utility of indium(III) salts as Lewis acids in organic synthesis has received a great deal of interest due to their relatively low toxicity, stability in air and water, recyclability, operational simplicity, strong tolerance to oxygen and nitrogen-containing substrates and functional groups.[8] Their potential as Lewis acid catalysts for fundamental reactions, such as the Diels-Alder,[9] Friedel-Crafts,[10] Mukaiyama aldol,[11] and Sakurai-Hosomi allylation reactions,[12] has been extensively investigated. Most recently, Yadav *et al.*[13] reported an $InCl_3$-catalysed conjugate addition of indoles with electron-deficient olefins, but, olefin substrate was limited to α,β-unsaturated ketones.

In continuation of our efforts in developing selective, efficient, mild and environmental friendly synthetic methodologies for the preparation of heterocycle derivatives,[14] herein, we wish to report an $InBr_3$-catalyzed Michael addition of indoles to various α,β-unsaturated ketones, as well as less active α,β-unsaturated esters procedure for the direct synthesis of 3-substituted indoles under efficient, simple and practical reaction conditions (Scheme 1). In addition, the notable advantages of this methodology are mild condition, short reaction times, high yields and free from any side reaction products.

Scheme 1



Results and discussion

In our preliminarily investigation on the model reaction of *N*-methyl indole with ethyl acrylate, it was found that the reaction could be finished under very simple reaction conditions in the presence of catalytic amount of $InBr_3$ (10 mol%) in the absence of any additive,

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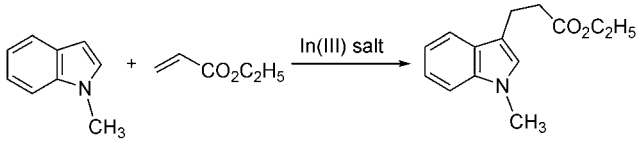
which gives the desired ethyl 3-(1-methyl-1*H*-indol-3-yl)propanoate in 91% yield (Table 1, Entry 1). The effect of solvent, catalyst, reaction temperature and time on the reaction was investigated and the results are summarized in Table 1. As can be seen from Table 1, the solvents play an important role in the reaction. It was found that $ClCH_2CH_2Cl$ is the best solvent among the solvents tested, and the reaction underwent smoothly in $ClCH_2CH_2Cl$ and generated the desired product in 91% yield, while DMF or CH_3CN afforded trace amount of the desired product. Moreover, use of dioxane, CH_3NO_2, toluene, C_2H_5OH and DMSO as solvents led to slower reactions (Table 1, Entries 1—8). Among a variety of catalyst species examined, $InBr_3$ was found to be the most effective one. When using $InCl_3$, $In(OAc)_3$, and $In(OTf)_3$ instead of $InBr_3$ as catalyst, their efficiencies were lower than that of $InBr_3$ for the model reaction (Table 1, Entries 1, and 9—11). It is important to note that no Michael addition product was isolated using $In(OAc)_3$ as catalyst. This clearly demonstrates the great effect of a conjugate anion on the activity of Lewis acid. Most of the reported conjugate additions of heterocyclic enamines, especially indoles have been restricted to highly reactive Michael acceptor, such as *α*,*β*-unsaturated ketones or nitroolefins. We were pleased to find that $InBr_3$ efficiently catalyzed the conjugate addition of indoles to weaker acceptor *α*,*β*-unsaturated esters (Table 1, Entries 1 and 9—11). With respect to the catalyst loading, when less than 10 mol% of $InBr_3$ was used, the reaction did not go to completion, but that a higher loading (more than 10 mol%) of the catalyst gave a satisfactory results (Table 1, Entries 12 and 13).

During the course of our further optimization of the reaction conditions, the reactions were generally complete in a matter of hours, but the time, as expected, was inversely proportional to the temperature. A reaction temperature of 80 ℃ for 12 h was found to be optimal (Table 1, Entries 14—16). Thus, the optimized reaction conditions for the reaction were found to be $InBr_3$ (10 mol%) in $ClCH_2CH_2Cl$ at 80 ℃ for 12 h.

