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A facile synthesis of isoindolo[2,1-*a*]quinolin-11-one via [4+2] reactions of *N*-acyliminium intermediates with olefines

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Abstract—A facile synthesis of isoindolo[2,1-*a*]quinolin-11-one has been developed to attain new molecules of this family via [4+2] reactions of *N*-acyliminium cation, produced from 2,3-dihydro-3-hydroxy-2-arylisoindol-1-one, in the presence of $BF_3{\cdot}OEt_2$ with olefins in moderate to good yields at ambient temperature.

Isoindolo[2,1-*a*]quinolinones are a class of molecules, which are endowed with an array of biological activities. For example, the 5,11-dioxosubstituted isoindolo[2,1-*a*]-quinolines have protective effects against N_2-induced hypoxia,[1] and trihydroxyisoindolo[2,1-*a*]quinolines show inhibitory activities against bacterial DNA-gyrase and human topoisomerase.[2]

The synthetic methods of isoindolo[2,1-*a*]quinolinones are not numerous. Available methods for preparation of the isoindolo[2,1-*a*]quinolinone skeleton generally require multi-step reactions[3] and are often unsatisfactory both in yield and generality. Among them are the reductive cyclization of the *o*-quinolyl-2-benzoic acid and its esters to afford 6,6a-dihydro-isoindolo[2,1-*a*]quinolin-11-ones;[3e,f] the intramolecular Friedel–Craft of 2-aryl-2,3-dihydro-3-oxoisoindole-1-acetic acid to produce isoindolo[2,1-*a*]quinoline-5,11-diones;[1,3g] condensation of substituted 2-amino-2-methoxyacetophenones with phthalic anhydrides in refluxing toluene in the presence of triethylamine to provide benzoyl-substituted isoindolo[2,1-*a*]quinoline-5,11-diones;[2,3h] the intramolecular Witting cyclization of 2-phthalimidobenzoylphosphoranes to afford isoindolo[2,1-*a*]quinoline-5,11-diones in moderate yields,[3h] and the *N*-acylation of *N*-(α-monoallylfurfural)anilines with maleic anhydride and subsequent intramolecular Diels–Alder reaction to produce the 3-aryl-2-methyl-3-aza-10-oxatricyclo[5.2.1.0]dec-8-ene-6-carboxylic acid followed by dehydration to give 5,6,6a,12-tetrahydroisoindolo[2,1-*a*]quinolin-11-one-10-carboxylic acids.[3i]

N-Acyliminium cation is known as a powerful intermediate in construction of nitrogen-containing heterocycles.[4] Numerous examples of *N*-acyliminium cation cyclization can be found in the synthesis of alkaloid natural products.[4,5] The intramolecular *N*-acyliminium ion cyclization of 2,3-dihydro-3-hydroxy2-[2-(1-methylprop-1-enyl)phenyl]-1*H*-isoindol-1-ones in the presence of *p*-toluensulfonic acid to give either 5-alkylene-6,6a-dihydroisoindolo[2,1-*a*]quinolin-11-ones[6a] or 5-mono, and 5,6a-disubstituted isoindolo[2,1-*a*]quinolin-11-ones has been reported recently.[6b] Till now, however, there have been no reports concerning the synthesis of isoindolo[2,1-*a*]quinolinones by the intermolecular [4+2] reaction of *N*-acyliminium cation with olefins. In connection with our studies on the synthesis of heterocyclic structures with biological activities,[7] we want to develop a new procedure for the synthesis of isoindolo[2,1-*a*]-quinolin-11-ones with specific patterns of substituents, and we report here a facile synthesis of isoindolo[2,1-*a*]-quinolin-11-one via [4+2] reactions of *N*-acyliminium cation generated from 2,3-dihydro-3-hydroxy-2-arylisoindol-1-one (**1a**–**c**) in the presence of $BF_3{\cdot}OEt_2$ with olefins, such as, styrene (**2a**), α-methylstyrene (**2b**), anethole (**2c**), ethyl vinyl ether (**2d**), indene (**2e**), dihydrofuran (**2f**), and dihydropyran (**2g**).

