Synthesis of Sterically Protected Isoindoles from *ortho*-Phthalaldehyde

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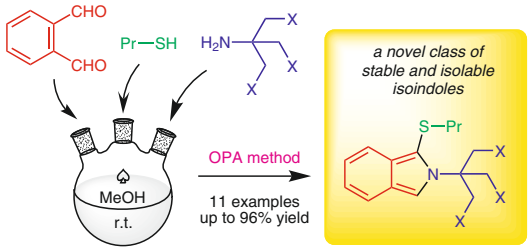

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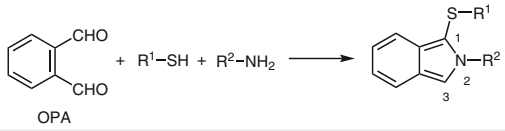
Abstract *o*-Phthalaldehyde (OPA) reacts with *O*-protected tris(hydroxyalkyl)aminomethanes in the presence of 1-propanethiol to afford a novel class of stable isoindoles. Steric protection provided by the bulkiness of C_3-symmetric primary amines derived from tris(hydroxymethyl)aminomethane could be 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.

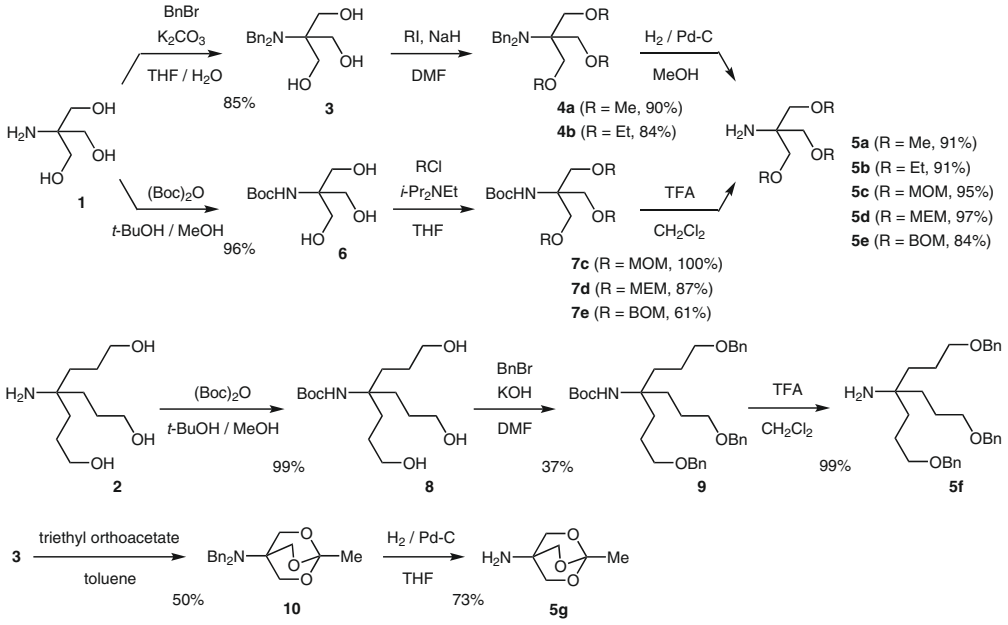
Key words *o*-phthalaldehyde, isoindole, steric protection, isoindolin-1-one

Benzo[*c*]pyrrole, also called isoindole,[1] 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).[2] As the resultant isoindole is sensitively detected by its fluorescence (λ_{ex} = 360 nm, λ_{em} = 455 nm), the three-component coupling reaction is generally used as one of the most valuable methods of analyzing primary amines including amino acids.[3,4] 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*-butylamine and *tert*-butylthiol, increases the stability of the isoindoles.[5] In general, appropriate steric protection of organic molecules is an effective strategy for stabilization.[6,7] 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.[8] In this paper, we report on the synthesis of sterically protected 1-alkylthio-2-alkyl-substituted isoindoles using C_3-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.