To investigate the generality of this method, the reaction of various indoles and different *α*,*β*-unsaturated esters was examined under the optimized reaction conditions (10 mol% of $InBr_3$, in $ClCH_2CH_2Cl$ at 80 ℃ for 12 h). All of the results are summarized in Table 2. As shown in Table 2, in general, the reactions proceeded smoothly with high selectivities for various indoles with *α*,*β*-unsaturated esters in good to excellent isolated yields (up to 96%, Table 2, Entries 1—11). The process worked noticeably more efficiently for *N*-substituted indole, such as *N*-methyl indole, *N*-ethyl indole, with different *α*,*β*-unsaturated esters and the yields of addition products were excellent (Table 2, Entries 1—3, 7—11 vs. 4—6). In addition, we found that the electron and steric effect of *α*,*β*-unsaturated esters's substituents (alcohol part) had little impact on the yields of the reac-

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst (mol%)	Solvent/Temp. (℃)	Yield[b]/%
1	$InBr_3$ (10)	$ClCH_2CH_2Cl$/80	91
2	$InBr_3$ (10)	DMSO/110	24
3	$InBr_3$ (10)	Toluene/110	59
4	$InBr_3$ (10)	CH_3CN/80	Trace
5	$InBr_3$ (10)	DMF/110	Trace
6	$InBr_3$ (10)	Dioxane/100	73
7	$InBr_3$ (10)	CH_3NO_2/100	66
8	$InBr_3$ (10)	C_2H_5OH/78	44
9	$InCl_3$ (10)	$ClCH_2CH_2Cl$/80	56
10	$In(OAc)_3$ (10)	$ClCH_2CH_2Cl$/80	NR
11	$In(OTf)_3$ (10)	$ClCH_2CH_2Cl$/80	44
12	$InBr_3$ (5)	$ClCH_2CH_2Cl$/80	61
13	$InBr_3$ (15)	$ClCH_2CH_2Cl$/80	91
14	$InBr_3$ (10)	$ClCH_2CH_2Cl$/60	55
15[c]	$InBr_3$ (10)	$ClCH_2CH_2Cl$/60	73
16[d]	$InBr_3$ (10)	$ClCH_2CH_2Cl$/60	90

[a] Reaction conditions: *N*-methyl indole (0.50 mmol), ethyl acrylate (0.50 mmol), In salt (10 mol%), stirred in solvent (1.5 mL) at the temperature indicated in Table 1 for 12 h. [b] Isolated yield. [c] Reaction was conducted for 24 h. [d] Reaction was conducted for 48 h. NR＝no reaction.

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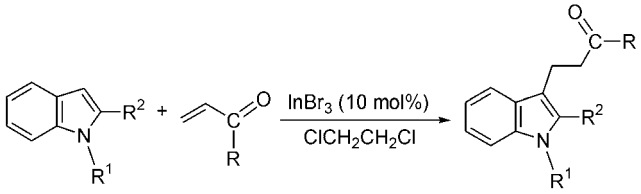
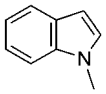
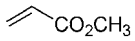
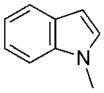
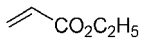
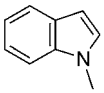
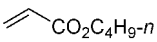
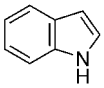
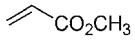
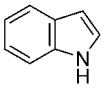
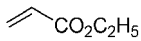
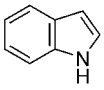
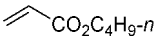
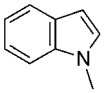
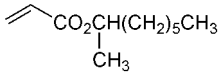
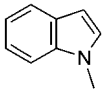
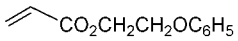
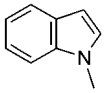
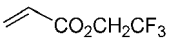
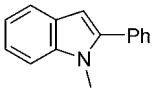
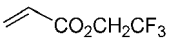
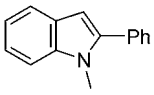
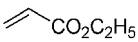
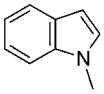
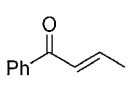
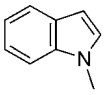
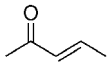
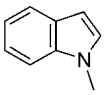
Table 2 $InBr_3$-catalyzed Michael addition of indoles to α,β-unsaturated compounds[a]



Entry	Indole	α,β-Unsaturated compound	Yield[b]/%
1			93
2			90
3			96
4			78
5			76
6			86
7			90
8			93
9			92
10			90
11			91
12[c]			92

Continued

Entry	Indole	α,β-Unsaturated compound	Yield[b]/%
13[c]			93
14[c]			94

[a] Reaction conditions: indole (1.0 mmol), α,β-unsaturated compound (1.0 mmol), $InBr_3$ (35.5 mg, 0.1 mmol) was stirred at 80 ℃ for 12 h. [b] Isolated yield. [c] Reactions were carried out at room temperature for 4 h.

tion. It is important to note that *N*-ethyl 2-phenyl indole also reacted with α,β-unsaturated esters to generate the corresponding product in excellent yields (Table 2, Entries 11 and 12). For the same indoles, α,β-unsaturated ketones and aldehydes, such as (*E*)-1-phenylbut-2-en-1-one, (*E*)-pent-3-en-2-one, and acrylaldehyde exhibit more reactivity than α,β-unsaturated esters. The reactions of indoles with α,β-unsaturated ketones and aldehydes underwent smoothly at room temperature (Table 2, Entries 12—14).

