Synthesis of Sterically Protected Isoindoles from ortho-Phthalaldehyde

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Abstract

o-Phthalaldehyde (OPA) reacts with O-protected tris(hydroxyalkyl)aminomethanes in the presence of 1-propanethiol to afford a novel class of stable isoindoles. Steric protection provided by the bulkiness of C3-symmetric primary amines derived from tris(hydroxyalkyl)aminomethane could be significant for the stabilization of 1-alkylthio-2-alkyl-substituted isoindoles derived from OPA. A plausible reaction mechanism is proposed to explain the formation of the isoindole and an isoindolin-1-one by-product.

Key words o-phthalaldehyde, isoindole, steric protection, isoindolin-1-one

Benzo[c]pyrrole, also called isoindole, is a regioisomer of benzo[b]pyrrole or, more commonly, indole. In 1971, Roth reported that o-phthalaldehyde (OPA) reacted with amino acids in alkaline medium in the presence of 2-mercaptoethanol to furnish 1-alkylthio-2-alkyl-substituted isoindoles (Scheme 1). As the resultant isoindole is sensitively detected by its fluorescence (λem = 360 nm, λex = 455 nm), the three-component coupling reaction is generally used as one of the most valuable methods of analyzing primary amines including amino acids. In the OPA method mentioned above, the intrinsically nonfluorescent property of OPA is advantageous to the analysis of primary amines, while a drawback is the instability of the resulting 1-alkylthio-2-alkyl-substituted isoindoles, despite isoindole having a 10π-electron aromatic system. It is said that the steric bulk of the side chains derived from thiols and amines, such as tert-butyramine and tert-butythiol, increases the stability of the isoindoles. In general, appropriate steric protection of organic molecules is an effective strategy for stabilization. However, from a synthetic point of view, the stabilization effects of these reagents are insufficient to isolate the resulting 1-alkylthio-2-alkyl-substituted isoindoles in pure forms. To the best of our knowledge, few reports are available on the synthesis of stable and isolable 1-alkylthio-2-alkyl-substituted isoindoles based on the OPA method. In 2012, Sipos et al. reported the synthesis and biological activities of isoindole and benzoisoindole derivatives of glycopeptide antibiotics, which have large molecular sizes and function as primary amines in the OPA method. In this paper, we report on the synthesis of sterically protected 1-alkylthio-2-alkyl-substituted isoindoles using C3-symmetric bulky amines derived from tris(hydroxyalkyl)aminomethane based on the OPA method. HPLC analysis of a mixture of stable isoindoles derived from alkyl thiols, OPA, and O-benzylated tris(hydroxypropyl)aminomethane was also conducted.

A novel series of 1-alkylthio-2-alkyl-substituted isoindoles, which are stable enough to be isolated, has been designed and synthesized, making use of C3-symmetric primary amines in the OPA method. The C3-symmetric primary amines employed in this study were chosen to enhance the steric protection effect in isoindole molecules by further increasing the steric bulk of the tert-butyramine. Thus, a series of C3-symmetric primary amines 5a-g was prepared from tris(hydroxymethyl)aminomethane (1) or tris(hydroxypropyl)aminomethane (2), as shown in Scheme

**Scheme 1** The reaction of OPA with a primary amine and thiol
2. N,N-Dibenzyl tris(hydroxymethyl)aminomethane (3) was synthesized from 1 using benzyl bromide according to a modified procedure.9 O-Alkylation of 3 with alkyl iodides followed by hydrogenolysis catalyzed by palladium on activated charcoal (Pd-C) gave primary amines 5a and 5b, respectively. N-Boc-tris(hydroxymethyl)aminomethane (6),10 obtained from 1, was O-alkylated by the corresponding alkyl chlorides to afford N-Boc-protected amines 7c–e. Deprotection of 7c–e using trifluoroacetic acid (TFA) gave primary amines 5c–e. O-Benzylated amine 5f was also synthesized from 2 according to a similar procedure used for the preparation of 5c–e. In addition, reaction of 3 with triethyl orthoacetate followed by removal of the benzyl groups by hydrogenolysis furnished 5g,11 which was regarded as a less bulky primary amine than the other O-protected amines 5a–f.

