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Diastereoselective Diels–Alder Reaction of 5-(Indol-2-yl)-pyran-2-one

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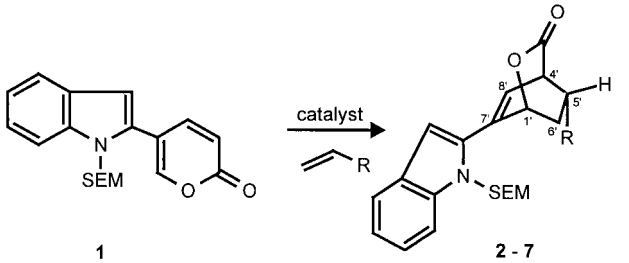
Abstract—5-(Indol-2-yl)-pyran-2-one undergoes cycloaddition to electron-poor and electron-rich dienophiles. Lanthanide shift reagents have been shown to be efficient catalysts for the inverse electron demand Diels–Alder reactions. The bicycloadducts were formed with complete stereoselectivity. Aminolysis of bicycloadducts with primary amines is described.

The Diels–Alder reaction is a standard method for preparing six-membered ring derivatives, which are versatile building-blocks for the synthesis of numerous natural products. The diastereoface differentiation and the *exo–endo* selectivity gives the Diels–Alder reaction a prominent position among the most useful tools to obtain chiral compounds.

In the course of our studies for the synthesis of indole alkaloids we were attracted by the thoroughly studied reactivity of substituted 2-pyrones in Diels–Alder reactions,[1–3] and from the synthetic versatility of the bicyclic lactone products. Interesting applications of Diels–Alder reaction of pyran-2-ones to the total synthesis of diverse targets were reported.[4] Among the numerous examples no aryl- or heteroarylpyran-2-ones were studied. We report here on the highly stereoselective cycloadditions of 5-(indol-2-yl)pyran-2-one **1**[5] with both electron-rich and electron-poor dienophiles (Table 1).

Initial cycloaddition of **1** with the electron-poor dienophiles acrolein and methylvinylketone produced the adducts **2** and **3** in good yield with total regio- and stereoselectivity (entries 1 and 2). The elucidation of the structures of **2** and **3** was possible on the basis of their ^{1}H NMR spectra. For compound **2**, the signal of H-1′ appeared at δ 5.74 as ddd (J=4, 3, 2 Hz) ascertaining the presence of two vicinal hydrogens and the presence of an allylic coupling constant (J=3 Hz) with H-8′ that appeared at δ 6.79 (dd, J=6, 3 Hz). The signals of H-6′*exo* and H-6′*endo* were assigned at δ 2.49 (ddd, J=14, 10, 4 Hz) and 2.28 (ddd, J=14, 4, 2 Hz) according to the values of their coupling constants of H-1′ (J H-1′, H-6′*exo*=4 Hz; J H-1′, H-6′*endo*=2 Hz).[1,2a,c] The presence of coupling constants of 10 and 4 Hz in the signals of H-6′*exo* and H-6′*endo*, respectively permitted to estimate the *endo* orientation of the carbaldehyde function. The signal of H-4′ appeared at δ 4.32 (dd, J=6, 2 Hz) coupled with the signals of H-8′ and H-5′ (δ 3.20, ddd, J=10, 4, 2 Hz). When the reaction of **1** with acrolein was conducted at 50°C, in an attempt to reduce the reaction time, the only product deriving from decarboxylation[1] of **2** and subsequent aromatization[6] was obtained.

Table 1.



1 **2 - 7**

Entry	R	Catalyst	Time	Prod.	Yield %
1	CHO		4 days	**2**	82
2	COMe		3 days	**3**	61
3	OEt	SiO_2	6 days	**4**	83
4	OEt	$Eu(FOD)_3$	5 hours	**4**	90
5	OBu	SiO_2	6 days	**5**	50
6	OBu	$Eu(FOD)_3$	1 day	**5**	70
7	SPh	SiO_2	5 days	**6**	40
8	SPh	$Eu(FOD)_3$	5 days	**6**	96
9	OCH_2Naph	SiO_2	7 days	**7**	35
10	OCH_2Naph	$Pr(FOD)_3$	4 days	**7**	65

Keywords: cycloaddition; indoles; pyrones; lanthanides.