Overall, almost all reactions were clean and gave the C_3-substitution product exclusively, and the target compounds were obtained in good to excellent yields with no formation of side products such as dimers or polymers, which are frequently encountered under the influence of strong protic acids.

Conclusion

In conclusion, $InBr_3$ has been demonstrated to be a highly selective and efficient catalyst for the Michael addition of indoles to a variety of α,β-unsaturated esters. The reactions were performed smoothly to generate the desired products 3-substituted indoles in good yields under safe experimental conditions. The notable advantages of this methodology are mild condition, short reaction time, high yields and free from any side reaction products. This method offers one of the important motifs for synthesis of 3-substituted indoles, as natural products, biologically active compounds and pharmaceutical agents.

Experimental

Physical measurements and materials

All ^1H NMR and ^{13}C NMR spectra were recorded on a 400 MHz Bruker FT-NMR spectrometers. All chemical shifts are given as δ value with reference to tetramethylsilane (TMS) as an internal standard. Products were purified by flash chromatography on 230—400 mesh silica gel, SiO_2.

The chemicals and solvents were purchased from commercial suppliers either from Aldrich, Fluka, USA

or Shanghai Chemical Company, China and were used without purification prior to use.

General procedure for the synthesis of 3-substituted indoles through the Michael addition of indoles to *α*,*β*-unsaturated esters

To a solution of indole **1** (1.0 mmol) and *α*,*β*-unsaturated ester **2** (1.0 mmol) in $ClCH_2CH_2Cl$ (3.0 mL) was added $InBr_3$ (0.1 mmol) in one portion. The reaction mixture was heated to 80 ℃ for 12 h with stirring under a nitrogen atmosphere. After cooling, the reaction mixture was extracted with ethyl acetate and the organic layer was dried over Na_2SO_4. Then, the organic solution was concentrated with a rotary evaporator, and the residue was purified by column chromatography on silica gel to afford the desired product.

Ethyl 3-(1-methyl-1*H*-indol-3-yl)propanoate[15] ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.57 (d, *J*=8.0 Hz, 1H), 7.24—7.15 (m, 1H), 7.10—7.06 (m, 1H), 6.80 (s, 1H), 4.11 (dd, *J*=7.1, 7.3 Hz, 2H), 3.65 (s, 3H), 3.07 (t, *J*=7.5 Hz, 2H), 2.66 (t, *J*=7.3 Hz, 2H), 1.21 (t, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 173.2, 136.9, 127.5, 126.2, 121.4, 118.7, 118.6, 113.3, 109.0, 60.2, 35.1, 32.4, 20.4, 14.1.

Methyl 3-(1-methyl-1*H*-indol-3-yl)propanoate[16] ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.56 (d, *J*=7.6 Hz, 1H), 7.25—7.16 (m, 2H), 7.11—7.07 (m, 1H), 6.81 (s, 3H), 3.66 (s, 3H), 3.64 (s, 3H), 3.07 (t, *J*=7.1 Hz, 2H), 2.68 (t, *J*=7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 173.7, 136.9, 127.4, 126.2, 121.5, 118.6, 113.3, 109.1, 51.4, 34.9, 32.4, 20.4.

Methyl 3-(1*H*-indol-3-yl)propanoate[17] ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.99 (s, 1H), 7.61—7.57 (m, 1H), 7.34—7.29 (m, 1H), 7.19 (t, *J*=7.3 Hz, 1H), 6.98 (s, 1H), 3.67 (s, 3H), 3.10 (t, *J*=7.3 Hz, 2H), 2.72 (t, *J*=7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) *δ*: 173.8, 136.2, 127.1, 122.0, 121.4, 119.3, 118.6, 111.1, 51.1, 34.7, 20.6.