In our attempt to synthesize stable and isolable 1-alkylthio-2-alkyl-substituted isoindoles by the OPA method, C3-symmetric primary amines 1, 2, and 5a–e were reacted with OPA and 1-propanethiol in anhydrous MeOH at room temperature in the dark using brown-tinted glassware as shown in Table 1. O-Protected amines 5a,b afforded isoindoles 11a,b with small amounts of isoindolin-1-ones 12a,b as by-products (entries 1 and 2). As expected, isoindoles 11a,b were stable and isolable by column chromatography on silica gel. When amines 5c–e were employed, the isolated yields of isoindoles 11c–e (54–60%) were relatively low, and isoindolin-1-ones 12c–e were obtained in 39–44% yields (entries 3–5). To examine the influence of the oxygen atom of C3-symmetric amine 5e originating from 1 on the formation of isoindolin-1-one 12e, O-benzylated

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**Scheme 2** Synthesis of C3-symmetric primary amines 5a–g starting from tris(hydroxymethyl)aminomethane (1) and tris(hydroxypropyl)aminomethane (2)

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**Table 1** Synthesis of 1-Alkylthio-2-alkyl-Substituted Isoindoles 11a–i by the OPA Method

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Yield of 11 (%)b</th>
<th>Yield of 12 (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OMe (5a)</td>
<td>65 (11a)</td>
<td>18 (12a)</td>
</tr>
<tr>
<td>2</td>
<td>OEt (5b)</td>
<td>85 (11b)</td>
<td>12 (12b)</td>
</tr>
<tr>
<td>3</td>
<td>OMOM (5c)</td>
<td>57 (11c)</td>
<td>41 (12c)</td>
</tr>
<tr>
<td>4</td>
<td>OMEM (5d)</td>
<td>54 (11d)</td>
<td>44 (12d)</td>
</tr>
<tr>
<td>5</td>
<td>OBOM (5e)</td>
<td>60 (11e)</td>
<td>39 (12e)</td>
</tr>
<tr>
<td>6</td>
<td>(CH2)2OBn (5f)</td>
<td>93 (11f)</td>
<td>ca. 6 (12f)c</td>
</tr>
<tr>
<td>7</td>
<td>orthoester (5g)</td>
<td>– (91g)</td>
<td>0 (12g)</td>
</tr>
<tr>
<td>8</td>
<td>OH (1)</td>
<td>– (11h)</td>
<td>0 (12h)</td>
</tr>
<tr>
<td>9</td>
<td>(CH2)2OH (2)</td>
<td>90 (11i)</td>
<td>0 (12i)</td>
</tr>
<tr>
<td>10</td>
<td>OMOM (5c)</td>
<td>– (11c)</td>
<td>56 (12c)</td>
</tr>
<tr>
<td>11</td>
<td>(CH2)2OH (2)</td>
<td>– (11i)</td>
<td>0 (12i)</td>
</tr>
</tbody>
</table>

a Reaction conditions: OPA (1 equiv), 1-propanethiol (1.1 equiv), amine (1.1 equiv).
b Isolated yield.
c Small amounts of impurities were included.
d Too labile to be isolated.
e Reaction without 1-propanethiol.
tris(hydroxypropyl)aminomethane 5f was reacted with OPA and 1-propanethiol. As a result, 1f afforded isoindole 11f in 93% yield and isoindolin-1-one 12f in ca. 6% yield (entry 6). On the other hand, isoindole 11g, synthesized from less bulky amine 5g, was too labile to be isolated (entry 7). In the reaction of triols 1 and 2, the 1-alkylthio-2-alkyl-substituted isoindoles 11h and 11i were also obtained, but 11b decomposed immediately after isolation by column chromatography on silica gel (entries 8 and 9). In addition, the reaction of OPA with amine 5c in the absence of 1-propanethiol was relatively slow and afforded isoindolin-1-one 12c in 56% yield (entry 10). In the reaction of 2 and OPA without 1-propanethiol, isoindolin-1-one 12i was not obtained at all (entry 11). When isoindole 11c, instead of OPA, was placed under the same reaction conditions as those noted in entry 3, 86% yield of 12c was recovered without production of 12c. Thus, the formation of isoindolin-1-one 12c is presumed not to be attributable to the hydrolysis of 11c under these reaction conditions.