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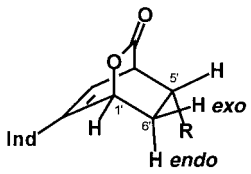
Table 2.



R=	CHO (**2**)	$COCH_3$ (**3**)	OEt (**4**)	OBu (**5**)	SPh (**6**)	OCH_2Naft (**7**)
δ H-1′	5.74	5.62	5.58	5.59	5.66	5.63
δ H-6′ *exo*	2.49	2.41	2.62	2.64	2.82	2.66
δ H-6′ *endo*	2.28	2.15–2.00	1.61	1.65	1.58	1.78
δ H-5′	3.20	3.19	4.12–4.02	4.10–4.03	3.81–3.60	4.32
J H-1′, H6′*exo*	4	3.5	3	4	3	4
J H-1′, H-6′*endo*	2	1	1	1	1	2
J H-6′*exo*, H-5′	10	10	7	9	10	8
J H-6′*endo*, H-5′	4	3.4	2	2	1.5	3

Inverse-electron-demand-Diels–Alder (IEDDA) reactions of **1** were studied with various electron-rich dienophiles, such as phenylthiovinylether, buthylvinylether, ethylvinylether and naphthylmethylvinylether in the presence of catalysts. We decided to investigate the use of SiO_2, lanthanide shift reagents, and a titanium complex as catalysts.

The commercial chromatography silica gel[2e] proved sufficiently powerful to catalyse the reaction but not sufficiently acidic to promote the CO_2 extrusion or polymerization of dienophiles (entries 3, 5, 7 and 9). In the absence of silica gel the reactions were sluggish and unuseful. An increase of the reaction rates was observed when $Eu(FOD)_3$ was used as catalyst (entries 4, 6 and 8).[7] The reaction of **1** with phenylthiovinylether in the presence of $Eu(FOD)_3$ afforded the product **6** with a considerably better yield (96%). $Pr(FOD)_3$ was used only in the case of naphthylmethylvinylether[8] (entry 10) obtaining compound **7** with 65% yield. The reactions showed total regio- and stereoselectivity unlike other examples of 5-substituted pyran-2-ones.[2a,e,h,4e,d] ^{1}H NMR spectra confirmed the stereochemistry of compounds **4**–**7**, by comparison with the relevant data of compound **2** (Table 2).

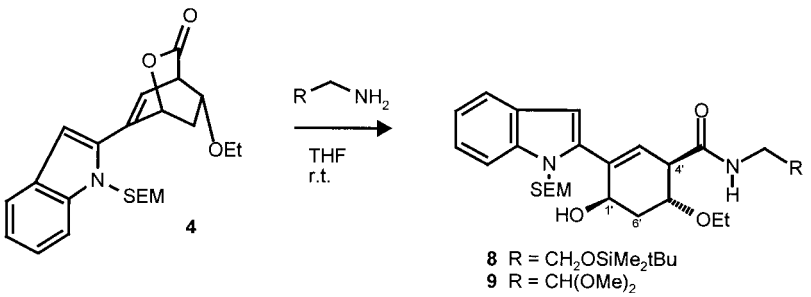
The extreme sensitivity of compounds **2**–**7** towards decarboxylation precluded the application of the most common Lewis acids as catalysts in the Diels–Alder reactions of **1**. The use of binol–titanium complex[3c] was unproductive.

To illustrate the potential of the richly functionalized bicycloadducts **2**–**7** as versatile intermediates, compound **4** was subjected to aminolysis with primary amines under very mild conditions producing the tetrasubstituted cyclohexenes **8** and **9** as single diastereoisomers (Scheme 1). The reactions of **4** with 2-*t*-butyldimethylsilyloxyethylamine and aminoacetaldeheyde dimethylacetal were conducted in THF at room temperature. The values of the coupling constants of the ^{1}H NMR signals of H-1′, H-6′ and H-4′ confirmed the relative stereochemistry of compounds **8** and **9**.

In summary, 5-(indol-2-yl)pyran-2-one **1** is a substituted 2-pyrone suited for regio- and stereoselectively producing isolable, highly functionalized, bridged bicyclic lactones via Diels–Alder cycloaddition under mild conditions. This is the first example of Diels–Alder reaction involving an heteroaryl pyran-2-one as diene system. We want to stress the chemoselectivity of this reaction also in the presence of electrophilic reagents that generally attack the indole system. The resulting intermediates possess an intrinsic reactivity that might be exploited for the synthesis of complex indole derivatives with potential biological activity. We are continuing our work along these lines.