The starting materials, 2,3-dihydro-3-hydroxy-2-arylisoindol-1-one **1a**–**c**, were easily prepared by the selective

Keywords: *N*-Acyliminium cation; 2,3-Dihydro-3-hydroxy-2-arylisoindol-1-one; 5,6,6a,12-Tetrahydroisoindolo[2,1-*a*]quinolin-11-ones.
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reduction of 2-arylphthalimides with equal molar sodium borohydride in methanol. A general procedure for the cycloaddition reactions were performed as following: 2,3-dihydro-3-hydroxy-2-arylisoindol-1-one (2.0 mmol) and olefins (2.5 mmol) were dissolved in 50 mL anhydrous methylene dichloride at room temperature, $BF_3{\cdot}OEt_2$ (2.1 mmol) was added in one portion under stirring. After stirring for half an hour, the reaction was quenched with an aqueous solution of sodium carbonate. After the organic phase was washed with water and dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure and the residue was recrystallized with 1:1 chloroform and hexane or purified on silica column eluted with 1:2 chloroform and hexane to give products **3a**–**r** in high yields as cis-adducts or cis- and trans-mixtures (Table 1). The reactions were completely regioselective giving only the isomers depicted in Scheme 1 and fully characterized by ^1H, ^{13}C, and 2D NMR spectroscopy.[8]

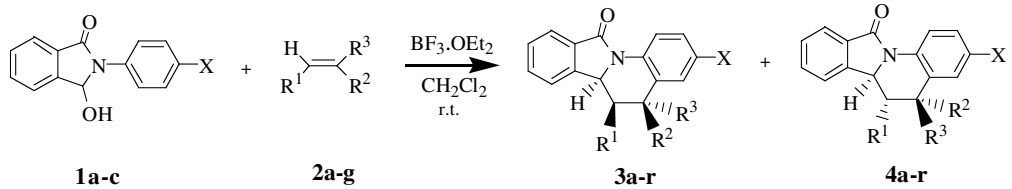
The reactions of **1a**–**c** with **2a**–**d** all afforded products as mixtures of cis and trans stereoisomers at different ratios. The separation of cis and trans mixtures was difficult and achieved by repeated preparative thin plate chromatography. The configurations of the separated products were assigned by ^1H and 2D NMR spectroscopy and confirmed by NOESY correlation (Fig. 1). For example, the cis configuration of the C-5 and C-6a in **3a** was assigned by the large vicinal coupling constants $J_{6a-6axial} = 12.3$ Hz, $J_{5-6axial} = 12.3$ Hz and both of which were indicative of the *anti*-axial–axial orientation of protons in C-6a and C-5 position with H-6_{axial} and could be deduced that the orientation of H-6a and H-5 was parallel. The trans configuration of the C-5 and C-6a in **4a** was assigned by the large vicinal coupling constants $J_{6a-6axial} = 12.9$ Hz indicative of the axial orientation of H-6a and by the significantly smaller vicinal coupling constants $J_{5-6} = 5.4$ Hz typical for a gauche conformation of H-5 and H-6 and indicative of the equatorial orientation of H-6a. For another pair of products **3b** and **4b**, the similar coupling constants for both $J_{6a-6axial}$ and $J_{6a-6equatorial}$ in ^1H NMR revealed that the difference of configuration of two stereoisomers was just the orientation of phenyl and methyl at C-5 position, which was turned upside down. This assignment was confirmed by the NOESY correlation as depicted in Figure 1.

In comparison with the reactions of **1b** with **2a**–**c**, the yields of products **3j** and **4j** obtained from the reaction of **1b** with **2d** were very low because there was a large quantity of no-cyclization product 2,3-dihydro-3-ethoxy-2-arylisoindol-1-one produced in the meantime.

Table 1. Synthesis of substituted 5,6,6a,12-tetrahydroisoindolo[2,1-*a*]quinolin-11-one

