$InBr_3$-Catalyzed Conjugate Addition of Indoles to *p*-Quinones: An Efficient Synthesis of 3-Indolylquinones

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Abstract: Indium(III) bromide catalyzes efficiently the conjugate addition of indoles to *p*-benzoquinones under mild conditions to afford the corresponding 3-indolylquinones in high yields with high selectivity. 1,4-Naphthoquinones also underwent Michael addition with indoles under similar conditions to give 3-indolylnaphthoquinones.

Key words: *p*-quinones, indoles, indium compounds, indol-3-ylbenzoquinones

The 3-indolylbenzoquinone is a core structure in various natural products such as asterriquinones.[1] Bis(indolyl)quinones (Figure 1) have been isolated from a wide range of fungi, including *Aspergillus terreus*, *Chaetomium* sp., and *Pseudomassaria* sp.[2] The asterriquinones exhibit a wide spectrum of biological activities including antitumor properties and function as inhibitors of HIV reverse transcriptase.[3] Asterriquinone A1, has been shown to arrest the cell cycle in G_1 and promote apoptotic cell death.[4] Recently, asterriquinone has been reported as an orally active nonpeptidyl mimetic of insulin with antidiabetic activity.[5] All these properties apparently stem from the ability of asterriquinones to either promote or prevent protein-protein interactions.

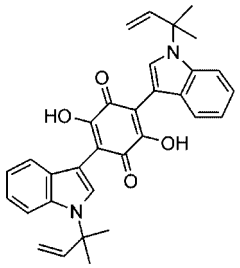


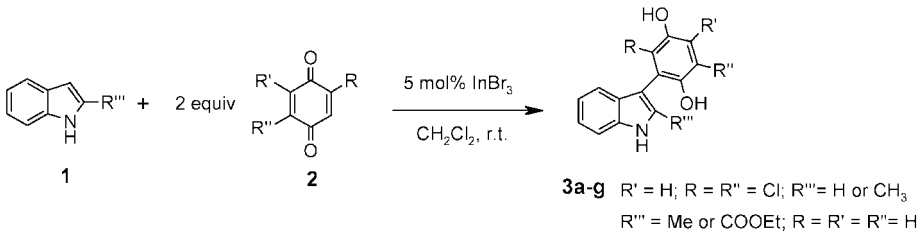
Figure 1 Asterriquinone A1

Generally, 3-indolylbenzoquinones are prepared by the condensation of indoles with quinones under acidic conditions.[6,7] Despite their wide range of pharmacological activities, the synthesis of indol-3-ylbenzoquinones has received little attention. Therefore, the development of an efficient and versatile catalytic method for the construction of indol-3-ylbenzoquinone core structure would widen the scope of this methodology.

Recently, indium halides have emerged as mild and water-tolerant Lewis acids imparting high regio-, chemo-, and stereoselectivity in various organic transformations.[8] Compared to conventional Lewis acids, particularly indium tribromide has advantages of low catalyst loading, moisture stability and catalyst recycling. Thus, indium(III) bromide has been shown to be a more efficient catalyst over conventional Lewis acids in promoting various transformations including glycosidation, thioacetalization, cyanation of ketones and conjugate addition reactions.[9]

In this report, we wish to describe a simple, convenient and efficient protocol for the synthesis of indol-3-ylbenzoquinones using indium tribromide as a novel catalyst. Thus, 2,5-dichloro-*p*-benzoquinone on treatment with indole in the presence of 5 mol% of indium(III) bromide at room temperature gave 2,5-dichloro-3-indolylhydroquinone **3a** in 85% yield (Scheme 1).

These 2,5-dihalo-3-indolylquinones are useful precursors in the total synthesis of asterriquinone natural products.[10] The 2,5-dichloro-3-indolylquinone can be easily converted to the corresponding 2,5-dihydroxy-3-indolylquinone



Scheme 1

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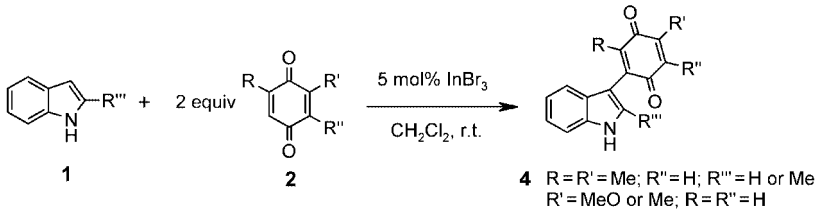
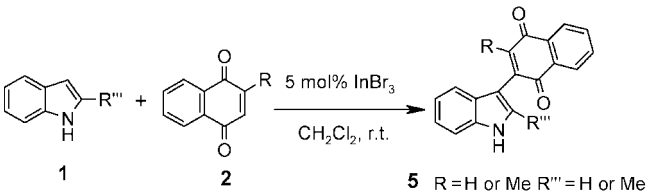