Experimental

Thin layer chromatography (TLC) for reaction monitoring: Merck silica gel 60 F_{254} plates. Flash column chromatography (FC): Merck silica gel 60 (230–400 mesh). ^{1}H- and ^{13}C NMR spectra: Bruker AC300 (300 and 75.2 MHz); in $CDCl_3$; chemical shifts δ in ppm. MS: VG



Scheme 1.

7070EQ-HF instrument (EI, 70 eV); *m/z*: relative intensity in %.

Diels–Alder reaction of 1 with acrolein and methylvinylketone

5-[1-[2-(Trimethylsilyl)ethoxymethyl]indol-2-yl]pyran-2-one (**1**) (1 mmol) was dissolved in acrolein (methylvinylketone) (20 mmol). This solution was stirred at room temperature. Purification by chromatography on silica gel, afforded the products.

5-*endo*-Carboxyaldehyde-7-[1-[2-(trimethylsilyl)ethoxymethyl]indol-2-yl]-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene (2). Yellow oil. Yield: 82%. R_f 0.38 (Et_2O). ^1H NMR ($CDCl_3$) δ 9.68 (1H, s), 7.65 (1H, d, J=8 Hz), 7.42 (1H, d, J=8 Hz), 7.29 (1H, t, J=8 Hz), 7,18 (1H, t, J=8 Hz), 6.79 (1H, dd, J=6, 3 Hz), 6.71 (1H, s), 5.74 (1H, ddd, J=3, 4, 2 Hz), 5.32 (2H, AB system), 4.32 (1H, dd, J=6, 2 Hz), 3.62 (2H, t, J=9 Hz), 3.20 (1H, ddd, J=10, 4, 2 Hz), 2.49 (1H, ddd, J=14, 10, 4 Hz), 2.28 (1H, ddd, J=14, 4, 2 Hz), 0.96 (2H, t, J=9 Hz), 0, 00 (9H, s); ^{13}C NMR ($CDCl_3$) δ:197.6, 171.7, 139.6, 137.1, 134.1, 127.4, 123.7, 123.4, 121.2, 121.0, 109.7, 104.5, 77.6, 72.7, 66.2, 45.1, 41.6, 26.8, 18.0, −1.4 (3C); IR ($CHCl_3$) cm^{-1} 1750, 1690, 1170; EIMS 351 (25%); 234 (30%); 206 (100%). Anal. Calcd for $C_{22}H_{27}NO_4Si$: C 66.46, H 6.85, N 3.52. Found: C 66.35, H 6.79, N 3.66.

5-*endo*-Acetyl-7-[1-[2-(trimethylsilyl)ethoxymethyl]indol-2-yl]-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene (3). White oil. Yield: 61%. R_f 0.15 (hexane:AcOEt 2:1). ^1H NMR ($CDCl_3$) δ 7.42 (1H, d, J=8 Hz), 7.38 (1H, dd, J=8 Hz), 7.20 (1H, t, J=8 Hz), 7.08 (1H, t, J=8 Hz), 6.70 (1H, dd, J=6, 2 Hz), 6.61 (1H, s), 5.62 (1H, m), 5.30 (2H, AB system), 3.91 (1H, dd, J=6, 2 Hz), 3.58 (2H, t, J=9 Hz), 3.19 (1H, ddd, J=10, 3.4, 2 Hz), 2.41 (1H, ddd, J=13, 10, 3.5 Hz), 2.15–2.00 (1H, m); 2.11 (3H, s); 0.87 (2H, t, J=9 Hz), −0.05 (9H, s); ^{13}C NMR ($CDCl_3$) δ 172.0, 170.7, 139.5, 136.0, 134.4, 127.4, 123.8, 123.5, 121.0, 120.8, 109.7, 104.2, 77.6, 72.9, 66.1, 43.4, 30.0, 28.4, 20.7, 17.9, −1.5 (3C); IR ($CHCl_3$) cm^{-1} 1750, 1710, 1160; Anal. Calcd for $C_{23}H_{29}NO_4Si$: C 67.12, H 7.11, N 3.40. Found: C 67.15, H 7.18, N 3.46.