Entry	Reactants				Time (min)	Prods	Yield (%)	Ratio[e] of cis- and trans-
	X	R^1	R^2	R^3				
1	H	H	Ph	CH_3	30	**3a**,**4a**[a]	91[c]	10:9
2	H	H	Ph	H	30	**3b**,**4b**[a]	92[c]	5:6
3	H	CH_3	Bn	H	30	**3c**,**4c**[a]	87[c]	5:1
4	H	–$CH_2C_6H_4$–		H	30	**3d**[a]	85[d]	8:1
5	H	–$(CH_2)_2O$–		H	30	**4e**[a]	61[d]	1:9
6	H	–$(CH_2)_3O$–		H	30	**4f**[a]	80[d]	1:8
7	CH_3	H	Ph	H	30	**3g**,**4g**[a]	87[c]	8:7
8	CH_3	H	Ph	CH_3	30	**3h**+**4h**[b]	94[c]	10:9
9	CH_3	CH_3	Bn	H	30	**3i**+**4i**[b]	92[c]	3:1
10	CH_3	H	H	EtO	30	**3j**,**4j**[a]	45[c]	6:5
11	CH_3	–$CH_2C_6H_4$–		H	30	**3k**[a]	82[d]	9:1
12	CH_3	–$(CH_2)_2O$–		H	30	**4l**[a]	65[d]	1:9
13	CH_3	–$(CH_2)_3O$–		H	30	**4m**[a]	85[d]	1:8
14	CH_3O	H	Ph	H	30	**3n**+**4n**[b]	93[c]	1:1
15	CH_3O	H	Ph	CH_3	30	**3o**+**4o**[b]	90[c]	9:10
16	CH_3O	CH_3	Bn	H	30	**3p**,**4p**[a]	85[c]	3:1
17	CH_3O	–$(CH_2)_2O$–		H	30	**4q**[a]	68[d]	1:10
18	CH_3O	–$(CH_2)_3O$–		H	30	**4r**[a]	87[d]	1:8

[a] Products, which are separated and purified.
[b] Mixtures of cis- and trans-isomers.
[c] Yields of cis- and trans-isomer mixtures.
[d] Refer to isolated pure products.
[e] Determined by ^1H NMR before separation.



1a-c **2a-g** **3a-r** **4a-r**

Scheme 1.

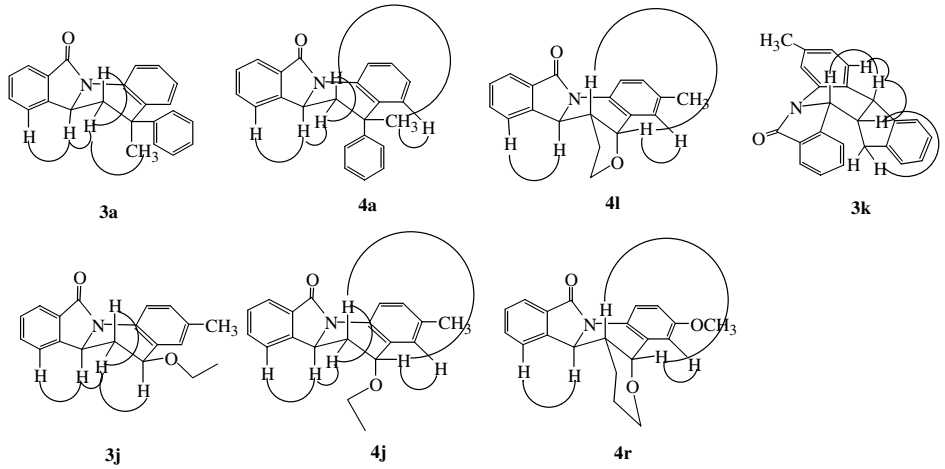
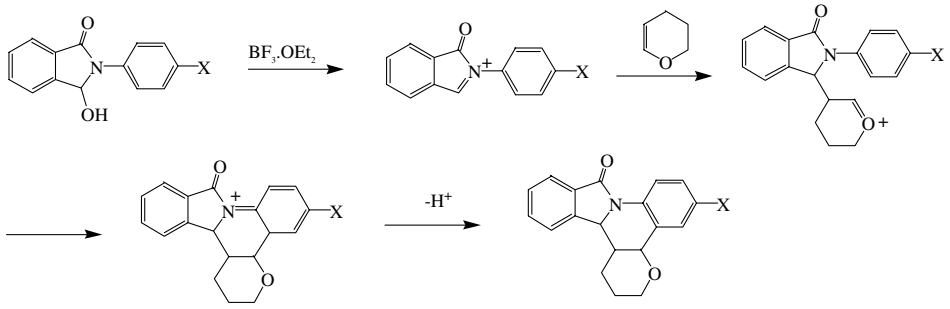


Figure 1. NOESY correlations of the **3a**, **4a**, **3j**, **4j**, **3k**, **4l**, **4r**.