Scheme 1 The reaction of OPA with a primary amine and thiol

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 C_3-symmetric primary amines in the OPA method. The C_3-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*-butylamine. Thus, a series of C_3-symmetric primary amines **5a–g** was prepared from tris(hydroxymethyl)aminomethane (**1**) or tris(hydroxypropyl)aminomethane (**2**), as shown in Scheme

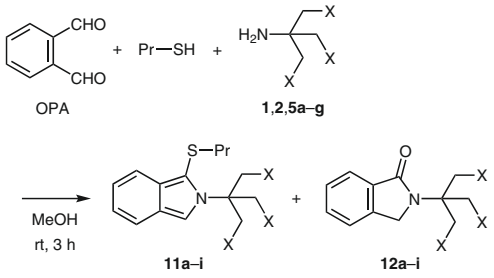


Scheme 2 Synthesis of C_3-symmetric primary amines **5a–g** starting from tris(hydroxymethyl)aminomethane (**1**) and tris(hydroxypropyl)aminomethane (**2**)

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, C_3-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 C_3-symmetric amine **5e** originating from **1** on the formation of isoindolin-1-one **12e**, *O*-benzylated

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



Entry	X	Yield of **11** (%)[b]	Yield of **12** (%)[b]
1	OMe (**5a**)	65 (**11a**)	18 (**12a**)
2	OEt (**5b**)	85 (**11b**)	12 (**12b**)
3	OMOM (**5c**)	57 (**11c**)	41 (**12c**)
4	OMEM (**5d**)	54 (**11d**)	44 (**12d**)
5	OBOM (**5e**)	60 (**11e**)	39 (**12e**)
6	$(CH_2)_2$OBn (**5f**)	93 (**11f**)	ca. 6 (**12f**)[c]
7	orthoester (**5g**)	–[d] (**11g**)	0 (**12g**)
8	OH (**1**)	–[d] (**11h**)	0 (**12h**)
9	$(CH_2)_2$OH (**2**)	90 (**11i**)	0 (**12i**)
10[e]	OMOM (**5c**)	– (**11c**)	56 (**12c**)
11[e]	$(CH_2)_2$OH (**2**)	– (**11i**)	0 (**12i**)

[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, **5f** 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 **11h** 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 **11c** 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.

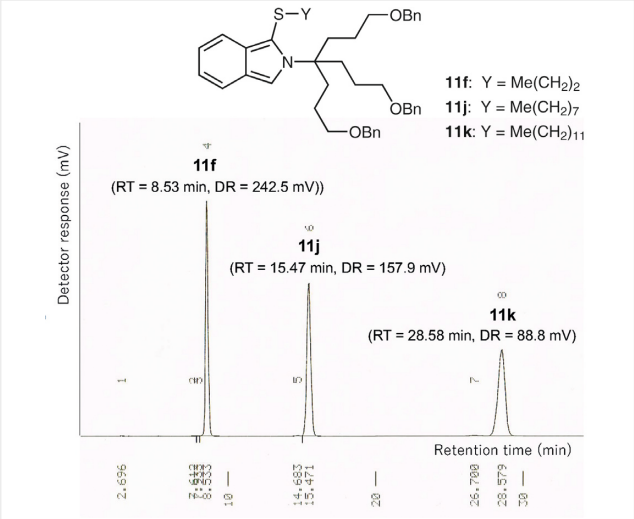
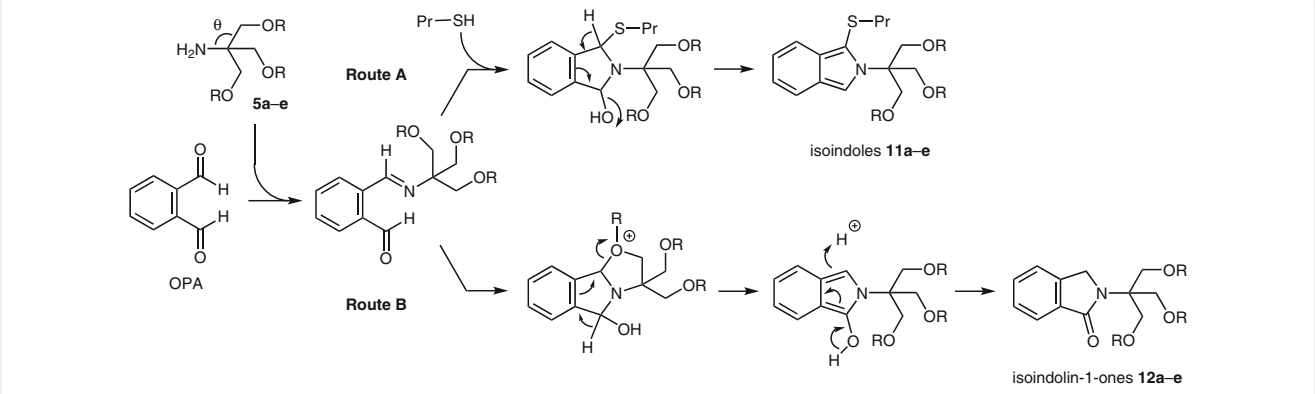


