Tetrahedron Letters 50 (2009) 3381–3384

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Rapid assembly of *anti*-1,3-diol units with 2-quaternary carbon stereocenter via samarium diiodide-promoted tandem Aldol/Evans-Tishchenko reaction

Xing-Wen Sun [a], Ming-Hua Xu [a,b,*], Guo-Qiang Lin [a,*]

[a] Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China
[b] Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, China

ARTICLE INFO

Article history:
Received 14 January 2009
Revised 10 February 2009
Accepted 16 February 2009
Available online 20 February 2009

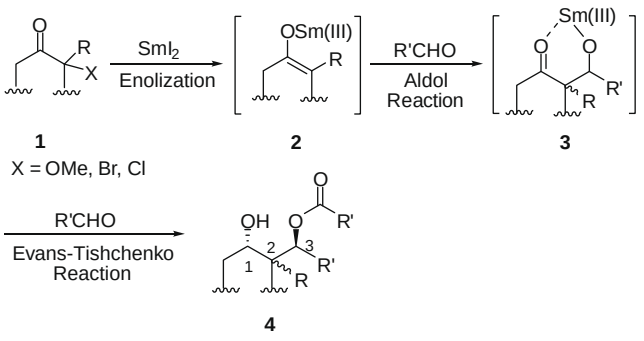
ABSTRACT

An efficient and practical method for highly diastereoselective synthesis of 2-quaternary *anti*-1,3-diol units with three adjacent stereogenic carbon centers has been developed. The reactions proceed regiospecifically at room temperature via samarium diiodide-promoted tandem Aldol condensation and Evans-Tishchenko reduction. The relative stereochemistry of the resulting 1,3-diol monoesters is identified by X-ray crystallography.

1,3-Diol units are ubiquitous skeletons that can be found in a wide range of naturally occurring products, biologically active compounds as well as medicinally important agents, such as macrolides, polyketides, and drug Statins.[1] Furthermore, certain enantiomerically pure 1,3-diol units are also used as efficient chiral auxiliaries and ligands for asymmetric synthesis.[2] Due to this great importance, tremendous efforts have been devoted to the development of methods for efficient synthesis of 1,3-diols. Among them, stereoselective construction of 1,3-diol units with broad structural diversity has attracted major attention over the past two decades.[3] Various elegant alternative procedures have already been developed for the preparation of these moieties,[4–9] often involving catalytic hydrogenation,[5] or stereoselective reduction of 1,3-diketones[6] and β-hydroxyketones (aldol adducts),[7] Prins cyclization,[8] and Aldol-Tishchenko reaction.[9] For preparation of 2-quaternary 1,3-diols, however, far fewer reports have appeared in the literature because of the inherent difficulties on quaternary carbon construction. Remarkable success was only achieved in samarium-catalyzed tandem semipinacol rearrangement/Tishchenko reaction of α-hydroxy epoxides.[10] Efficient and straightforward access to 2-quaternary 1,3-diols remains a challenging topic in organic synthesis.

In the past several years, we have been interested in samarium diiodide-mediated reactions for the synthesis of diverse structurally important molecules.[11] Very recently, we reported a new approach for the preparation of quaternary carbon-containing α-aminoketone derivatives by SmI_2-promoted regiospecific electrophilic amination of α-heterosubstituted ketones. In this work, the formation of samarium enolate intermediates of ketones was considered. Inspired by these results,[11j,12] we further envisioned that an Aldol condensation between the samarium enolate **2** and aldehyde might be carried out to give the corresponding β-hydroxyketone intermediate **3**. Accordingly, **3** might be activated for the addition of another equivalent of aldehyde, subsequently underwent samarium-catalyzed intramolecular Evans-Tishchenko reduction[13] to provide 2-quaternary 1,3-diol product **4** in a diastereoselective manner (Scheme 1). Herein, we wish to report our development of a new and efficient approach to *anti*-1,3-diol units with 2-quaternary carbon stereocenter via SmI_2-promoted tandem Aldol/Evans-Tishchenko reaction.