Scheme 2.

Obviously, this product came from the reaction of *N*-acyliminium cation with alcohol probably produced by the hydrolysis of ethyl vinyl ether (**2d**).

Similar reactions of **1a**–**c** were conducted with **2e**–**g** to afford products also as mixtures of cis and trans stereoisomers. But only one isomer was the dominant product as shown in Table 1, for example, **3d**, **4e**, and **4f** from the reactions of **1a** with **2d**–**f**. It was noticeable that the stereoselectivity of reaction of **1a** with **2d** was different from that of **1a** with **2e** and **2f**. Their configurations were assigned by ^{1}H NMR similarly and all the assigned configurations were supported by the NOESY correlation as shown in Figure 1.

As carbocation intermediates are involved in the formation of 5,6,6a,12-tetrahydroisoindolo[2,1-*a*]quinolin-11-ones, it could be certain that the [4+2] reaction of *N*-acyliminium cation with olefins was not a concerted reaction, but a two-step addition reaction. The plausible mechanism can be visualized as initial dehydroxylation of 2,3-dihydro-3-hydroxy-2-arylisoindol-1-one **1a**–**c** by $BF_3{\cdot}OEt_2$ to produce *N*-acyliminium cation followed by electrophilic attack of *N*-acyliminium cation to olefins, such as dihydropyran (**2f**), leading to a new cation. Then, the intramolecular Friedel–Crafts reaction of the cation afforded 5,6,6a,12-tetrahydroisoindolo[2,1-*a*]-quinolin-11-one **3a**–**r** (Scheme 2).

In summary, an efficient methodology for a variety of isoindolo[2,1-*a*]quinolin-11-ones has been developed. To the best of our knowledge, this is the first report for the synthesis of 5,6,6a,12-tetrahydroisoindolo[2,1-*a*]quinolin-11-ones via [4+2] reaction of *N*-acyliminium cation. The further investigation of synthetic application of this strategy is underway.