Scheme 2

which is a core structure in asterriquinone.[7a] Similarly, 2-methyl-, *N*-methyl-, 5-bromo-, and 7-ethyl substituted indoles reacted smoothly with 2,5-dichlorobenzoquinone under the reaction conditions to give the corresponding 2,5-dichloro-3-indolylhydroquinones (Table 1, entries **3b**–**e**). However, treatment of parent benzoquinone with indole under similar conditions gave bis(indolyl)hydroquinone **3h**[1] in 80% yield. Furthermore, substituted quinones such as 2-methyl-, 2-methoxy-, 2,6-dimethyl-*p*-benzoquinones and indole or 2-methylindole gave the corresponding indol-3-ylbenzoquinones in high yields (Scheme 2, Table 1, entries **4i**–**l**).

In a similar fashion, 1,4-naphthoquinone (**2**, R = H) and 2-methyl-1,4-naphthoquinone (**2**, R = Me) afforded 2-(3-indolyl)-1,4-naphthoquinones **5** under identical conditions (Scheme 3, Table 1, entries **5m**–**o**).



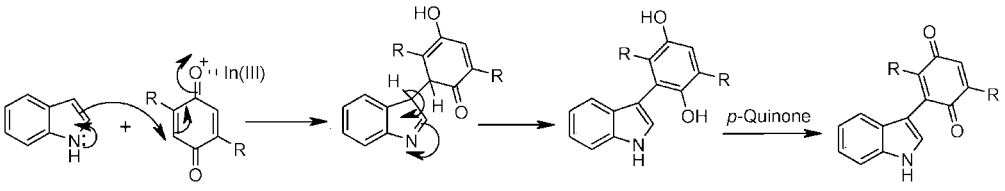
Scheme 3

In all cases, the reaction proceeds rapidly at room temperature with high regioselectivity. As solvent, dichloromethane appears to give the best results. The products were characterized by NMR, IR and mass spectroscopic data and also by comparison with authentic samples.[7b] The probable mechanism seems to be the addition of indole to the unsaturated position of the quinone, which is activated by indium tribromide. The initial addition product tautomerizes to the hydroquinone, which subsequently undergoes rapid oxidation with another equivalent of *p*-quinone resulting in the formation of the indol-3-ylquinone (Scheme 4).

This method is clean and free from chlorinated side products, which are normally observed under protic acid (conc. HCl in THF) conditions. This method also works well with electron-deficient, 2-ethoxycarbonylindole to give the corresponding indol-3-ylhydroquinone in 78% yield (entry **3g**). However, most of the reported methods fail to produce 3-indolylquinones with electron-deficient indoles. Thus, this method is an efficient and very useful synthetic procedure for the synthesis of natural product core structures. Among various Lewis acids such as $InCl_3$, $CeCl_3 \cdot 7H_2O$ and YCl_3 studied for this reaction, indium(III) bromide was found to be the most effective in terms of conversion and reaction rates. However, similar yields and selectivity were also obtained using 5 mol% of $BiCl_3$ under these reaction conditions. The scope and generality of this process is illustrated with respect to various indoles and a wide range of quinones and the results are presented in Table 1.

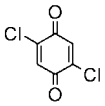
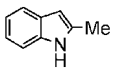
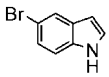
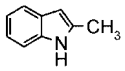
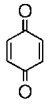
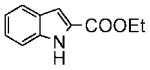
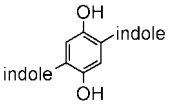
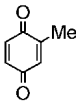
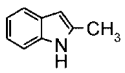
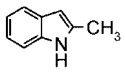
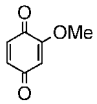
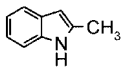
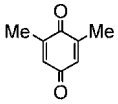
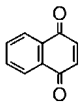
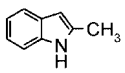
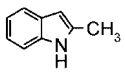
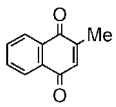
In summary, we have described a simple, convenient and high yielding protocol for the preparation of 3-indolylquinones via the nucleophilic addition of indoles to quinones using $InBr_3$ as a novel catalyst. This method is applicable to both electron-rich as well as electron-deficient indoles and is useful for the total synthesis of naturally occurring asterriquinones. The attractive features of this process are mild reaction conditions, short reaction times, cleaner reactions with improved yields, no formation of by-products such as chloroquinones, ready availability of starting materials, high regioselectivity, and simplicity in experimental procedure. The use of air and moisture stable indium reagent makes this process useful and attractive for the synthesis of 3-indolylquinone core structures.