Initially, we examined the reaction of 2-methoxy-2-phenylcyclohexanone (**1a**) with two equivalents of benzaldehyde in the presence of SmI_2 to check the potential of our hypothesis. It has been known in the previous electrophilic amination study that the samarium enolate formation is important to increase the reaction yield.[11j] The ketone substrate **1a** was first stirred with SmI_2 for half an hour before the addition of aldehyde reagent. To our delight, the reaction proceeded smoothly as we expected at 0 °C in

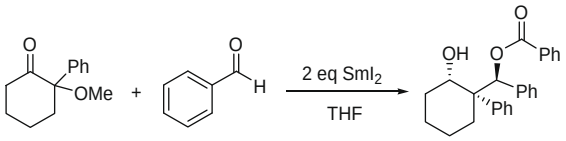


Scheme 1. Reaction proposal.

* Corresponding authors. Tel./fax: +86 21 5080 7388 (M.-H.X.).
E-mail addresses: xumh@mail.sioc.ac.cn (M.-H. Xu), lingq@mail.sioc.ac.cn (G.-Q. Lin).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.02.104

Table 1
Screening and optimization of the reaction conditions[a]



1a **4a**

Entry	Temp	Aldehyde (equiv)	Additive (equiv)	Yield[b] (%)
1	0 °C	2	—	86
2	rt	2	—	84
3	rt	3	—	88
4	rt	3	2.0 HMPA	95

[a] All reactions were carried out with 0.5 mmol of 2-methoxy-2-phenyl-cyclohexanone (**1a**), in 11 mL of THF.
[b] Isolated yield after chromatographic purification.

THF, the desired 1,3-diol product **4a** was indeed isolated in 86% yield and confirmed by NMR spectra (Table 1, entry 1). When the reaction temperature was raised to room temperature, a similar yield of 84% was obtained (entry 2). Further optimization of the reaction conditions indicated that an excellent yield of 95% could be achieved by employing slight excess of benzaldehyde (3 equiv) and using 2 equiv of HMPA[14] as additive (entry 4). In all cases, the reaction completed in 2 h and gave a single diastereomer.

The optimized experimental procedure for the SmI_2-promoted Aldol/Evans-Tishchenko reaction is as follows: Under nitrogen, to a solution of freshly made SmI_2 (1 mmol) in THF (5 mL) was added HMPA (0.17 mL, 1 mmol). After the mixture was stirred at room temperature for 15 min, substrate **1a** (102 mg, 0.5 mmol) in freshly distilled THF (3 mL) was added and the stirring continued for an additional 30 min. Benzaldehyde (159 mg, 1.5 mmol) in THF (3 mL) was then added, and the reaction mixture was stirred for 2 h. Subsequently, the reaction was quenched with saturated $Na_2S_2O_3$ aqueous solution. The aqueous layer was separated and extracted with ethyl acetate. The combined organic layer was washed successively with water, brine, and dried over Na_2SO_4, then concentrated under vacuum. The crude product was purified by column chromatography on silica gel to give 2-quaternary 1,3-diol **4a** in 95% yield.

As described above, it is noteworthy that the tandem Aldol condensation and Evans-Tishchenko reduction of 2-methoxy-2-phenyl-cyclohexanone (**1a**) with benzaldehyde occurred in a regio- and stereoselective fashion to give a single 1,3-diol diastereomer. The relative stereochemistry of the obtained product was identified unambiguously through X-ray crystallographic analysis of 1,3-diol monoester **4a**,[15] and a 1,3-*anti*-1,2-*syn* configuration was found (Fig. 1).

With the optimal reaction conditions identified, the scope of the tandem Aldol/Evans-Tishchenko procedure was investigated by employing various ketone substrates as well as differently substituted aldehydes. As demonstrated in Table 2, the reaction sequence was found very effective for a wide range of α-methoxy substituted cyclic ketone substrates and aldehydes bearing either electron-donating or electron-withdrawing groups.[16] In most cases, good to excellent yields were observed (entries 1–7). With R^1 4-methylphenyl substitution, a very high yield of 98% was obtained (entry 7). When seven-membered ring ketone was examined, the reaction still went smoothly to give the desired 2-quaternary 1,3-diol monoester **4i** in 72% yield (entry 8). It is worth noting that excellent diastereoselectivities were observed in all cases, leading to the efficient and rapid creation of three adjacent stereogenic centers in one step. We also explored the possibility of using aliphatic aldehyde such as propionaldehyde, unfortunately, the reaction did not take place, probably due to its relatively lower electrophilicity as compared to the aromatic aldehyde.