Diels–Alder reactions of 1 with silica gel as catalyst

To a solution of 5-[1-[2-(trimethylsilyl)ethoxymethyl]indol-2-yl]pyran-2-one (**1**) (1 mmol) in CH_2Cl_2 (10 ml), commercial chromatography silica gel (EM Science #60., 5 g/mmol of indolylpyrone) and dienophile (ethylvinylether, butylvinylether, phenylvinylthioether, naphthylmethylvinylether) (3 mmol) was added at room temperature. After stirring for the time shown in Table 1 the solvent was evaporated and purification by chromatography on silica gel, afforded the product.

5-*endo*-Ethoxy-7-[1-[2-(trimethylsilyl)ethoxymethyl]indol-2-yl]-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene (4). Yellow oil. Yield: 83%. R_f 0.15(Et_2O:hexane 1:2). ^1H NMR ($CDCl_3$) δ 7.56 (1H, d, J=8 Hz), 7.42 (1H, d, J=8 Hz), 7.22 (1H, t, J=8 Hz), 7.11 (1H, t, J=8 Hz), 6.71 (1H, bd, J=5 Hz), 6.63 (1H, s), 5.58 (1H, m), 5.43 (2H, AB system), 4.12–4.02 (2H, m), 3.66 (2H, t, J=8 Hz), 3.60–3.51 (1H, m), 3.49–3.38 (1H, m), 2.62 (1H, ddd, J=13, 7, 3 Hz), 1.61 (1H, ddd, J=13, 2, 1 Hz), 1.11 (3H, t, J=8 Hz), 0.9 (2H, t, J=8 Hz), 0.00 (9H,s), ^{13}C NMR ($CDCl_3$) δ 172.0, 139.5, 134.9, 134.8, 127.6, 122.9, 123.4, 121.1, 120.9, 109.7, 103.8, 77.5, 72.9, 71.3, 66.1, 64.3, 46.9, 35.2, 18.0, 15.3, −1.4 (3C); EIMS 414 (25%), 341 (75%), 283 (100%). IR ($CHCl_3$) cm^{-1} 1740, 1450; Anal. Calcd for $C_{23}H_{31}NO_4Si$: C 66.79, H 7.56, N 3.39. Found: C 66.71, H 7.65, N 3.43.

5-*endo*-Butoxy-7-[1-[2-(trimethylsilyl)ethoxymethyl]indol-2-yl]-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene (5). Yellow oil. Yield: 50%. R_f 0.15 (Et_2O:hexane 1:2). ^1H NMR ($CDCl_3$) δ 7.59 (1H, d, J=8 Hz), 7.42 (1H, d, J=8 Hz), 7.26 (1H, t, J=8 Hz), 7.13 (1H, t, J=8 Hz), 6.72 (1H, bd, J=5 Hz), 6.65 (1H, s), 5.59 (1H, m), 5.42 (2H, AB system), 4.10–4.03 (2H, m), 3.65 (2H, t, J=9 Hz), 3.54–3.32 (2H, m), 2.64 (1H, ddd, J=15, 9, 4 Hz), 1.65 (1H, ddd, J=15, 2, 1 Hz), 1.57–1.46 (2H, m), 1.42–1.28 (2H, m), 0.95 (3H, t, J=8 Hz), 0.87 (2H, t, J=8 Hz), 0.00 (9H, s); ^{13}C NMR ($CDCl_3$) δ:171.9, 1349.4, 134.9, 134.7, 127.5, 123.9, 123.3, 121.0, 120.8, 109.8, 103.8, 77.4, 72.4, 71.4, 69.6, 66.1, 48.9, 35.1, 31.8, 19.2, 17.9, 13.8, −1.5 (3C); IR ($CHCl_3$) cm^{-1} 1740, 1450; Anal. Calcd for $C_{25}H_{35}NO_4Si$: C 67.99, H 7.99, N 3.17. Found: C 70.01, H 7.96, N 3.15.