Melting points were recorded on Büchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as inter-



Scheme 4

Table 1 Indium(III) Bromide-Catalyzed Addition of Indoles to *p*-Quinones

Entry	Indole	Quinone	Product[a]	Time (min)	Yield (%)[b]
a			**3a**	35	85
b			**3b**	25	90
c			**3c**	45	83
d			**3d**	50	79
e			**3e**	40	84
f			**3f**	30	86
g			**3g**	30	78
h			 **3h′**	45	80[c]
i			**4i**	30	82
j			**4j**	35	85
k			**4k**	30	88
l			**4l**	35	84
m			**5m**	50	80
n			**5n**	35	85
o			**5o**	50	83

[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Isolated and unoptimized yields.
[c] Bis(indolyl)hydroquinone was isolated.

nal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

Indium(III) Bromide-Catalyzed Addition of Indoles to *p*-Quinones and 1,4-Naphthoquinones; General Procedure

A mixture of *p*-quinone **2** (2.5 mmol), indole **1** (1 mmol) and $InBr_3$ (5 mol%) in CH_2Cl_2 (10 mL) was stirred at r.t. for the specified time (see Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with H_2O (15 mL) and extracted with CH_2Cl_2 (2 × 10 mL). Evaporation of the solvent followed by purification on silica gel (Merck, 100–200 mesh, EtOAc–hexane, 0.5–9.5) afforded pure indol-3ylquinone.

2,5-Dichloro-3-(1*H*-indol-3-yl)-1,4-benzenediol (3a)

Solid, mp 81–82 °C.

IR (KBr): 3425, 2923, 2852, 1642, 1561, 1420, 1244, 1008, 878, 744, 592 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 5.15 (br s, 1 H, OH), 5.30 (br s, 1 H, OH), 7.05 (d, *J* = 1.9 Hz, 1 H), 7.10–7.35 (m, 5 H), 8.70 (br s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 113.0, 116.5, 118.0, 119.6, 120.4, 120.8, 122.3, 124.0, 126.4, 127.8, 128.4,130.9, 138.2, 147.8.

EIMS: *m*/*z* (%) = 293 (M^+, 10), 256 (20), 119 (100), 82 (30), 43 (70), 29 (20).

2,5-Dichloro-3-(2-methyl-1*H*-indol-3-yl)-1,4-benzenediol (3b)

Solid, mp 182–183 °C.

IR (KBr): 3405, 2922, 1653, 1446, 1247,1219, 1136, 854, 771 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.38 (s, 3 H), 5.10 (br s, 1 H, OH), 5.35 (br s, 1 H, OH), 7.05–7.38 (m, 5 H), 8.25 (br s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.2, 106.7, 111.4, 116.0, 119.2, 119.4, 119.7, 120.9, 121.6, 125.0, 128.5, 135.3, 136.3, 145.6, 147.2.

EIMS: *m*/*z* (%) = 307 (M^+, 100), 273 (15), 237 (10), 154 (35), 137 (45), 95 (50), 69 (100), 55 (100).

2,5-Dichloro-3-(1-methyl-1*H*-indol-3-yl)-1,4-benzenediol (3c)

Solid, mp 146 °C.

IR (KBr): 3459, 2921, 2852, 1615, 1433, 1378, 1129, 853, 736 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 5.30 (br s, 2 H OH), 7.05 (d, *J* = 1.8 Hz, 1 H), 7.10–7.45 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.6, 107.8, 110.2, 115.4, 118.7, 119.7, 120.2, 120.5, 121.4, 124.7, 127.3, 130.4, 136.8, 146.3, 146.9.

EIMS: *m*/*z* (%) = 307 (M^+, 20), 273 (15), 207 (10), 144 (15), 121 (20), 109 (30), 95 (50), 83 (50), 69 (100), 55 (50).

3-(5-Bromo-1*H*-indol-3-yl)-2,5-dichloro-1,4-benzenediol (3d)

Solid, mp 220 °C.

IR (KBr): 3458, 2923, 2853, 1653, 1460, 1377, 1128, 852, 767 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 1.8 Hz, 1 H), 7.25–7.30 (m, 2 H), 7.35–7.40 (m, 1 H), 7.56–7.60 (m, 1 H), 8.70 (br s, 1 H, NH).