Figure 1 HPLC analysis for resolution of a mixture of isoindoles **11f**, **11j**, and **11k** formed from 1-propanethiol, 1-octanethiol, and 1-dodecanethiol, respectively

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.[5] 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 C_3-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-dodecanthiol), and C_3-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



Scheme 3 Plausible reaction pathways for the formation of **11a–e** and **12a–e**

method for thiols 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. ^{1}H NMR (500 MHz) and ^{13}C 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 reactions were monitored by TLC employing 0.25 mm silica gel plates (Merck 5715; 60 F_{254}). Column chromatography was carried out on silica gel [Silica Gel 60N (Kanto Chemical) or Silica Gel PSQ 60B (Fuji Silysia Chemical)]. Anhydrous THF, CH_2Cl_2, DMF, and toluene were used as purchased from Kanto Chemical. All other reagents were used as purchased.

N,*N*-Dibenzyl-1,3-dimethoxy-2-(methoxymethyl)propan-2-amine (4a)

To a suspension of NaH (50–72% in mineral oil, 394 mg, 8.21–11.8 mmol) in anhydrous DMF (5 mL) was added **3** (900 mg, 2.99 mmol) in anhydrous DMF (5 mL) and MeI (614 µL, 9.85 mmol). The reaction mixture was stirred at r.t. for 4 h under argon. H_2O (10 mL) was added and the reaction mixture was extracted with EtOAc (50 mL). The organic layer was washed with H_2O (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [silica gel 60N; *n*-hexane–EtOAc, 9:1] to afford **4a**.

Yield: 922 mg (90%); pale-yellow oil.

IR (neat): 3026, 2980, 2889, 2810, 2059, 1946, 1869, 1810, 1603, 1453, 1107 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27–7.26 (m, 4 H), 7.16–7.13 (m, 4 H), 7.08–7.05 (m, 2 H), 3.98 (s, 4 H), 3.52 (s, 6 H), 3.25 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.4, 128.4, 127.6, 126.0, 73.6, 64.0, 59.1, 54.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{29}NO_3Na$: 366.2045; found: 366.2031.

Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.15; H, 8.65; N, 4.09.

N,*N*-Dibenzyl-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.

IR (neat): 2974, 2867, 1494, 1454, 1377, 1113 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.26 (m, 4 H), 7.15–7.12 (m, 4 H), 7.07–7.04 (m, 2 H), 4.00 (s, 4 H), 3.55 (s, 6 H), 3.38 (q, *J* = 7.0 Hz, 6 H), 1.16 (t, *J* = 7.0 Hz, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.8, 128.4, 127.5, 125.8, 71.3, 66.6, 64.1, 54.8, 15.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{35}NO_3Na$: 408.2515; found: 408.2504.

Anal. Calcd for $C_{24}H_{35}NO_3$: C, 74.77; H, 9.15; N, 3.63. Found: C, 74.62; H, 9.31; N, 3.58.

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 H_2 atmosphere. The reaction mixture was filtered and concentrated in vacuo. The residue was dissolved in $CHCl_3$ (30 mL) and washed with sat. aq $NaHCO_3$ (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford **5a**.

Yield: 118 mg (91%); pale-yellow oil.

IR (neat): 3383, 2980, 2892, 2814, 1456, 1109 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.35 (s, 9 H), 3.29 (s, 6 H), 1.52 (br s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 75.0, 59.4, 55.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_7H_{17}NO_3Na$: 186.1106; found: 186.1091.

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.