Based on these results, plausible reaction pathways for the formation of isoindoles 11a–e (route A) and isoindolin-1-ones 12a–e (route B) have been proposed (Scheme 3). Route A is the standard pathway for the three-component coupling reaction based on the OPA method. On the other hand, neighboring group participation by an oxygen atom of the ether bond of each of amines 5a–e is involved in route B. In this case, the formation of the five-membered 1,3-oxazolidin-1-ium intermediate by intramolecular cyclization prevents intermolecular nucleophilic attack of 1-propanethiol. The ratios of the products of 11a–e and 12a–e seem to depend on the bond angle θ (N–C–C) of the corresponding C3-symmetric primary amines 5a–e. Amines 5c–e, which are presumed to have smaller θ values compared with 5a and 5b, are liable to follow pathway B. In the case of amine 5f, in which three oxygen atoms of 5e are replaced by three methylene units, this kind of neighboring group participation of an oxygen atom via a seven-membered 1,3-oxazepan-1-ium intermediate might be difficult to achieve.

Furthermore, 1-octanethiol and 1-dodecanethiol readily reacted with OPA and 5f to afford stable and isolable isoindoles 11j and 11k in 96% and 91% yields, respectively. To provide some preliminary data on the application as a novel method of analyzing thiols, HPLC analysis of an equimolar mixture of isoindoles 11f, 11j, and 11k was investigated with an ODS column. The results showed that isoindoles 11f, 11j, and 11k were easily resolved from one another, as shown in Figure 1. The area ratio for these three peaks derived from isoindoles 11f, 11j, and 11k (32.35:33.94:33.18) was almost identical to the respective molar ratio (1:1:1).

In summary, we have synthesized a novel series of 1-alkylthio-2-alkyl-substituted isoindoles 11a–f and 11i–k by the three-component coupling reaction of OPA, thiols (1-propanethiol, 1-octanethiol, and 1-dodecanethiol), and C3-symmetric bulky amines 2 and 5a–f. These isoindoles were stable enough to be isolated by column chromatography over silica gel. To the best of our knowledge, this is the first report of the synthesis of stable and isolable isoindoles based on the OPA method using modest molecular weight amines. Efforts toward the development of a novel analytical method of analyzing thiols, HPLC analysis of an equimolar mixture of isoindoles 11e was almost identical to the respective molar ratio (1:1:1).
method for thios by employing the formation of sterically protected isoindoles based on the OPA method are under way.

All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained with a JASCO FT/IR-6200 IR Fourier transform spectrometer. 1H NMR (500 MHz) and 13C NMR (125 MHz) spectra were recorded with a Bruker AV500 spectrometer. Chemical shifts are given in δ values (ppm) using TMS as an internal standard. HRMS (ESI) were recorded with a Waters LCT Premier spectrometer. Elemental combustion analyses were performed with a J-SCIENCE LAB JM10 microcorder. All reagents were used as purchased from Kanto Chemical. All other reagents were used as purchased.