EIMS: *m*/*z* (%) = 373 (20), 237 (15), 154 (60), 137 (100), 123 (50), 115 (20), 109 (80).

2,5-Dichloro-3-(7-ethyl-1*H*-indol-3-yl)-1,4-benzenediol (3e)

Solid, mp 73–75 °C.

IR (KBr): 3391, 2926, 2855, 2359, 1675, 1454, 1218, 1012, 770 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 6.9 Hz, 3 H), 2.80 (q, *J* = 6.9 Hz, 2 H), 5.15 (br s, 1 H, OH), 5.25 (br s, 1 H, OH), 7.10–7.45 (m, 5 H), 8.40 (br s, 1 H, NH).

EIMS: *m*/*z* (%) = 321 (M^+, 100), 306 (60), 195 (10), 156 (20), 97 (50), 71 (80), 57 (80), 43 (50).

2-(2-Methyl-1*H*-indol-3-yl)-1,4-hydroquinone (3f)

Solid, mp 106–108 °C.

IR (KBr): 3279, 2923, 1636, 1565, 1457, 1294, 1010, 774 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 4.40 (br s, 1 H, OH), 4.60 (br s, 1 H, OH), 6.70–6.80 (m, 2 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 7.05–7.20 (m, 2 H), 7.30–7.45 (m, 2 H), 8.05 (br s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.9, 109.9, 110.8, 114.3, 116.1, 116.8, 118.3, 118.9, 120.5, 122.9, 128.3, 133.3, 135.6, 147.8, 149.8.

EIMS: *m*/*z* (%) = 239 (M^+, 30), 155 (10), 141 (20), 199 (100), 82 (95), 47 (80).

Ethyl 3-(2,5-Dihydroxyphenyl)-2-indolecarboxylate (3g)

Solid, mp 129–130 °C.

IR (KBr): 3412, 2964, 2929, 2360, 1562, 1436, 1334, 1219, 1123, 854, 770 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.0 Hz, 3 H), 4.30 (q, *J* = 7.0 Hz, 2 H), 5.25 (br s, 2 H, OH), 6.75–6.81 (m, 1 H), 6.85–6.90 (m, 1 H), 7.10–7.20 (m, 2 H), 7.30–7.45 (m, 2 H), 7.60 (d, *J* = 8.0 Hz, 1 H), 9.05 (br s, 1 H NH).

EIMS: *m*/*z* (%) = 297 (10), 252 (60), 168 (20),139 (20), 110 (20), 68 (25), 42 (100).

2,5-Bis(1*H*-indol-3-yl)-1,4-hydroquinone (3h)[1]

Solid, mp 116–118 °C.

IR (KBr): 3398, 1618, 1457, 1337, 1096, 743 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 4.80 (br s, 2 H, OH), 7.05 (d, *J* = 1.7 Hz, 2 H), 7.10–7.45 (m, 8 H), 7.80 (d, *J* = 8.1 Hz, 2 H), 8.30 (br s, 2 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 112.8, 113.9, 116.9, 117.6, 120.2, 122.2, 124.2, 126.5, 127.2, 137.3, 147.9.

EIMS: *m*/*z* (%) = 341 (M^+, 100), 257 (10), 228 (12), 156 (15), 142 (70), 84 (80), 47 (20).

2-(1*H*-Indol-3-yl)-5-methylbenzo-1,4-quinone (4i)

Solid, mp 182 °C.

IR (KBr): 3276, 1739, 1667, 1635, 1565, 1295, 1253, 1119, 714 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.10 (s, 3 H), 6.58–6.61 (m, 1 H), 7.15 (d, *J* = 1.8 Hz, 1 H), 7.20–7.30 (m, 3 H), 7.38–7.42 (m, 1 H), 7.88–7.90 (m, 1 H), 8.50 (br s, 1 H NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.9, 108.0, 112.9, 120.3, 121.5, 122.9, 125.8, 132.0, 133.5, 134.0, 137.3, 140.8, 145.7, 187.6, 188.4.

EIMS: *m*/*z* (%) = 237 (M^+, 50), 209 (10), 141 (50), 120 (60), 88 (100), 43 (15).

2-Methyl-5-(2-methyl-1*H*-indol-3-yl)benzo-1,4-quinone (4j)

Solid, mp 196–197 °C.