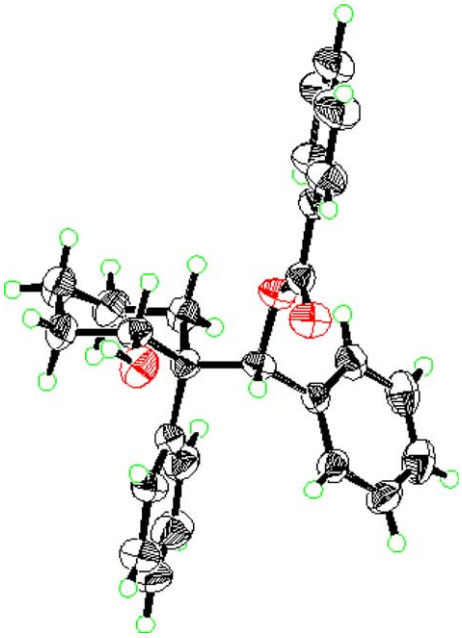
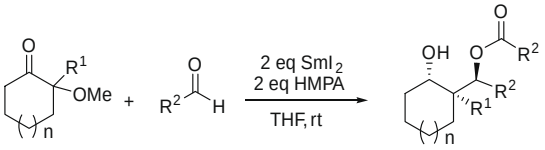


Figure 1. X-ray crystallographic structure of **4a**, ellipsoids at 50% probability.

Table 2
SmI_2-promoted tandem Aldol/Evans-Tishchenko reaction[a]

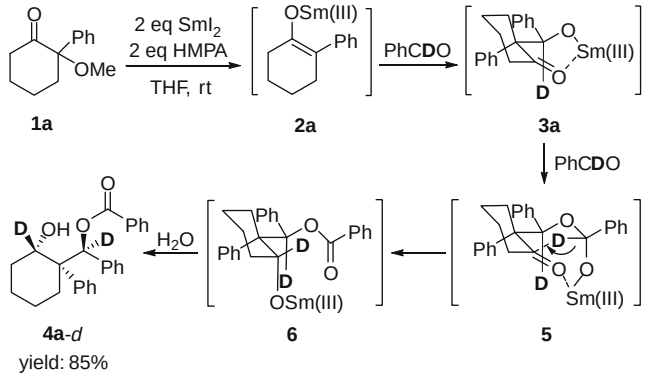


n = 0,1 **4** n = 0,1

Entry	R^1	R^2	*n*	Product	Yield[b] (%)
1	Ph	4-$MeOC_6H_4$	0	**4b**	94
2	Ph	4-$NO_2C_6H_4$	0	**4c**	93
3	Ph	4-ClC_6H_4	0	**4d**	84
4	Ph	4-BrC_6H_4	0	**4e**	85
5	4-BrC_6H_4	Ph–	0	**4f**	92
6	4-ClC_6H_4	Ph–	0	**4g**	85
7	4-MeC_6H_4	Ph–	0	**4h**	98
8	Ph	Ph–	1	**4i**	72

[a] All reactions were carried out under the optimized conditions.
[b] Isolated yield after chromatographic purification.

To better understand the reaction pathway as well as the observed relative stereochemistry, we further conducted a supporting experiment. A plausible reaction mechanism is presented in Scheme 2. First, upon the treatment of 2 equiv of SmI_2, 2-methoxy-2-phenyl-cyclohexanone (**1a**) was subjected to a regiospecific enolization to produce a samarium enolate intermediate **2a**. A rapid aldol reaction occurred between the samarium enolate **2a** and 1 equiv of benzaldehyde-α-d_1,[17] affording samarium metalated aldolate **3a**. In the presence of samarium catalyst, **3a** underwent Tishchenko reduction with another equivalent of benzaldehyde-α-d_1 immediately. The excellent stereochemical control achieved in the reaction sequence could be explained by the formation of a cyclic Evans-type intermediate **5**, in which samarium was coordinated to both carbonyl and hemiacetal oxygen. Subsequent intramolecular [1,5]-D transfer followed by protonation of intermediate **6** yielded the observed 2-quaternary 1,3-*anti*-1,2-*syn* diol monoester product **4a**–d (85%).



Scheme 2. Proposed mechanism for the generation of 2-quaternary *anti*-1,3-diol **4a**–*d*.