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8. All compounds showed spectroscopic and analytical data in accordance with structure. Spectroscopic data for selected compounds:
Compound **3a**: colorless needles, mp: 147–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (s, 3H, CH_3), 1.98 (dt, 1H, J = 12.9 Hz), 2.59 (dd, 1H, J = 12.9, 2.4 Hz), 4.98 (d, 1H, J = 11.1 Hz, H-6a), 6.85 (d, 1H, J = 7.8 Hz, H-5), 7.00 (d, 1H, J = 7.8 Hz, H-4), 7.18 (q, 1H, J = 8.4, 4.8 Hz, H-3), 7.24–7.29 (m, 5H); 7.42–7.54 (m, 3H, H-7, H-8, H-9), 7.96 (d, 1H, J = 7.8 Hz, H-10), 8.54 (d, 1H, J = 7.5, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.8 (*C*H$_3$), 42.3 (C-6), 45.8 (*C*-5), 55.0 (C-6a), 120.4 (C-4), 121.6 (C-2), 124.4 (C-9), 124.5 (*C*H), 127.0 (C-10), 127.2 (2*C*H), 127.7 (C-7), 128.1 (2*C*H), 129.1 (C-1), 132.0 (C-8), 132.3, 132.8, 136.3, 144.3 (C-6b), 149.7, 165.8 (C-11). MS *m*/*z* 325 (M$^+$, 11), 310 (2), 296 (2), 246 (12), 232 (4), 220 (5), 178 (7), 105 (100). Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.88; N 4.30. Found: C, 84.80; H, 5.98; N 4.22.
Compound **4a**: colorless needles, mp: 175–176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (s, 3H, CH_3), 1.89 (t, 1H, J = 12.9 Hz), 2.62 (d, 1H, J = 13.5 Hz), 4.50 (d, 1H, J = 12.3 Hz, H-6a), 7.13–7.54 (m, 11H); 7.91 (d, 1H, J = 6.9 Hz, H-10), 8.71 (d, 1H, J = 8.1, H-1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.2 (*C*H$_3$), 42.6 (C-6), 46.3 (*C*-5), 56.0 (C-6a), 120.5 (C-2), 121.7 (C-4), 124.3 (C-9), 126.3 (C-10), 127.0 (*C*H), 127.2 (2*C*H), 128.2 (2*C*H), 128.6 (C-1), 130.0 (C-7), 132.0 (C-8), 132.6, 135.5, 144.3 (C-6b), 149.5 (C-1′), 166.0 (C-11). MS *m*/*z* 325 (M$^+$, 27), 310 (11), 296 (20), 282 (9), 246 (16), 232 (100). Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.88; N 4.30. Found: C, 84.75; H, 6.03; N, 4.28.
Compound **3f**: colorless needles, mp: 86–87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, 3H, J = 6.9 Hz, CH_3), 1.64 (q, 1H, J = 12.3 Hz), 2.36 (s, 3H, CH_3), 2.76 (ddd, 1H, J = 12.3; 6.3, 3.6 Hz), 3.54–3.80 (m, 2H, CH_2), 4.81 (d, 1H, J = 12.9, H-6a), 4.88 (dd, 1H, J = 10.5, 6.0 Hz, H-5), 7.17 (d, 1H, J = 8.1 Hz, H-2), 7.41 (s, 1H, H-4), 7.50–7.66 (m, 3H), 7.94 (d, 1H, J = 6.9 Hz, H-10), 8.55 (d, 1H, J = 8.7 Hz, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.5 (*C*H$_3$), 21.0 (*C*H$_3$), 33.3 (C-6), 57.8 (C-6a), 63.7 (O*C*H$_2$), 73.4 (C-5), 119.5 (C-2), 121.6 (C-4), 124.1 (C-9), 126.6 (C-10), 127.5, 128.6 (C-7), 129.0 (C-1), 131.9 (C-8), 132.6, 133.1, 133.6, 143.7 (C-6b), 165.6 (C-11). MS *m*/*z* 293 (M$^+$, 42), 264 (7), 248 (89), 232 (12), 222 (38), 73 (100). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.63; H, 6.72; N, 4.86.
Compound **4f**: colorless needles, mp: 121–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, 3H, J = 7.2 Hz, CH_3), 1.64 (td, 1H, J = 13.5; 2.7 Hz), 2.57 (s, 3H, CH_3), 2.76 (dt, 1H, J = 13.5; 2.4 Hz), 3.66–3.84 (m, 2H, CH_2), 4.54 (d, 1H, J = 2.4 Hz, H-5), 5.09 (dd, 1H, J = 12.9, 2.4 Hz, H-6a), 7.17 (d, 1H, J = 1.5 Hz, H-4), 7.23 (dd, 1H, J = 8.7; 1.5 Hz, H-2), 7.48–7.63 (m, 3H); 7.93 (d, 1H, J = 7.8 Hz, H-10), 8.55 (d, 1H, J = 8.1 Hz, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6 (*C*H$_3$), 20.9 (C-6), 33.4 (*C*H$_3$), 54.5 (C-6a), 64.1 (O*C*H$_2$), 73.0 (C-5), 119.9 (C-2), 121.7 (C-4), 124.1 (C-9), 128.4 (C-10), 130.0 (C-7), 131.0 (C-1), 132.0 (C-8), 132.8, 133.1, 133.8, 144.6 (C-6b), 166.1 (C-11). MS *m*/*z* 293 (M$^+$, 8), 267 (1), 246 (95), 232 (9), 73 (100). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.58; H, 6.78; N, 4.92.