5-*endo*-Sulfanyl-7-[1-[2-(trimethylsilyl)ethoxymethyl]-indol-2-yl]-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene (6). Amorphous solid. Yield: 40%. R_f 0.25 (AcOEt:hexane 1:4). ^1H NMR ($CDCl_3$) δ: 7.59 (1H, d, J=8 Hz), 7.48 (2H, d, J=8 Hz), 7.38–7.21 (5H, m), 7.12 (1H, t, J=8 Hz), 6.88 (1H, bd, J=5 Hz), 6.71 (1H, s), 5.66 (1H, m), 5.58 (2H, AB system), 3.81–3.60 (4H, m), 2.82 (1H, ddd, J=15, 10, 3 Hz), 1.58 (1H, ddd, J=15, 1.5, 1 Hz), 1.02–0.91 (2H, m), 0.00 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 173.2, 139.6, 134.6, 134.1, 133.4, 132.5 (2C), 128.7 (2C), 128.5, 127.5, 125.4, 123.6, 121.1, 120.9, 109.8, 104.4, 80.8, 73.0, 66.2, 45.9, 40.6, 33.8, 16.0, −1.4 (3C); IR ($CHCl_3$) cm^{-1} 1745, 1445; Anal. Calcd for $C_{27}H_{31}NO_3SiS$: C 67.88, H 6.55, N 2.93. Found: C 67.91, H 6.59, N 2.95.

5-*endo*-Naphthylmethoxy-7-[1-[2-(trimethylsilyl)ethoxymethyl]indol-2-yl]-3-oxo-2-oxabicyclo[2.2.2]oct-7-ene (7). Amorphous solid. Yield: 65%. R_f 0.21 (AcOEt:hexane 2:8). ^1H NMR ($CDCl_3$) δ: 8.09–8.00 (1H, m), 7.91–7.80 (2H, m), 7.65–7.40 (6H, m), 7.24 (1H, t, J=8 Hz), 7.13 (1H, t, J=8 Hz), 6.76 (1H, dd, J=7, 2 Hz), 6.68 (1H, s), 5.63 (1H, ddd, J=4, 2, 2 Hz), 5.40 (2H, AB system), 5.00 (2H, AB system), 4.32 (1H, ddd, J=8, 3, 3 Hz), 4.37 (1H, dd, J=7, 3 Hz), 3.60 (2H, t, J=8 Hz), 2.66 (1H, ddd, J=12, 8, 4 Hz), 1.78 (1H, ddd, J=12, 3, 2 Hz), 0.90 (2H, t, J=8 Hz), −0.05 (9H, s); ^{13}C NMR ($CDCl_3$) δ:171.5, 142.0, 135.2, 133.9, 133.0, 132.0, 129.0, 128.7, 128.5, 126.5, 126.3, 125.9, 125.2, 124.1, 123.7, 123.4 (2C), 121.1, 120.9, 109.8, 104.0, 77.0, 73.0, 71.3, 69.8, 66.1, 47.2, 35.1, 18.1, −1.5 (3C); IR ($CHCl_3$) cm^{-1} 1740, 1450; Anal. Calcd for $C_{32}H_{35}NO_4Si$: C 73.11, H 6.71, N 2.66. Found: C 73.15, H 6.76, N 2.57.

Diels–Alder reactions of 1 with lanthanide shift reagents as catalyst

After stirring a solution of catalyst (10%) and 5-[1-[2-(trimethylsilyl)ethoxymethyl]indol-2-yl]pyran-2-one (**1**)

(1 mmol) in CH_2Cl_2 (10 ml), at 0°C for 20 min, dienophile (ethylvinylether, butylvinylether, phenylvinylthioether, naphthylmethylvinylether) (3 mmol) was added. After stirring for the time shown in Table 1 the solvent was evaporated and purification by chromatography on silica gel, afforded the product.

Reaction of 4 with primary amines

To a solution of **4** (0.6 mmol) in THF (5 ml) primary amine (12 mmol) was added and the mixture was stirred for 24 h. Evaporation of the solvent and purification by flash chromatography gave the products **8** or **9**.