In summary, we have developed a new strategy as one of efficient and simple method for the synthesis of 2-quaternary *anti*-1,3-diol units with three adjacent stereogenic carbon centers through SmI_2-promoted tandem Aldol condensation and Evans-Tishchenko reduction. The advantages of this method which include high yields, mild conditions, high regioselectivity, and diastereoselectivity make this tool potentially very useful. Further studies on exploring the asymmetric version of the reaction and its applications are in progress.

Acknowledgments

Financial support from the National Natural Science Foundation of China (20402018, 20721003), the Major State Basic Research Development Program (2006CB-806106), the Shanghai Rising-Star Program (08QH14027), and the Chinese Academy of Sciences is acknowledged.

References and notes

1. Macrolides (a) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021; (b) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041; Polyketides (c) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054; (d) Rohr, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2847; Statins (e) Müller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 362.
2. (a) Hoeve, W.; Wynberg, H. *J. Org. Chem.* **1985**, *50*, 4508; (b) Geisler, F. M.; Helmchen, G. *Synthesis* **2006**, 2201; (c) Gardiner, J. M.; Crewe, P. D.; Smith, G. E.; Veal, K. T. *Chem. Commun.* **2003**, 618; (d) Michaud, G.; Bulliard, M.; Ricard, L.; Genet, J. P.; Marinetti, A. *Chem. Eur. J.* **2002**, *8*, 3327.
3. (a) Bode, S. E.; Wolberg, M.; Müller, M. *Synthesis* **2006**, 557; (b) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635; (c) Schneider, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1375.
4. (a) Gao, J.; Zhe, Z.-B.; Jian, Y.-J.; Wu, Y. *Tetrahedron* **2008**, *64*, 9377; (b) Bartoli, G.; Bosco, M.; Di Martino, E.; Marcantoni, E.; Sambri, L. *Eur. J. Org. Chem.* **2001**, 2901; (c) Enders, D.; Nuhring, A.; Runsink, J.; Raabe, G. *Synthesis* **2001**, 1406; (d) Petrignet, J.; Roisnel, T.; Gree, R. *Tetrahedron Lett.* **2006**, *47*, 7745; (e) Ahmed, M. M.; Mortensen, M. S.; O'Doherty, G. A. *J. Org. Chem.* **2006**, *71*, 7741; (f) Yu, C. M.; Youn, J.; Jung, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 1553; (g) Clueau, J.; Capdevielle, P.; Cossy, J. *Tetrahedron Lett.* **2005**, *46*, 6945.
5. (a) Patti, A.; Pedotti, S. *Tetrahedron: Asymmetry* **2006**, *17*, 1824; (b) Labeeuw, O.; Roche, C.; Phansavath, P.; Genêt, J. P. *Org. Lett.* **2007**, *9*, 105; (c) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
6. (a) Kalaitzakis, D.; Rozzell, J. D.; Smonou, I.; Kambourakis, S. *Adv. Synth. Catal.* **2006**, *348*, 1958; (b) Benedetti, F.; Berti, F.; Donati, I.; Fregonese, M. *Chem. Commun.* **2002**, 828; (c) Bartoli, G.; Bosco, M.; Bellucci, M. C.; Dalpozzo, R.; Marcantoni, E.; Sambri, L. *Org. Lett.* **2000**, *2*, 45.
7. (a)*Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004. and references cited therein; (b) Sarko, C. R.; Collibee, S. E.; Knorr, A. L.; DiMare, M. *J. Org. Chem.* **1996**, *61*, 868.
8. (a) Yadav, J. S.; Rao, P. P.; Reddy, M. S.; Rao, N. V.; Prasad, A. R. *Tetrahedron Lett.* **2007**, *48*, 1469; (b) Yadav, J. S.; Sridhar, R. M.; Rao, P. P.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4397; (c) Lin, Y. L.; Cheng, M. H.; Chen, W. C.; Peng, S. M.; Wang, S. L.; Kuo, H.; Liu, R. S. *J. Org. Chem.* **2001**, *66*, 1781.