Compound **4l**: colorless needles, mp: 208–209 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H, CH_3), 2.34–2.41 (m, 1H, H-6), 2.47–2.53 (m, 2H, CH_2) 3.94 (q, 1H, J = 13.2, 8.4 Hz, OCH_2), 4.25 (q, 1H, J = 13.2, 6.9 Hz, OCH_2), 4.40 (d, 1H, J = 11.7 Hz, H-6a), 4.67 (d, 1H, J = 5.4 Hz, H-5), 7.23 (dd, 1H, J = 8.1, 2.4 Hz, H-2), 7.36 (d, 1H, J = 2.4 Hz, H-4), 7.50–7.65 (m, 3H), 7.94 (d, 1H, J = 7.5 Hz, H-10), 8.27 (d, 1H, J = 8.1 Hz, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9 (*C*H$_3$), 29.4 (*C*H$_2$), 42.3 (C-6), 58.5 (O*C*H$_2$), 66.1 (C-6a), 76.8 (C-5), 120.3 (C-2), 122.2 (C-4), 124.5 (C-9), 128.4 (C-10), 130.0 (C-7), 131.0 (C-1), 132.0 (C-8), 132.9, 134.2 (C-3), 138.3, 144.3 (C-6b), 165.2 (C-11). MS *m*/*z* 291 (M$^+$, 21), 262 (7), 246 (22), 141 (12), 115 (47), 71 (100). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.28; H, 5.95; N, 4.75.
Compound **3k**: colorless needles, mp: 176–177 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H, CH_3), 2.29 (d, 1H, C*H*H), 3.56 (dq, 1H, J = 8.4, 3.3 Hz, CH*H*) 3.94 (q, 1H, J = 13.2, 8.4 Hz, OC*H*H), 4.25 (q, 1H, J = 13.2, 6.9 Hz, OCH*H*), 4.55 (d, 1H, J = 8.1 Hz, H-5), 4.98 (d, 1H, J = 3.6 Hz, H-6a), 6.93 (d, 1H, J = 7.5 Hz, H-2), 7.02 (d, 1H, J = 8.4 Hz), 7.07 (t, 1H, J = 7.5 Hz), 7.15 (t, 1H, J = 7.5 Hz), 7.33 (s, 1H, H-4), 7.45–7.60 (m, 4H), 7.92 (d, 1H, J = 7.5 Hz, H-10), 8.27 (d, 1H, J = 8.1 Hz, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4 (*C*H$_3$), 30.9 (*C*H$_2$), 43.0 (C-6), 46.0 (C-5), 59.5 (C-6a), 120.7 (C-2), 122.2 (C-4), 124.4 (C-9), 125.1 (C-10), 127.0 (*C*H), 127.7 (*C*H), 128.0 (*C*H), 128.9 (C-7), 129.5 (*C*H), 132.3 (C-8), 133.1 (C-4a), 133.5 (C-10a), 134.4 (C-12a), 141.9 (*C*H), 144.3 (*C*H), 145.7 (C-6b), 166.5 (C-11). MS *m*/*z* 337 (M$^+$, 36), 308 (11), 246 (10), 189 (13), 115 (22), 43 (100). Anal. Calcd for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15. Found: C, 85.33; H, 5.82; N, 4.07.
Compound **4r**: colorless needles, mp: 181–182 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (d, 1H, J = 13.5 Hz), 1.81 (dd, 1H, J = 13.5, 2.1 Hz), 1.94 (tt, 1H, J = 13.5, 3.9 Hz), 2.08 (tq, 1H, J = 12.9, 3.9 Hz), 2.50 (d, 1H, J = 13.5 Hz), 3.80 (s, 3H, OCH_3), 3.83 (dt, 1H, J = 11.7, 2.4 Hz), 4.21 (dd, 1H, J = 11.7, 3.9 Hz), 4.53 (d, 1H, J = 1.8, H-5), 5.27 (d, 1H, J = 11.4 Hz, H-6a), 6.91 (d, 1H, J = 7.8 Hz, H-4), 6.97 (dd, 1H, J = 8.1, 2.4 Hz, H-2), 7.27–7.60 (m, 3H, H-7, H-8, H-9), 7.95 (d, 1H, J = 8.1 Hz, H-10), 8.44 (d, 1H, J = 9.0 Hz, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6 (*C*H$_2$), 24.3 (*C*H$_2$), 39.3 (*C*-6), 55.5 (O*C*H$_3$), 56.4 (C-6a), 69.4 (O*C*H$_2$), 75.7 (C-5), 114.7 (C-4), 115.6 (C-2), 121.4 (C-1), 123.7 (C-9), 124.3 (C-10), 127.1 (C-12a), 128.4 (C-7), 129.4 (C-4a), 131.4 (C-8), 133.3 (C-10), 142.9 (C-6b), 156.1 (C-3),165.4 (C-11). MS *m*/*z* 321 (M$^+$, 19), 278 (4), 262 (100), 219 (20), 191 (7), 131 (15). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.68; H, 6.05; N, 4.29.