IR (neat): 3385, 2976, 2867, 1110, 864 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.49 (q, *J* = 7.0 Hz, 6 H), 3.33 (s, 6 H), 1.55 (br s, 2 H), 1.17 (t, *J* = 7.0 Hz, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 72.6, 66.8, 55.7, 15.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ $C_{10}H_{23}NO_3Na$: 228.1576; found: 228.1565.

tert-Butyl [1,3-Dihydroxy-2-(hydroxymethyl)propan-2-yl]carbamate (6)[10b]

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).

IR (KBr): 3300, 2962, 1680, 1549, 1468, 1369, 1296, 1176 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.76 (br s, 1 H), 4.50 (t, *J* = 5.3 Hz, 3 H), 3.51 (d, *J* = 5.6 Hz, 6 H), 1.37 (s, 9 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 154.9, 77.7, 60.3, 60.1, 28.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{19}NO_5Na$: 244.1161; found: 244.1141.

Anal. Calcd for $C_9H_{19}NO_5$: C, 48.86; H, 8.66; N, 6.33. Found: C, 48.73; H, 8.68; N, 6.31.

tert-Butyl {6-[(Methoxymethoxy)methyl]-2,4,8,10-tetraoxaundecan-6-yl}carbamate (7c)

To a solution of **6** (500 mg, 2.26 mmol) and DIPEA (1.30 mL, 7.46 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) were 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 (Na_2SO_4), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [silica gel PSQ 60B; *n*-hexane–EtOAc, 2:1] to afford **7c**.

Yield: 796 mg (100%); pale-yellow oil.

IR (neat): 3450, 3359, 2934, 2889, 2824, 1718, 1502, 1366, 1245, 1150, 1112, 1047 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): 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).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.7, 96.8, 79.1, 67.1, 57.8, 55.3, 28.3.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{31}NO_8Na$: 376.1947; found: 376.1922.

Anal. Calcd for $C_{15}H_{31}NO_8$: C, 50.98; H, 8.84; N, 3.96. Found: C, 50.68; H, 8.83; N, 4.02.

tert-Butyl (9-{[(2-Methoxyethoxy)methoxy]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: 576 mg (87%); pale-yellow oil.

IR (neat): 3450, 3348, 2931, 2885, 1716, 1500, 1456, 1366, 1246, 1173, 1116, 1045 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.08 (br s, 1 H), 4.71 (s, 6 H), 3.82 (s, 6 H), 3.69–3.67 (m, 6 H), 3.56–3.54 (m, 6 H), 3.39 (s, 9 H), 1.41 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.7, 95.9, 79.1, 71.7, 67.3, 66.9, 59.0, 57.9, 28.3.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{43}NO_{11}Na$: 508.2734; found: 508.2727.

tert-Butyl (6-{[(Benzyloxy)methoxy]methyl}-1,11-diphenyl-2,4,8,10-tetraoxaundecan-6-yl)carbamate (7e)[10b]

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

Yield: 481 mg (61%); pale-yellow oil.

IR (neat): 3436, 3063, 3032, 2939, 2885, 1716, 1498, 1366, 1170, 1112, 1046 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.27 (m, 15 H), 5.01 (br s, 1 H), 4.76 (s, 6 H), 4.59 (s, 6 H), 3.91 (s, 6 H), 1.41 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.7, 137.7, 128.4, 127.9, 127.7, 95.0, 79.2, 69.4, 67.4, 57.9, 28.4.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{43}NO_8Na$: 604.2886; found: 604.2878.

6-[(Methoxymethoxy)methyl]-2,4,8,10-tetraoxaundecan-6-amine (5c)

To a solution of **7c** (400 mg, 1.13 mmol) in anhydrous CH_2Cl_2 (5.5 mL) was added TFA (2.00 mL, 26.0 mmol) at 0 °C. After stirring for 50 min at 0 °C, 2N Na_2CO_3 (25 mL) was added and the mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [silica gel PSQ 60B; $CHCl_3$–MeOH, 9:1] to afford **5c**.

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

IR (neat): 3378, 2929, 2885, 1587, 1467, 1442, 1403, 1213, 1149, 1110, 1040 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.64 (s, 6 H), 3.49 (s, 6 H), 3.36 (s, 9 H), 1.56 (br s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 96.8, 69.9, 55.3, 55.2.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{23}NO_6Na$: 276.1423; found: 276.1401.