9. For two reviews (a) Mahrwald, R. *Curr. Org. Chem.* **2003**, *7*, 1713; (b) Mlynarski, J. *Eur. J. Org. Chem.* **2006**, 4779; For other examples (c) Mascarenhas, C. M.; Miller, S. P.; White, P. S.; Morken, J. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 601; (d) Kodama, T.; Shuto, S.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2002**, *67*, 7706; (e) Gnanadesikan, V.; Horiuchi, Y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7782; (f) Reutrakul, V.; Jaratjaroonphong, J.; Tuchinda, P.; Kuhakarn, C.; Kongsaeree, P.; Prabpai, S.; Pohmakotr, M. *Tetrahedron Lett.* **2006**, *47*, 4753; (g) Stodulski, M.; Jaźwiński, J.; Mlynarski, J. *Eur. J. Org. Chem.* **2008**, 5553; (h) Mlynarski, J.; Rakiel, B.; Stodulski, M.; Suszczyńska, A.; Frelek, J. *Chem. Eur. J.* **2006**, *12*, 8158.
10. (a) Fan, C.-A.; Wang, B.-M.; Tu, Y.-Q.; Song, Z.-L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3877; (b) Tu, Y.-Q.; Sun, L.-D.; Wang, P.-Z. *J. Org. Chem.* **1999**, *64*, 629; (c) Fan, C.-A.; Hu, X.-D.; Tu, Y.-Q.; Wang, B.-M.; Song, Z.-L. *Chem. Eur. J.* **2003**, *9*, 4301.
11. (a) Xu, M.-H.; Wang, W.; Lin, G.-Q. *Org. Lett.* **2000**, *2*, 2229; (b) Wang, W.; Xu, M.-H.; Lei, X.-S.; Lin, G.-Q. *Org. Lett.* **2000**, *2*, 3773; (c) Xu, M.-H.; Wang, W.; Xia, L.-J.; Lin, G.-Q. *J. Org. Chem.* **2001**, *66*, 3953; (d) Wang, W.; Zhong, Y.-W.; Lin, G.-Q. *Tetrahedron Lett.* **2003**, *44*, 4613; (e) Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 4747; (f) Zhong, Y.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 3953; (g) Huang, L.-L.; Xu, M.-H.; Lin, G.-Q. *J. Org. Chem.* **2005**, *70*, 529; (h) Zhong, Y.-W.; Dong, Y.-Z.; Fang, K.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 11956; (i) Zhu, C.; Shi, Y.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 1243; (j) Sun, X.-W.; Wang, W.; Xu, M.-H.; Lin, G.-Q. *Tetrahedron Lett.* **2008**, *49*, 5807.
12. (a) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135; (b) Nakamura, Y.; Takeuchi, S.; Ohgo, S.; Yamaoka, M.; Yoshida, A.; Mikami, K. *Tetrahedron* **1999**, *55*, 4595.
13. (a) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447; (b) Lu, L.; Chang, H.-Y.; Fang, J.-M. *J. Org. Chem.* **1999**, *64*, 843.
14. For HMPA effect in SmI_2 chemistry, see: (a) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763; (b) Shabangi, M.; Sealy, J. M.; Flowers, R. A., II *Tetrahedron Lett.* **1998**, *39*, 4429; (c) Hou, Z.; Wakatsuki, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1205; (d) Enemaerke, R. J.; Hertz, T.; Skrydstrup, T.; Daasbjerg, K. *Chem. Eur. J.* **2000**, *6*, 3747.
15. Crystallographic data for **4a** ($C_{26}H_{26}O_3$): T = 20.0 °C; formular weight: 386.49; crystal system: monoclinic; lattice type: primitive; cell determination (2θ range): 23 (25.0–34.3°), omega scan peak width at half-height: 0.25°; lattice parameters: a = 13.053(4) Å, b = 14.982(5) Å, c = 11.487(5) Å, β = 112.74(3)°; V = 2071(1) Å^3; space group: $P2_1/c$ (#14); Z value: = 4; D_{calcd}: 1.239 g/cm^3, $F(000)$ = 824.00, μ(Mo Kα): 0.80 cm^{-1}; R indices [$I > 2\sigma(I)$]: R_1 = 0.047, wR_2 = 0.087.
16. *Characterization data for products* **4a–i**: **4a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41–1.88 (m, 7H), 2.24–2.28 (m, 1H), 3.31 (br s, 1H), 3.99–4.08 (m, 1H), 6.54 (s, 1H), 6.84 (d, J = 6.6 Hz, 2H), 7.08–7.25 (m, 6H), 7.47–7.62 (m, 5H), 8.12 (d, J = 7.5 Hz, 2H) ppm.; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.06, 24.29, 27.62, 30.06, 51.66, 79.20, 126.64, 127.16, 127.48, 127.76, 127.95, 127.55, 129.80, 130.02, 133.39, 133.63, 136.71, 139.41, 166.38 ppm; FT-IR (KBr) ν 3526, 3061, 2931, 2860, 1703, 1600, 1450, 1284, 1121, 972, 713, 695, 601 cm^{-1}; EI-MS (m/z, %) 264 (13.97), 175 (33.08), 158 (88.26), 105 (100), 91 (25.62), 77 (28.84), Anal. Calcd for $C_{26}H_{26}O_3$: C, 80.80; H, 6.78. Found: C,80.87; H, 