Ethyl 3-(1*H*-indol-3-yl)propanoate[18] ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 8.01 (s, 1H), 7.62—7.59 (m, 1H), 7.34—7.31 (m, 1H), 7.21—7.16 (m, 1H), 7.14—7.10 (m, 1H), 6.98—6.97 (m, 1H), 4.13 (dd, *J*=7.0, 7.4 Hz, 2H), 3.12—3.08 (m, 2H), 1.73—1.69 (m, 2H), 1.23 (t, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 173.5, 136.2, 127.1, 122.0, 121.4, 119.2, 118.7, 114.9, 111.1, 60.3, 34.9, 20.6, 14.2.

1-Phenyl-3-(1-methyl-1*H*-indol-3-yl)-butan-1-one[19] ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.43—7.41 (br, s, 1H), 7.30 (t, *J*=8.1 Hz, 2H), 7.24 (dd, *J*=7.3, 7.5 Hz, 3H), 7.16 (dd, *J*=6.7, 6.5 Hz, 2H), 7.01 (t, *J*=7.3 Hz, 1H), 6.82 (s, 1H), 4.82 (t, *J*=7.6 Hz, 1H), 3.70 (s, 3H), 3.26—3.11 (m, 2H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 207.6, 144.1, 137.2, 128.4, 127.6, 126.8, 126.3, 126.1, 121.7, 119.4, 118.8, 117.2, 109.2, 50.4, 38.3, 32.7, 30.3, 26.9.

4-(1-Methyl-1*H*-indol-3-yl)pentan-2-one[20] ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.63—7.61 (m, 1H), 7.26—7.18 (m, 2H), 7.11—7.07 (m, 1H), 6.79 (s, 1H), 3.68 (s, 3H), 3.63—3.56 (m, 1H), 2.89 (dd, *J*=5.9, 10.2 Hz, 1H), 2.67 (dd, *J*=8.4, 7.8 Hz, 1H), 2.06 (s, 3H), 1.36 (d, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 208.5, 137.0, 126.5, 124.9, 121.5, 119.3, 119.1, 118.5, 109.2, 50.5, 32.5, 32.4, 30.2, 26.8, 21.3.

Butyl 3-(1-methyl-1*H*-indol-3-yl)propanoate ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.26—7.18 (m, 2H), 7.11—7.07 (m, 1H), 4.08—4.05 (m, 2H), 3.68 (s, 3H), 3.09—3.06 (m, 2H), 2.71—2.66 (m, 2H), 1.60—1.53 (m, 2H), 1.37—1.28 (m, 2H), 0.90 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 173.4, 136.9, 127.5, 126.2, 121.5, 118.7, 118.6, 113.4, 109.1, 64.2, 35.1, 32.4, 30.6, 20.5, 19.0, 13.6. Anal. calcd for $C_{16}H_{21}NO_2$: C 74.10, H 8.16, N 5.40; found C 74.39, H 8.01, N 5.57.

Butyl 3-(1*H*-indol-3-yl)propanoate ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 8.02 (br, s, 1H), 7.59 (d, *J*=7.7 Hz, 1H), 7.32—7.29 (m, 1H), 7.21—7.15 (m, 1H), 7.12—7.08 (m, 1H), 6.95—6.94 (m, 1H), 4.04 (t, *J*=6.7 Hz, 2H), 3.11—3.07 (m, 2H), 2.71 (t, *J*=7.4 Hz, 2H), 1.61—1.54 (m, 2H), 1.37—1.28 (m, 2H), 0.90 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 173.5, 136.2, 127.1, 121.9, 121.4, 119.2, 118.6, 114.9, 111.1, 64.3, 35.0, 30.6, 20.6, 19.0, 13.6. Anal. calcd for $C_{15}H_{19}NO_2$: C 73.44, H 7.81, N 5.71; found C 73.29, H 8.05, N 5.87.

Octan-2-yl 3-(1-methyl-1*H*-indol-3-yl)propanoate ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.59—7.57 (m, 1H), 7.28—7.26 (m, 1H), 7.23—7.21 (m, 1H), 7.12—7.10 (m, 1H), 6.85 (s, 1H), 3.99 (dd, *J*=2.2, 3.7 Hz, 2H), 3.71 (s, 3H), 3.09 (t, *J*=7.7 Hz, 2H), 2.70 (t, *J*=7.3 Hz, 2H), 1.56—1.50 (m, 1H), 1.34—1.29 (m, 2H), 1.27—1.25 (m, 6H), 0.89—0.87 (m, 3H), 0.86—0.84 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 173.6, 137.0, 127.5, 126.2, 126.1, 121.5, 118.7, 118.6, 113.4, 109.1, 66.8, 38.7, 35.2, 32.5, 30.3, 28.9, 23.7, 22.9, 20.6, 14.0, 10.9. Anal. calcd for $C_{20}H_{29}NO_2$: C 76.15, H 9.27, N 4.44; found C 76.02, H 9.41, N 4.67.