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, $CDCl_3$): δ = 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).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 95.9, 71.7, 70.1, 66.8, 59.0, 55.4.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{35}NO_9Na$: 408.2210; found: 408.2204.

6-{[(Benzyloxy)methoxy]methyl}-1,11-diphenyl-2,4,8,10-tetraoxaundecan-6-amine (5e)[10b]

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

Yield: 140 mg (84%); pale-yellow oil.

IR (neat): 3379, 3088, 3063, 3031, 2936, 2880, 1586, 1498, 1455, 1381, 1162, 1111, 1041 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 15 H), 4.77 (s, 6 H), 4.59 (s, 6 H), 3.58 (s, 6 H), 1.62 (br s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.7, 128.4, 127.8, 127.7, 95.0, 70.2, 69.4, 55.4.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{35}NO_6Na$: 504.2362; found: 504.2313.

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, $CHCl_3$).

IR (KBr): 3405, 3305, 3262, 2949, 2873, 1691, 1546, 1454, 1366, 1279, 1166 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): 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 (s, 9 H), 1.36–1.27 (m, 6 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 153.9, 76.7, 61.3, 56.1, 31.0, 28.2, 26.5.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{31}NO_5Na$: 328.2100; found: 328.2104.

Anal. Calcd for $C_{15}H_{31}NO_5$: C, 58.99; H, 10.23; N, 4.59. Found: C, 58.69; H, 10.16; N, 4.53.

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 r.t. under argon. The reaction mixture was stirred for 21 h at r.t., for 2 h at 40 °C, and for 2 h at 60 °C. H_2O (20 mL) was added and the mixture was extracted with EtOAc (30 mL). The organic layer was washed with H_2O (2 × 20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The oily 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, 1497, 1454, 1390, 1364, 1248, 1170, 1100, 736, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 15 H), 4.48 (s, 6 H), 4.42 (br s, 1 H), 3.45 (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).

^{13}C NMR (125 MHz, $CDCl_3$): 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.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{36}H_{49}NO_5Na$: 598.3508; found: 598.350.

Anal. Calcd for $C_{36}H_{49}NO_5$: C, 75.10; H, 8.58; N, 2.43. Found: C, 74.80; H, 8.54; N, 2.60.

1,7-Bis(benzyloxy)-4-[3-(benzyloxy)propyl]heptan-4-amine (5f)

Synthesized from **9** according to the procedure used to prepare **5c**.

Yield: 266 mg (99%); yellow oil.

IR (neat): 3061, 3031, 2945, 2855, 1719, 1454, 1361, 1276, 1102 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 15 H), 4.49 (s, 6 H), 3.45 (t, *J* = 6.6 Hz, 6 H), 1.63–1.57 (m, 8 H), 1.41–1.38 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.5, 128.3, 127.6, 127.5, 72.9, 70.9, 52.8, 36.4, 24.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{41}NO_3Na$: 498.2984; found: 498.2968.

***N*,*N*-Dibenzyl-1-methyl-2,6,7-trioxabicyclo[2.2.2]octan-4-amine (10)**

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–$CHCl_3$, 1:9] to afford **10**.

Yield: 536 mg (50%); white solid; mp 122–123 °C.

IR (KBr): 3299, 3063, 2969, 2889, 1952, 1875, 1542, 1255, 1042 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.19 (m, 10 H), 4.07 (s, 6 H), 3.76 (s, 4 H), 1.42 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.8, 128.3, 128.1, 127.2, 108.3, 68.6, 53.8, 53.1, 22.9.

1-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-4-amine (5g)[11]

Synthesized from **10** according to the procedure used to prepare **5a**.

Yield: 16.0 mg (73%); white solid; mp 116–117 °C.

IR (KBr): 3548, 3470, 3414, 3239, 2953, 2893, 2026, 1854, 1734, 1618 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.90 (s, 6 H), 1.46 (s, 3 H), 1.00 (br s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.2, 72.7, 44.9, 22.9.

Anal. Calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.35; H, 7.59; N, 9.46.