6.76; **4a–d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33–1.81 (m, 7H), 2.16–2.20 (m, 1H), 3.27 (br s, 1H), 6.76 (d, J = 6.9 Hz, 2H), 7.00–7.13 (m, 6H), 7.38–7.55 (m, 5H), 8.04 (d, J = 7.8 Hz, 2H) ppm. Compound **4b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47–1.82 (m, 7H), 2.11–2.17 (m, 1H), 2.46 (br s, 1H), 3.73 (s, 3H), 3.75 (s, 3H), 4.03–4.09 (m, 1H), 5.63 (s, 1H), 6.69 (d, J = 4.5 Hz, 2H), 7.26–7.35 (m, 6H), 7.72–7.83 (m, 4H), 8.06 (d, J = 9 Hz, 2H) ppm.; ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.45, 23.59, 25.52, 31.76, 48.76, 55.89, 71.80, 82.68, 114.30, 114.41, 122.63, 126.06, 126.48, 128.96, 129.20, 130.85, 130.98, 131.51, 147.71, 158.21, 165.01, 166.91; FT-IR (KBr) ν 3515, 3062, 2929, 2861, 1723, 1610, 1440, 1294, 1123, 973, 695, 601 cm^{-1}; ESI-MS: 469.5 (M^++Na^+); Anal. Calcd for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77. Found: C, 75.26; H, 6.80. Compound **4c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42–1.88 (m, 7H), 2.16–2.22 (m, 1H), 2.98 (br s, 1H), 4.03–4.07 (m, 1H), 6.79 (s, 1H), 7.07 (d, J = 4.5 Hz, 2H), 7.32–7.46 (m, 6H), 8.02–8.13 (m, 4H), 8.26 (d, J = 9 Hz, 2H) ppm.; FT-IR (KBr) ν 3625, 3072, 2930, 2868, 1728, 1615, 1445, 1296, 1123, 971, 693 cm^{-1}; ESI-MS: 499.5 (M^++Na^+); Anal. Calcd for $C_{26}H_{24}N_2O_7$: C, 65.54; H, 5.08; N, 5.88. Found: C, 65.43; H, 5.08; N, 5.79. Compound **4d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46–1.79 (m, 7H), 2.17–2.21 (m, 1H), 3.02 (br s, 1H), 4.07–4.09 (m, 1H), 6.45 (s, 1H), 6.59 (d, J = 4.5 Hz, 2H), 7.06–7.19 (m, 6H), 7.21–7.38 (m, 4H), 7.93 (d, J = 7.5 Hz, 2H) ppm.; ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.42, 23.45, 25.56, 30.79, 47.89, 70.98, 81.99, 126.01, 126.45, 128.01, 128.30, 128.59, 128.81, 129.55, 131.32, 131.52, 137.45, 138.56, 147.65, 165.49 ppm; FT-IR (KBr) ν 3525, 3064, 2930, 2863, 1733, 1611, 1440, 1124, 975, 697, 605 cm^{-1}; ESI-MS: 478.3 (M^++Na^+); Anal. Calcd for $C_{26}H_{24}Cl_2O$: C, 68.58; H, 5.31; Cl, 15.57. Found: C, 68.51; H, 5.39; Cl, 15.39. Compound **4e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42–1.88 (m, 7H), 2.19–2.23 (m, 1H), 3.11 (br s, 1H), 4.03–4.07 (m, 1H), 6.49 (s, 1H), 6.67 (d, J = 4.5 Hz, 2H), 7.22–7.29 (m, 6H), 7.62–7.73 (m, 4H), 7.96 (d, J = 9 Hz, 2H) ppm.; ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.05, 24.59, 25.62, 31.76, 48.76, 72.00, 78.68, 120.30, 120.41, 126.63, 126.96, 127.48, 128.76, 129.20, 130.45, 130.98, 131.21, 132.01, 138.21, 156.91; FT-IR (KBr) ν 3515, 3062, 2929, 2861, 1723, 1610, 1440, 1294, 1123, 973, 695, 601 cm^{-1}; ESI-MS: 567.3 (M^++Na^+); Anal. Calcd for $C_{26}H_{24}Br_2O_3$: C, 57.38; H, 4.44; Br, 29.36. Found: C, 57.49; H, 4.52; Br, 29.60. Compound **4f**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42–2.08 (m, 7H), 2.29–2.33 (m, 1H), 3.29 (br s, 1H), 4.06–4.09 (m, 1H), 6.57 (s, 1H), 6.84 (d, J = 3.75 Hz, 2H), 7.12–7.26 (m, 6H), 7.30 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 8.16 (d, J = 7.5 Hz, 2H) ppm.; FT-IR (KBr) ν 3530, 3059, 2930, 2854, 1709, 976, 713, 688, 616 cm^{-1}; Anal. Calcd for $C_{26}H_{25}BrO_3$: C, 67.10; H, 5.41; Br, 17.17. Found: C, 67.19; H, 5.35; Br, 17.29. Compound **4g**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41–1.86 (m, 7H), 2.20–2.25 (m, 1H), 3.78–3.83 (m, 1H), 5.91 (s, 1H), 6.84 (d, J = 5.5 Hz, 2H), 7.19–7.25 (m, 6H), 7.37–7.41 (m, 4H), 7.97 (d, J = 3.75 Hz, 2H) ppm. FT-IR (KBr) ν 3542, 3081, 2947, 2880, 1703, 1640, 1442, 1276, 1135, 976, 725, 697 cm^{-1}; ESI-MS: 443.9 (M^++Na^+); Anal. Calcd for $C_{26}H_{25}ClO_3$: C, 74.19; H, 5.99. Found: C, 74.30; H, 6.05. Compound **4h**:^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41–