6-Ethoxy-4-hydroxy-3-[1-[2-(trimethylsilyl)ethoxymethyl]-indol-2-yl]cycloex-2-ene carboxylic acid 2-*t*-butyldimethylsilylhydroxyethyl) amide (8). Amorphous solid. Yield 74%. R_f 0.24 (AcOEt:hexane 2:3); ^{1}H NMR (Acetone d_6) δ (ppm): 7.52 (1H, d, J=8 Hz), 7.51 (1H, d, J=8 Hz), 7.30–7.23 (1H, m), 7.18 (1H, t, J=8 Hz), 7.09 (1H, t, J=8 Hz), 6.55 (1H, s), 6.09 (1H, d, J=3 Hz), 5.53 (2H, A part of AB system), 4.72–4.68 (1H, m), 4.15–4.08 (1H, m), 4.10–4.02 (1H, m), 3.80–3.71 (1H, m), 3.70–3.61 (2H, m), 3.60–3.48 (2H, m), 3.46–3.31 (2H, m), 3.15 (1H, dd, J=8, 2 Hz), 2.80 (1H, bs), 2.37 (1H, ddd, J=12, 6, 2 Hz), 1.79 (1H, ddd, J=12, 12, 6 Hz), 1.20 (3H, t, J=6 Hz), 1.25 (11H, bs), 0.25 (6H, s), 0.00 (9H, s); ^{13}C NMR (Acetone d_6) δ (ppm): 172.2, 140.4, 139.6, 132.6, 129.7, 129.4, 121.9, 120.3 (2C), 110.5, 101.9, 73.0, 72.6, 67.5, 65.2, 63.9, 62.1, 51.0, 41.9, 36.7, 25.6 (3C), 19.15, 17.5, 15.4, −1.5 (3C), −5.8 (2C); IR ($CHCl_3$) cm^{-1} 1660, 1450; Anal. Calcd for $C_{31}H_{52}N_2O_5Si_2$: C 63.22, H 8.90, N 4.76. Found: C 63.45, H 9.05, N 4.77.

6-Ethoxy-4-hydroxy-3-[1-[2-(trimethylsilyl)ethoxymethyl]-indol-2-yl]cycloex-2-ene carboxylic acid 2,2-dimethoxyethyl amide (9). Amorphous solid. Yield 82%. R_f 0.16 (AcOEt:hexane 2:3); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.55 (1H, d, J=8 Hz), 7.42 (1H, d, J=8 Hz), 7.24 (1H, t, J=8 Hz), 7.13 (1H, t, J=8 Hz), 6.80 (1H, bs), 7.11 (1H, s), 6.25 (1H, d, J=3 Hz); 5.62 (1H, A part of AB system), 5.48 (1H, B part of AB system), 4.65 (1H, bt, J=4 Hz), 4.40 (1H, t, J=6 Hz), 3.98 (1H, ddd, J=12, 8, 4 Hz), 3.78 (1H, qd, J=14, 7 Hz), 3.64–3.42 (5H, m), 3.4 (6H, s), 3.12 (1H, dd, J=9, 2 Hz), 2.90–2.80 (1H, bs), 2.43 (1H, dt, J=14, 3 Hz), 1.78 (1H, ddd, J=13, 9, 4 Hz), 1.33 (3H, t, J=7 Hz), 0.87 (2H, m), 0.00 (9H, s); ^{13}C NMR ($CDCl_3$) δ (ppm): 172.0, 139.1, 138.4, 131.9, 128.6, 127.9, 122.3, 120.5 (2C), 109.7, 102.9, 102.4, 72.6, 72.3, 67.9, 65.9, 64.0, 54.0 (2C), 49.2, 40.9, 35.5, 17.9, 15.3, −1.5 (3C); IR ($CHCl_3$) cm^{-1} 1660, 1470, 1250, 1100; Anal. Calcd for $C_{27}H_{42}N_2O_6Si$: C 62.51, H 8.17, N 5.40. Found: C 62.75, H 8.36, N 5.65.

Acknowledgements

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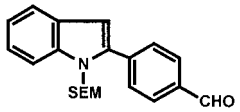
6. 2-(4-Phenylcarboxyaldehyde)[(trimethylsilyl)ethoxymethyl]-1H-indole. R_f 0.15 (Et_2O:hexane 1:1). ^{1}H NMR ($CDCl_3$) δ: 10.11 (1H, s), 8.05 (2H, AA′ part of AA′BB′ system), 7.90 (2H, BB′ part of AA′BB′ system), 7.65 (1H, d, J=8 Hz), 7.52 (1H, d, J=8 Hz), 7.30 (1H, t, J=8 Hz), 7.18 (1H, t, J=8 Hz), 6.74 (1H, s), 5.49 (2H, s), 3.61 (2H, t, J=8 Hz), 0.95 (2H, t, J=8 Hz), 0.02 (9H, s); FABMS: 352 (MH^+).



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