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

To a solution of OPA (42.0 mg, 0.313 mmol) in anhydrous MeOH (5 mL), 1-propanethiol (31.0 µL, 0.346 mmol) and amine **5a** (56.5 mg, 0.346 mmol) were added. After stirring in the dark for 3 h at r.t., the reaction mixture was evaporated in vacuo. The oily residue was purified by column chromatography [silica gel 60N; *n*-hexane–EtOAc, 9:1 to 3:1] to afford isoindole **11a** (69.0 mg, 65%) accompanied by the formation of isoindolin-1-one **12a** (16.0 mg, 18%).

2-[1,3-Dimethoxy-2-(methoxymethyl)propan-2-yl]-1-(propylthio)-2*H*-isoindole (11a)

Yield: 69.0 mg (65%); pale-blue solid; mp 67–68 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (br dq, 1 H), 7.50 (br dt, 1 H), 7.44 (d, *J* = 0.5 Hz, 1 H), 6.99 (ddd, *J* = 8.5, 6.5, 0.9 Hz, 1 H), 6.91 (ddd, *J* = 8.4, 6.4, 0.9 Hz, 1 H), 4.21 (s, 6 H), 3.33 (s, 9 H), 2.66 (t, *J* = 7.4 Hz, 2 H), 1.66 (sext, *J* = 7.5 Hz, 2 H), 1.01 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 131.7, 123.1, 122.2, 120.9, 120.6, 119.1, 115.7, 109.1, 72.6, 67.8, 59.3, 41.4, 23.0, 13.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{27}NO_3SNa$: 360.1609; found: 360.1608.

Anal. Calcd for $C_{18}H_{27}NO_3S$: C, 64.06; H, 8.06; N, 4.15. Found: C, 63.76; H, 8.09; N, 4.10.

2-[1,3-Diethoxy-2-(ethoxymethyl)propan-2-yl]-1-(propylthio)-2*H*-isoindole (11b)

Yield: 122 mg (85%); pale-blue solid; mp 48–49 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (br dq, 1 H), 7.53 (d, *J* = 0.6 Hz, 1 H), 7.51 (br dt, 1 H), 6.99 (ddd, *J* = 8.5, 6.4, 0.9 Hz, 1 H), 6.91 (ddd, *J* = 8.4, 6.4, 0.9 Hz, 1 H), 4.25 (s, 6 H), 3.47 (q, *J* = 7.0 Hz, 6 H), 2.66 (t, *J* = 7.4 Hz, 2 H), 1.66 (sext, *J* = 7.5 Hz, 2 H), 1.13 (t, *J* = 7.0 Hz, 9 H), 1.00 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 131.7, 123.0, 122.0, 120.6, 120.5, 119.2, 116.2, 108.9, 70.5, 68.2, 66.9, 41.4, 23.0, 15.1, 13.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{33}NO_3SNa$: 402.2079; found: 402.2076.

2-{6-[(Methoxymethoxy)methyl]-2,4,8,10-tetraoxaundecan-6-yl}-1-(propylthio)-2*H*-isoindole (11c)

Yield: 91.0 mg (57%); pale-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (br dq, 1 H), 7.51–7.50 (br m, 0.5 H), 7.49–7.48 (br m, 1.5 H), 7.00 (ddd, *J* = 8.5, 6.5, 0.9 Hz, 1 H), 6.92 (ddd, *J* = 8.4, 6.5, 0.9 Hz, 1 H), 4.59 (s, 6 H), 4.43 (s, 6 H), 3.29 (s, 9 H), 2.71 (t, *J* = 7.4 Hz, 2 H), 1.67 (sext, *J* = 7.4 Hz, 2 H), 1.02 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 131.7, 123.1, 122.2, 121.0, 120.4, 119.2, 115.5, 109.4, 96.8, 67.5, 67.3, 55.5, 41.5, 22.9, 13.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{33}NO_6SNa$: 450.1926; found: 450.1885.

2-(9-{[(2-Methoxyethoxy)methoxy]methyl}-2,5,7,11,13,16-hexaoxaheptadecan-9-yl)-1-(propylthio)-2*H*-isoindole (11d)

Yield: 113 mg (54%); pale-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.6 Hz, 1 H), 7.48 (d, *J* = 8.3 Hz, 1 H), 7.48 (s, 1 H), 7.01–6.98 (m, 1 H), 6.93–6.90 (m, 1 H), 4.68 (s, 6 H), 4.43 (s, 6 H), 3.56–3.54 (m, 6 H), 3.49–3.47 (m, 6 H), 3.37 (s, 9 H), 2.69 (t, *J* = 7.4 Hz, 2 H), 1.66 (sext, *J* = 7.4 Hz, 2 H), 1.01 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 131.7, 123.0, 122.3, 121.0, 120.4, 119.2, 115.6, 109.4, 95.8, 71.7, 67.7, 67.3, 67.1, 59.0, 41.5, 23.0, 13.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{45}NO_9SNa$: 582.2713; found: 582.2701.