1.86 (m, 7H), 2.20–2.24 (m, 1H), 2.05 (s, 3H), 3.06 (s, 1H), 3.98–4.03 (m, 1H), 6.51 (s, 1H), 6.84 (d, J = 3.75 Hz, 2H), 7.12–7.26 (m, 6H), 7.47–7.64 (m, 4H), 8.12 (d, J = 3.75 Hz,2H) ppm.; ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.92, 21.13, 24.21, 27.84, 30.04, 51.33, 73.45, 79.29, 127.16, 127.45, 128.05, 128.50, 128.53, 129.80, 129.90, 130.00, 133.31, 136.11, 136.27, 136.92, 166.30; FT-IR (KBr) ν 3532, 3071, 2937, 2870, 1713, 1630, 1440, 1274, 1131, 974, 723, 695 cm^{-1}; ESI-MS: 423.2 (M^++Na^+); Anal. Calcd for $C_{27}H_{28}O_3$: C, 80.97; H, 7.05. Found: C, 80.89; H, 6.88. Compound **4i**:^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44–1.89 (m, 9H), 2.25–2.29 (m, 1H), 3.05 (br s, 1H), 4.00–4.06 (m, 1H), 5.39 (s,1H), 6.44 (s, 1H), 6.64 (d, J = 3.75 Hz, 2H), 7.12–7.26 (m, 6H), 7.48–7.61 (m, 4H), 8.14 (d, J = 7.5 Hz, 2H) ppm.; FT-IR (KBr) ν 3519, 3067, 2939, 2868, 1711, 1613, 1459, 1291, 1128, 980, 711, 691, 610 cm^{-1}; ESI-MS: 423.5 (M^++Na^+); Anal. Calcd for $C_{27}H_{28}O_3$: C, 80.97; H, 7.05. Found: C, 81.09; H, 7.01.

17. Purchased from Acros Organic, 95% atom% D.