IR (KBr): 3398, 2362, 1616, 1457, 1219 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.15 (s, 3 H), 2.40 (s, 3 H), 6.65–6.70 (m, 1 H), 6.75–6.80 (m, 1 H), 7.05–7.25 (m, 3 H), 7.40–7.48 (m, 1 H), 8.10 (br s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6, 15.4, 105.9, 111.2, 119.2, 120.1, 121.5, 127.6, 132.9, 133.8, 138.3, 142.3, 145.4, 146.3, 187.2, 187.8.

EIMS: *m*/*z* (%) = 251 (M^+, 40), 186 (50), 154 (30),121 (40), 77 (100), 41 (40).

2-Methoxy-5-(2-methyl-1*H*-indol-3-yl)benzo-1,4-quinone (4k)
Solid, mp 198–199 °C.

IR (KBr): 3270, 2362, 1738, 1667, 1635, 1591, 1565, 1458, 1421, 1294, 1118, 715 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 3.90 (s, 3 H), 5.98–6.05 (m, 1 H), 6.78–6.81 (m, 1 H), 7.10–7.20 (m, 2 H), 7.25–7.30 (m, 1 H), 7.45–7.50 (m, 1 H), 8.20 (br s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 87.9, 106.7, 108.6, 111.8, 119.7, 120.8, 122.2, 128.1, 129.8, 136.3, 139.4, 143.4, 159.3, 182.4, 187.6.

EIMS: *m*/*z* (%) = 267 (M^+, 35), 156 (40), 142 (100), 69 (50), 43 (70).

3,5-Dimethyl-2-(2-methyl-1*H*-indol-3-yl)benzo-1,4-quinone (4l)
Solid, mp 72–74 °C.

IR (KBr): 2361, 1521, 1376, 1263, 772 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.0 (s, 3 H), 2.20 (s, 3 H), 2.30 (s, 3 H), 6.70 (s, 1 H), 7.05–7.20 (m, 2 H), 7.25–7.30 (m, 2 H), 8.10 (br s, 1 H, NH).

EIMS: *m*/*z* (%) = 265 (M^+, 100), 250 (50), 222 (20), 194 (20), 168 (30), 118 (15), 69 (25), 43 (50).

2-(1*H*-Indol-3-yl)-1,4-naphthoquinone (5m)
Solid, mp 176 °C.

IR (KBr): 3398, 2362, 1617, 1457, 1219, 772 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.27–7.35 (m, 2 H), 7.40–7.48 (m, 2 H), 7.71–7.80 (m, 2 H), 7.95–8.05 (m, 1 H), 8.10–8.19 (m, 2 H), 8.55–8.60 (m, 1 H), 8.65 (br s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 107.7, 112.9, 120.3, 121.7, 123.0, 125.1, 125.5, 126.9, 128.0, 131.9, 132.3, 132.8, 134.0, 134.4, 137.0, 142.5, 184.6, 185.3.

EIMS: *m*/*z* (%) = 273 (M^+, 20), 158 (100), 142 (90), 104 (75), 76 (70), 43 (90).

2-(2-Methyl-1*H*-indol-3-yl)-1,4-naphthoquinone (5n)
Solid, mp 180 °C.

IR (KBr): 3274, 2922, 1739, 1634, 1457, 1254, 714 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.50 (s, 3 H), 7.10 (s, 1 H), 7.15–7.20 (m, 2 H), 7.25–7.30 (m, 1 H), 7.50–7.60 (m, 1 H), 7.70–7.80 (m, 2 H), 8.10–8.20 (m, 2 H), 8.25 (br s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 107.6, 111.1, 119.7, 121.2, 122.6, 126.3, 127.4, 128.0, 132.6, 133.2, 133.9, 134.1, 135.1, 135.9, 137.5, 144.8, 185.2, 185.7.

EIMS: *m*/*z* (%) = 287 (M^+, 20), 270 (15), 230 (100).

2-Methyl-3-(2-methyl-1*H*-indol-3-yl)-1,4-dihydro-1,4-naphthalenedione (5o)
Solid, mp 130 °C.

IR (KBr): 3389, 2927, 2855, 2360, 1656, 1561, 1245, 1010, 769, 595 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.10 (s, 3 H), 2.30 (s, 3 H), 7.05–7.20 (m, 2 H), 7.25–7.30 (m, 2 H), 7.70–7.80 (m, 2 H), 8.10–8.25 (m, 2 H), 8.30 (br s, 1 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 16.3, 106.6, 112.1, 120.1, 120.4, 121.7, 127.0, 127.4, 128.9, 133.2, 133.3, 135.0, 136.6, 136.9, 141.8, 145.6, 184.6, 186.3.

EIMS: *m*/*z* (%) = 301 (M^+, 15), 286 (15), 149 (60), 69 (70), 42 (100).

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