2-(6-{[(Benzyloxy)methoxy]methyl}-1,11-diphenyl-2,4,8,10-tetraoxaundecan-6-yl)-1-(propylthio)-2*H*-isoindole (11e)

Yield: 148 mg (60%); orange oil.

^{1}H NMR (500 MHz, $CDCl_3$): 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).

^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{39}H_{45}NO_6SNa$: 678.2865; found: 678.2883.

2-{1,7-Bis(benzyloxy)-4-[3-(benzyloxy)propyl]heptan-4-yl}-1-(propylthio)-2*H*-isoindole (11f)

Yield: 224 mg (93%); pale-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): 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 (sext, *J* = 7.4 Hz, 2 H), 1.40–1.34 (m, 6 H), 0.94 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.4, 131.9, 128.3, 127.6, 127.5, 122.5, 121.9, 120.8, 120.3, 119.2, 114.3, 109.7, 72.9, 70.2, 66.9, 41.5, 32.9, 23.7, 22.8, 13.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{42}H_{51}NO_3SNa$: 672.3487; found: 672.3490.

Anal. Calcd for $C_{42}H_{51}NO_3S$: C, 77.62; H, 7.91; N, 2.16. Found: C, 77.32; H, 7.98; N, 2.13.

4-(3-Hydroxypropyl)-4-[1-(propylthio)-2*H*-isoindol-2-yl]heptane-1,7-diol (11i)

Yield: 127 mg (90%); mp 116–118 °C (pale-yellow needles, $CHCl_3$/*n*-hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (dd, *J* = 8.5, 0.8 Hz, 1 H), 7.50 (dt, *J* = 8.4, 0.9 Hz, 1 H), 7.43 (s, 1 H), 7.03 (ddd, *J* = 8.5, 6.5, 0.9 Hz, 1 H), 6.94 (ddd, *J* = 8.4, 6.5, 0.9 Hz, 1 H), 3.62 (t, *J* = 6.2 Hz, 6 H), 2.71 (t, *J* = 7.4 Hz, 2 H), 2.45–2.42 (m, 6 H), 1.69 (sext, *J* = 7.4 Hz, 2 H), 1.39 (br s, 3 H), 1.36–1.30 (m, 6 H), 1.03 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 131.9, 122.6, 122.2, 121.0, 120.3, 119.1, 114.3, 109.5, 66.9, 62.5, 41.6, 32.5, 26.4, 22.9, 13.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{33}NO_3SNa$: 402.2079; found: 402.2067.

2-{1,7-Bis(benzyloxy)-4-[3-(benzyloxy)propyl]heptan-4-yl}-1-(octylthio)-2*H*-isoindole (11j)

Yield: 206 mg (96%); pale-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (br d, 1 H), 7.48 (br d, 1 H), 7.38 (s, 1 H), 7.33–7.24 (m, 15 H), 7.01 (ddd, *J* = 8.5, 6.5, 0.9 Hz, 1 H), 6.93 (ddd, *J* = 8.4, 6.5, 0.8 Hz, 1 H), 4.44 (s, 6 H), 3.42 (t, *J* = 6.3 Hz, 6 H), 2.67 (t, *J* = 7.4 Hz, 2 H), 2.43–2.40 (m, 6 H), 1.61–1.54 (m, 2 H), 1.39–1.24 (m, 16 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.4, 131.8, 128.3, 127.55, 127.48, 122.6, 121.9, 120.8, 120.3, 119.2, 114.2, 109.8, 72.9, 70.2, 66.9, 39.6, 32.9, 31.8, 29.4, 29.3, 29.2, 29.0, 23.7, 22.7, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{47}H_{61}NO_3SNa$: 742.4270; found: 742.4276.