2.5 Synthesis

(3-Aryl-3-methyl)-1,3-dimethoxy-2-(methoxymethyl)propan-2-amine (5a)

A mixture of 4a (270 mg, 0.790 mmol) and 10% Pd/C (84.0 mg, 0.0790 mmol) in MeOH (10 mL) was stirred at r.t. for 1.5 h under H2 atmosphere. The reaction mixture was filtered and concentrated in vacuo. The residue was dissolved in CHCl3 (30 mL) and washed with sat. aq NaHCO3 (20 mL). The organic layer was dried (MgSO4), filtered, and concentrated in vacuo to afford 5a. Yield: 118 mg (91%); pale-yellow oil.

1-3-Diethoxy-2-(ethoxymethyl)propan-2-amine (5b)

Synthesized from 4b according to the procedure used to prepare 5a. Yield: 170 mg (91%); pale-yellow oil.

tert-Butyl [1,3-Dihydroxy-2-(hydroxymethyl)propan-2-yl]carbamate (6)

To a solution of 1 (2.00 g, 16.5 mmol) in t-BuOH (27.5 mL)/MeOH (12.5 mL) was added di-tert-butyl dicarbonate (4.70 g, 21.5 mmol). After stirring for 18 h at r.t., the reaction mixture was evaporated in vacuo and the residue was washed with cool EtOAc to afford 6. Yield: 3.52 g (96%); white solid; mp 142.7–145 °C (colorless needles, EtOAc).

(3-Aryl-3-methyl)-1,3-diethoxy-2-(ethoxymethyl)propan-2-amine (4b)

Synthesized from 3 and ethyl iodide according to the procedure used to prepare 4a.

Yield: 467 mg (84%); pale-yellow oil.

1,3-Dimethoxy-2-(methoxymethyl)propan-2-amine (5a)

A mixture of 4a (270 mg, 0.790 mmol) and 10% Pd/C (84.0 mg, 0.0790 mmol) in anhydrous THF (6.6 mL) was added MOMCl (0.790 mL, 7.46 mmol). After stirring for 2 h at r.t., DIPEA (1.30 mL, 7.46 mmol) and MOMCl (0.790 mL, 7.46 mmol) was added to the reaction mixture. After stirring for a further 2 h at r.t., DIPEA (1.30 mL, 7.46 mmol) and MOMCl (0.790 mL, 7.46 mmol) were again added to the reaction mixture. After stirring for a final 2 h at r.t., the reaction mixture was evaporated in vacuo. The residue was dissolved in EtOAc (50 mL) and washed with brine (2 × 20 mL). The organic layer was dried (Na2SO4), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [silica gel 60N; n-hexane–EtOAc, 9:1] to afford 7c. Yield: 796 mg (100%); pale-yellow oil.
IR (neat): 3378, 2929, 2885, 1587, 1467, 1442, 1403, 1213, 1149, 1150, 1112, 1047 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 5.03 (br s, 1 H), 4.63 (s, 6 H), 3.82 (s, 6 H), 3.36 (s, 9 H), 1.42 (s, 9 H).

13C NMR (125 MHz, CDCl₃): δ = 154.7, 96.8, 79.1, 67.1, 57.8, 55.3, 28.3.


Anal. Calcd for C₁₁H₁₇NO₃: C, 65.15; H, 8.84; N, 4.02. Found: C, 65.14; H, 8.86; N, 4.02.

**tert-Butyl (9-{[(2-Methoxyethoxy)ethoxy]methyl}-2,5,7,11,13,16-hexaoxaheptadecan-9-yl)carbamate (7d)**

Synthesized from 6 and MEMCl according to the procedure used to prepare 7c.

Yield: 756 mg (87%); pale-yellow oil.

IR (neat): 3348, 3088, 3063, 2936, 2880, 1586, 1498, 1455, 1381, 1162, 1111, 1041 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 7.34–7.27 (m, 15 H), 4.77 (s, 6 H), 4.59 (s, 6 H), 3.58 (s, 6 H), 1.62 (br s, 2 H).

13C NMR (125 MHz, CDCl₃): δ = 137.7, 128.4, 127.8, 95.0, 70.2, 69.4, 55.4.