2-Phenoxyethyl 3-(1-methyl-1*H*-indol-3-yl)propanoate ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.58—7.56 (m, 1H), 7.30—7.18 (m, 4H), 7.12—7.07 (m, 1H), 6.89—6.85 (m, 2H), 6.82 (s, 1H), 4.42—4.40 (m, 2H), 4.10—4.07 (m, 2H), 3.63 (s, 3H), 3.09 (t, *J*=7.7 Hz, 2H), 2.74 (t, *J*=7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 173.2, 158.3, 136.8, 129.4, 127.4, 126.3, 121.5, 121.0, 118.7, 118.6, 114.5, 113.1, 109.1, 65.7, 62.7, 34.9, 32.4, 26.8, 20.4. Anal. calcd for $C_{20}H_{21}NO_3$: C 74.28, H 6.55, N 4.33; found C 74.49, H 6.41, N 4.52.

2,2,2-Trifluoroethyl 3-(1-methyl-1*H*-indol-3-yl)-propanoate ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.58 (d, *J*=8.1 Hz, 1H), 7.30—7.21 (m, 2H), 7.13—7.10 (m, 1H), 6.86 (s, 1H), 4.45 (dd, *J*=8.5, 8.5 Hz, 2H), 3.73 (s, 3H), 3.12 (t, *J*=7.5 Hz, 2H), 2.81 (t, *J*=7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 171.7, 136.9, 127.3, 126.4, 121.6, 118.8, 118.6, 112.6, 109.2, 60.4, 60.0, 34.5, 32.6, 20.2. Anal. calcd for $C_{14}H_{14}F_3NO_2$: C 58.95, H 4.95, N 4.91; found C 58.79, H 5.11, N 5.07.

2,2,2-Trifluoroethyl 3-(1-ethyl-2-phenyl-1*H*-indol-3-yl)propanoate ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.63—7.61 (m, 1H), 7.65—7.62 (m, 1H), 7.51—7.44 (m, 3H), 7.40—7.36 (m, 3H), 7.28—7.23 (m, 1H), 7.18—7.14 (m, 1H), 4.35 (dd, *J*=3.1, 8.4 Hz, 2H), 4.05—3.99 (m, 2H), 3.08—3.02 (m, 2H), 2.68—2.62 (m, 2H), 1.23—1.18 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 171.5, 137.7, 135.7, 131.9, 130.4, 128.5, 128.3, 127.3, 124.3, 121.7, 119.3, 118.7, 110.9, 109.7, 60.3,

59.9, 38.5, 34.8, 19.9, 15.3. Anal. calcd for $C_{21}H_{20}F_3NO_2$: C 67.19, H 5.37, N 3.73; found C 67.35, H 5.29, N 3.57.

Ethyl 3-(1-ethyl-2-phenyl-1*H*-indol-3-yl)propanoate ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.65 (d, J=8.1 Hz, 1H), 7.49—7.42 (m, 3H), 7.38—7.34 (m, 3H), 7.23 (t, J=7.0 Hz, 1H), 7.24 (t, J=7.0 Hz, 1H), 4.07—3.98 (m, 4H), 3.01 (t, J=8.1 Hz, 2H), 2.55 (t, J=8.2 Hz, 2H), 1.20—1.15 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.2, 137.5, 135.7, 132.0, 130.4, 128.4, 128.2, 127.4, 121.5, 119.1, 118.8, 111.6, 109.5, 60.2, 38.4, 35.6, 20.1, 15.3, 14.1. Anal. calcd for $C_{21}H_{23}NO_2$: C 78.47, H 7.21, N 4.36; found C 78.29, H 7.11, N 4.54.

3-(1-Methyl-1*H*-indol-3-yl)propanal[21] ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.73 (t, J = 2.6 Hz, 1H), 7.64—7.61 (m, 1H), 7.30—7.25 (m, 2H), 7.23—7.21 (m, 1H), 7.13—7.09 (m, 2H), 6.82 (s, 1H), 3.73 (s, 3H), 2.89—2.83 (m, 1H), 2.73—2.66 (m, 1H), 1.42 (d, J= 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 202.9, 125.1, 121.7, 119.0, 118.8, 109.4, 51.0, 32.6, 25.8, 21.6.

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