2-{1,7-Bis(benzyloxy)-4-[3-(benzyloxy)propyl]heptan-4-yl}-1-(dodecylthio)-2*H*-isoindole (11k)

Yield: 210 mg (91%); pale-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.6 Hz, 1 H), 7.48 (d, *J* = 8.4 Hz, 1 H), 7.38 (s, 1 H), 7.33–7.24 (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), 2.67 (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, 24 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): 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, 29.56, 29.5, 29.38, 29.36, 29.1, 29.0, 23.7, 22.7, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{51}H_{69}NO_3SNa$: 798.4896; found: 798.4892.

Anal. Calcd for $C_{51}H_{69}NO_3S$: 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, 2876, 1684, 1471, 1383, 1304, 1103 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): 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).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6, 142.1, 133.5, 131.1, 127.6, 123.2, 122.3, 71.1, 63.4, 59.3, 50.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{21}NO_4Na$: 302.1368; found: 302.1342.

2-[1,3-Diethoxy-2-(ethoxymethyl)propan-2-yl]isoindolin-1-one (12b)

Yield: 14.0 mg (12%); yellow oil.

IR (neat): 2974, 2870, 1684, 1469, 1393, 1301, 1103 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): 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* = 7.0 Hz, 6 H), 1.14 (t, *J* = 7.0 Hz, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): 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.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{27}NO_4Na$: 344.1838; found: 344.1834.

2-{6-[(Methoxymethoxy)methyl]-2,4,8,10-tetraoxaundecan-6-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}.

^{1}H NMR (500 MHz, $CDCl_3$): 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).

^{13}C NMR (125 MHz, $CDCl_3$): 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.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{27}NO_7Na$: 392.1685; found: 392.1664.

2-(9-{[(2-Methoxyethoxy)methoxy]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, $CDCl_3$): 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), 4.72 (s, 6 H), 4.66 (s, 2 H), 4.17 (s, 6 H), 3.64–3.62 (m, 6 H), 3.53–3.50 (m, 6 H), 3.37 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.4, 141.9, 133.3, 131.2, 127.7, 123.2, 122.3, 96.0, 71.7, 67.0, 66.3, 62.8, 59.0, 50.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{39}NO_{10}Na$: 524.2472; found: 524.2473.

2-(6-{[(Benzyloxy)methoxy]methyl}-1,11-diphenyl-2,4,8,10-tetraoxaundecan-6-yl)isoindolin-1-one (12e)

Yield: 87.0 mg (39%); pale-yellow oil.

IR (neat): 2943, 2886, 1684, 1454, 1383, 1169, 1112, 1044 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.6 Hz, 1 H), 7.51 (td, *J* = 7.5, 1.1 Hz, 1 H), 7.42 (t, *J* = 7.5 Hz, 1 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).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5, 141.8, 137.7, 133.3, 131.2, 128.4, 127.8, 127.73, 127.67, 123.3, 122.3, 95.1, 69.5, 66.5, 62.9, 50.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{36}H_{39}NO_7Na$: 620.2624; found: 620.2635.

2-{1,7-Bis(benzyloxy)-4-[3-(benzyloxy)propyl]heptan-4-yl}isoindolin-1-one (12f)

Yield: 13.0 mg (ca. 6%); pale-yellow oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.5 Hz, 1 H), 7.49 (td, *J* = 7.4, 1.2 Hz, 1 H), 7.43 (d, *J* = 7.4 Hz, 1 H), 7.36–7.22 (m, 16 H), 4.47 (s, 2 H), 4.46 (s, 6 H), 3.46 (t, *J* = 6.7 Hz, 6 H), 2.13–2.05 (m, 6 H), 1.62–1.52 (m, 6 H).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{39}H_{45}NO_4Na$: 614.3246; found: 614.3204.

HPLC Equipment and Conditions

A Gulliver HPLC system (JASCO) equipped with a Rheodyne 7125 injection valve (20 µL loop), UV/Vis detector (UV-970), and HPLC pump (PU-980) was used. HPLC analysis was performed with a TSKgel ODS-80Ts analytical column (250 × 4.6 mm id, 5 µm, Tosoh) by measuring absorbance at 330 nm. The mobile phase was a mixture of MeOH and water (200:1, v/v) at a flow rate of 1.0 mL min^{-1}.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591932.

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