HRMS (ESI): m/z [M + Na]+ calcd for C₂₈H₃₅NO₆Na: 504.2362; found: 504.2362.

**tert-Butyl [1,7-Dihydroxy-4-(3-hydroxypropyl)heptan-4-yl]carbamate (8)**

Synthesized from 2 according to the procedure used to prepare 6.

Yield: 1.62 g (99%); mp 103.7–105 °C (colorless needles, CHCl₃).

IR (KBr): 3379, 3088, 3063, 2936, 2880, 1586, 1498, 1455, 1381, 1162, 1111, 1041 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 7.36–7.27 (m, 15 H), 4.47 (s, 6 H), 4.36 (t, J = 5.0 Hz, 3 H), 3.44–3.31 (m, 6 H), 1.49–1.47 (m, 6 H), 1.36–1.27 (m, 6 H).

13C NMR (125 MHz, CDCl₃): δ = 154.7, 137.7, 128.4, 127.9, 127.7, 95.0, 79.2, 69.4, 67.4, 57.9, 28.4.


**6-{[(1-Methoxyethoxy)methoxy]methyl}-2,4,8,10-tetraoxaundecan-6-amine (5c)**

To a solution of 7c (400 mg, 1.13 mmol) in anhydrous CH₂Cl₂ (5.5 mL) was added TFA (2.00 mL, 260 °C). After stirring for 50 min at 0 °C, 2N Na₂CO₃ (25 mL) was added and the mixture was extracted with CHCl₃ (3 × 30 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [silica gel PSQ 60B; CHCl₃–MeOH, 9:1] to afford 5c.

Yield: 272 mg (95%); pale-yellow oil.

IR (neat): 3352, 2945, 2856, 1715, 1479, 1454, 1390, 1364, 1248, 1170, 1100, 736, 698 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 6.07 (br s, 1 H), 4.36 (t, J = 5.0 Hz, 3 H), 3.34–3.31 (m, 6 H), 1.49–1.47 (m, 6 H), 1.36–1.27 (m, 6 H).

13C NMR (125 MHz, CDCl₃): δ = 153.9, 76.7, 61.3, 56.1, 31.0, 28.2, 26.5.


**tert-Butyl (1,7-Bis(benzyloxy)-4-[3-(benzyloxy)propyl]heptan-4-yl)carbamate (9)**

To a solution of 8 (300 mg, 0.982 mmol) and benzyl bromide (0.760 mL, 6.38 mmol) in anhydrous DMF (1.6 mL) was added KOH (379 mg, 6.75 mmol) at rt. under argon. The reaction mixture was stirred for 21 h at rt., for 2 h at 40 °C, and for 2 h at 60 °C. H₂O (20 mL) was added and the mixture was extracted with EtOAc (30 mL). The organic layer was washed with H₂O (2 × 20 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by column chromatography [silica gel PSQ 60B; n-hexane–EtOAc, 5:1 to 1:1] to afford 9.

Yield: 211 mg (37%); colorless oil.

IR (neat): 3352, 2945, 2856, 1715, 1479, 1454, 1390, 1364, 1248, 1170, 1100, 736, 698 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 7.35–7.26 (m, 15 H), 4.48 (s, 6 H), 4.40 (br s, 1 H), 3.72 (t, J = 6.4 Hz, 6 H), 1.67–1.65 (m, 6 H), 1.60–1.53 (m, 6 H), 1.39 (s, 9 H).

9-{[(2-Methoxyethoxy)methoxy]methyl}-2,5,7,11,13,16-hexaoxaheptadecan-9-amine (5d)

Synthesized from 7d according to the procedure used to prepare 5c.

Yield: 193 mg (97%); colorless oil.

IR (neat): 2928, 2881, 1457, 1413, 1365, 1244, 1200, 1117, 1043 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 7.25–7.19 (m, 15 H), 4.72 (s, 6 H), 3.69–3.67 (m, 6 H), 3.56–3.55 (m, 6 H), 3.50 (s, 6 H), 3.40 (s, 9 H), 1.66 (br s, 2 H).

13C NMR (125 MHz, CDCl₃): δ = 95.9, 71.7, 70.1, 66.8, 59.0, 55.4.

1C NMR (125 MHz, CDCl3): δ = 154.1, 138.5, 128.3, 127.6, 127.5, 78.5, 72.9, 70.6, 56.9, 31.9, 28.4, 23.7.


1H NMR (500 MHz, CDCl3): δ = 7.25–7.19 (m, 10 H), 4.07 (s, 6 H), 3.76 (s, 6 H), 1.46 (s, 3 H), 1.00 (br s, 6 H).

13C NMR (125 MHz, CDCl3): δ = 138.9, 128.3, 128.1, 127.2, 127.1, 72.9, 70.9, 52.8, 36.4, 24.0.


Anal. Calcd for C36H49NO5: C, 75.10; H, 8.58; N, 2.43. Found: C, 74.80; H, 8.09; N, 4.10.

Preparation of Isoindoles 11a–f and 11i–k; Typical Procedure

To a solution of 3 (1.00 g, 3.32 mmol) in toluene (6 mL) was added triethyl orthoacetate (605 μL, 3.32 mmol) at 0 °C. After stirring for 45 min at 80 °C, for 1.25 h at 100 °C, and for 36 h at 120 °C, the reaction mixture was evaporated in vacuo. The residue was purified by column chromatography [silica gel PSQ 60B; n-hexane–CH2Cl2, 1:9] to afford isoindole 11a (69.0 mg, 65%) accompanied by the for-
1H NMR (500 MHz, CDCl₃): δ = 7.66 (d, J = 8.6 Hz, 1 H), 7.50 (s, 1 H), 7.47 (d, J = 8.4 Hz, 1 H), 7.33–7.27 (m, 15 H), 7.01 (ddd, J = 8.5, 6.5, 0.8 Hz, 1 H), 6.93 (ddd, J = 8.3, 6.5, 0.7 Hz, 1 H), 4.72 (s, 6 H), 4.52 (s, 6 H), 4.48 (s, 6 H), 2.66 (t, J = 7.5 Hz, 2 H), 1.61 (sext, J = 7.4 Hz, 2 H), 0.94 (t, J = 7.4 Hz, 3 H).

13C NMR (125 MHz, CDCl₃): δ = 137.6, 131.8, 128.4, 127.8, 127.7, 123.1, 122.3, 121.1, 120.4, 119.3, 115.5, 109.6, 94.9, 69.6, 67.7, 67.4, 41.5, 22.9, 13.5.

HRMS (ESI): m/z [M + Na]⁺ calcd for C₃₀H₃₀NO₅SNa: 678.2865; found: 678.2883.

2-(1,7-Bis(benzyloxy)-4-[3-(benzyloxy)propyl]heptan-4-yl)-1-(propylthio)-2H-isindole (11f)
Yield: 224 mg (93%); pale-yellow oil.

1H NMR (500 MHz, CDCl₃): δ = 7.68 (d, J = 8.5 Hz, 1 H), 7.48 (d, J = 8.4 Hz, 1 H), 7.39 (s, 1 H), 7.33–7.25 (m, 15 H), 7.03–7.00 (m, 1 H), 6.94–6.91 (m, 1 H), 4.44 (s, 6 H), 3.42 (t, J = 6.3 Hz, 6 H), 2.65 (t, J = 7.4 Hz, 2 H), 2.43–2.40 (m, 6 H), 1.60–1.54 (m, 2 H), 1.38–1.25 (m, 2 H), 0.88 (t, J = 6.9 Hz, 3 H).

13C NMR (125 MHz, CDCl₃): δ = 138.4, 131.8, 128.3, 127.55, 127.47, 122.6, 121.9, 120.8, 120.3, 119.2, 114.2, 109.8, 72.9, 70.2, 66.9, 39.6, 32.9, 31.9, 29.7, 29.64, 29.5, 29.38, 29.36, 29.1, 29.0, 23.7, 22.7, 14.1.


Anal. Calc. for C₃₁H₃₁NO₅S: C, 78.92; H, 8.96; N, 1.80. Found: C, 78.62; H, 9.01; N, 1.83.

2-(1,3-Dimethoxy-2-(methoxymethyl)propan-2-yl)isoindolin-1-one (12a)
Yield: 16.0 mg (18%); white solid; mp 63.5–66.0 °C.

IR (KBr): 2976, 2878, 1684, 1471, 1383, 1304, 1111 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 7.78 (d, J = 7.5 Hz, 1 H), 7.51 (td, J = 7.4, 1.1 Hz, 1 H), 7.44–7.39 (m, 2 H), 4.66 (s, 2 H), 3.97 (s, 6 H), 3.35 (s, 9 H).

13C NMR (125 MHz, CDCl₃): δ = 169.6, 142.1, 133.5, 131.1, 127.6, 123.2, 122.3, 71.1, 63.4, 59.3, 50.1.


2-(1,3-Diethoxy-2-(ethoxymethyl)propan-2-yl)isoindolin-1-one (12b)
Yield: 14.0 mg (12%); yellow oil.

IR (neat): 2947, 2890, 1678, 1469, 1393, 1301, 1113 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 7.78 (d, J = 7.5 Hz, 1 H), 7.50 (td, J = 7.4, 1.1 Hz, 1 H), 7.43–7.39 (m, 2 H), 4.71 (s, 2 H), 4.03 (s, 6 H), 3.50 (q, J = 6.0 Hz, 2 H), 1.41 (t, J = 7.4 Hz, 3 H).

13C NMR (125 MHz, CDCl₃): δ = 169.6, 142.2, 133.7, 130.9, 127.4, 123.2, 122.2, 68.9, 66.8, 63.6, 50.3, 15.2.


2-(6-[(Methoxymethoxy)methyl]-2,4,8,10-tetraoxaheptadecan-9-yl)isoindolin-1-one (12c)
Yield: 57.2 mg (41%); pale-yellow oil.

IR (neat): 2947, 2890, 2823, 1684, 1470, 1152, 1111, 1041 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 7.80 (d, J = 7.6 Hz, 1 H), 7.52 (td, J = 7.5, 1.1 Hz, 1 H), 7.45–7.39 (m, 2 H), 4.69 (s, 2 H), 4.64 (s, 6 H), 4.17 (s, 6 H), 3.33 (s, 9 H).

13C NMR (125 MHz, CDCl₃): δ = 169.5, 141.9, 133.4, 131.2, 127.7, 123.3, 122.3, 96.9, 66.2, 62.8, 55.4, 50.0.


2-[(2-Methoxymethoxy)methyl]-2,5,7,11,13,16-hexaoxaheptadecan-9-yl]isoindolin-1-one (12d)
Yield: 83.2 mg (44%); pale-yellow oil.
IR (neat): 2930, 2886, 2819, 1685, 1470, 1452, 1118, 1046 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.78 (d, J = 7.6 Hz, 1 H), 7.52 (td, J = 7.5, 1.1 Hz, 1 H), 7.45–7.38 (m, 2 H), 7.37 (d, J = 7.5 Hz, 1 H), 7.34–7.26 (m, 15 H), 4.76 (s, 6 H), 4.66 (s, 2 H), 4.55 (s, 6 H), 4.26 (s, 6 H).

¹³C NMR (125 MHz, CDCl₃): δ = 169.4, 141.9, 133.3, 131.2, 128.4, 127.8, 127.5, 123.3, 122.3, 96.0, 71.7, 67.0, 66.3, 62.8, 59.0, 50.0.


2-{1,7-Bis(benzyloxy)-4-[3-(benzyloxy)propyl]heptan-4-yl}isoin-...