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Double intramolecular oxymercuration: the first stereoselective synthesis of the C10–C34 fragment of asimitrin

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Abstract—The first stereoselective synthesis of the C10–C34 fragment of asimitrin, a nonclassical acetogenin, has been achieved. A key feature of our approach is the application of stereoselective double intramolecular oxymercuration for the efficient preparation of a mono-hydroxylated unsymmetrical bis-THF ring with two flanking hydroxyl groups. A chelation-controlled Grignard reaction plays a pivotal role in the elaboration of a commercially available carbohydrate.

Since the identification of the Annonaceous acetogenin uvaricin,[1] isolated from the roots of *Uvaria accuminata*, as an in vivo active antitumor agent, there has been significant interest in the isolation and biological evaluation of acetogenins derived from the Annonaceae family.[2] Annonaceous acetogenins are known to be highly potent and selective antitumor agents. More interestingly, some members of this family have been shown to possess the ability to combat resistance in multi drug-resistant cancerous cells.[3,4] The origin of the selective cytotoxicity of acetogenins is believed to result from their complexation with ubiquinone-linked NADH oxidase present in the plasma membrane of tumor cells. Acetogenins also bind NADH-ubiquinone oxidoreductase (Complex I), which is a membrane protein present in the mitochondrial electron-transport system.[5–9] Complex I has been implicated in several diseases including idiopathic Parkinson's disease, maturity onset diabetes, stroke-like episodes, and Huntington's disease.[10] However, the precise mode of complexation of acetogenins with the target proteins has not been delineated. Important characteristic structural features of Annonaceous acetogenins include a butenolide segment, one or more tetrahydrofuran rings, and alkyl chain residues on either side.

Mucoxin, a nonclassical acetogenin, is the first of its kind found to contain a trisubstituted hydroxylated tetrahydrofuran ring.[11] Recently, asimitrin **1** a ring-hydroxylated unsymmetrical bis-tetrahydrofuran acetogenin (Fig. 1) was isolated from the seeds of *Asimina triloba*.[12] This novel type of acetogenin was found to be cytotoxic selectively against prostate (PC-3) at about 10,000 times and colon adrenocarcinoma (HT-29) at about 100 times the potency of adriamycin. Such powerful antitumor activity and the unique structure of **1** have made it an attractive target similar to other classical bis-THF acetogenins for synthetic chemists.

We have recently shown that stereoselective intramolecular oxymercuration can be employed effectively for the synthesis of the bis-tetrahydrofuran ring system present in nonclassical acetogenins with excellent selectivity.[13] As a further test of this protocol for the synthesis of the bis-tetrahydrofuran system present in asimitrin, we describe herein the first stereoselective synthesis of the

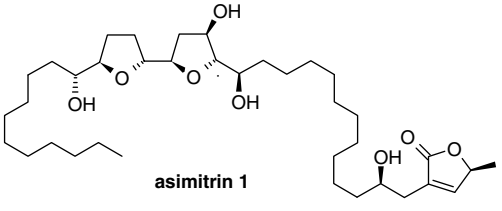

Figure 1. Structure of asimitrin **1**.

Keywords: Acetogenins; Asimitrin; Adjacent bis-tetrahydrofuran; Intramolecular oxymercuration; Chelation-controlled Grignard reaction.
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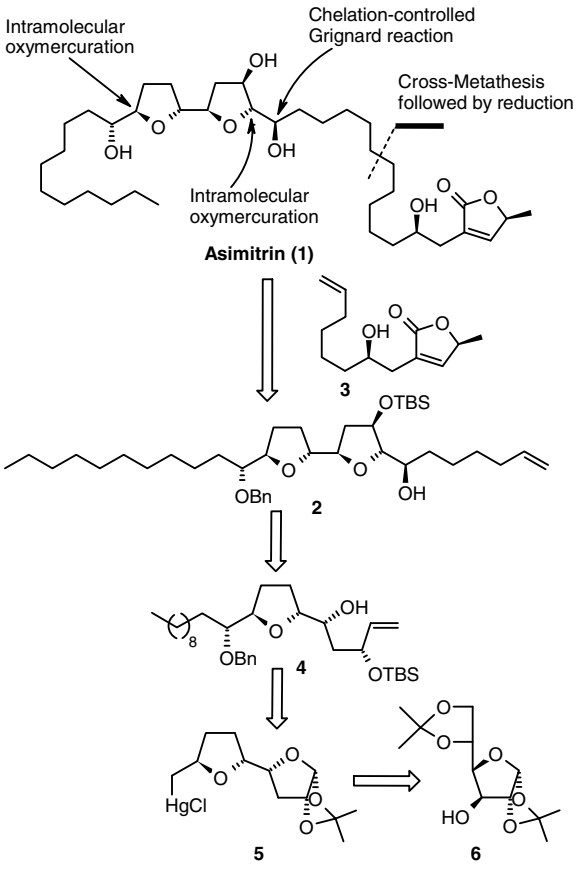
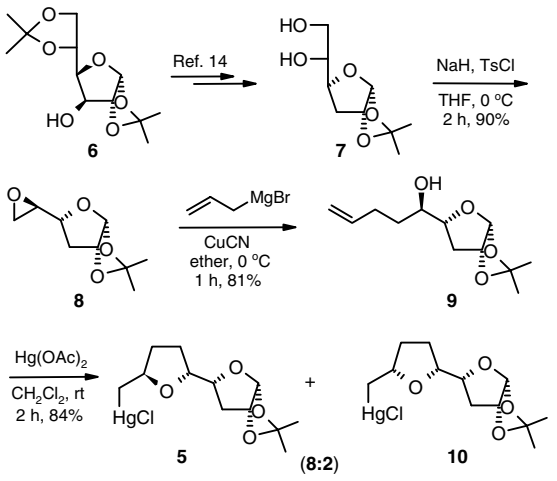


Scheme 1. Retrosynthetic analysis.

C10–C34 fragment (incorporating the adjacent bis-tetrahydrofuran moiety) of asimitrin.

Our synthetic strategy towards **1** was based on a convergent approach involving a cross metathesis for coupling the bis-THF core **2** with γ-lactone segment **3** as illustrated in Scheme 1. The bis-THF core would be prepared from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, which plays a central role, serving not only as the source of the C17, C19, and C20 stereocenters, but also setting the stage for introducing the C16 and C23 stereocenters through stereoselective intramolecular oxymercuration and chelation-controlled Grignard reactions.

The synthetic endeavor commenced from commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose: the secondary hydroxyl group was converted to its triflate derivative. Treatment with DBU resulted in elimination of the triflate group to afford the olefin. Hydrogenation of the resulting double bond, in the presence of Raney-Ni in ethanol at 40 psi, gave the reduced product whose spectral and analytical data were in good agreement with the reported values.[14] Selective deprotection of the 5,6-*O*-isopropylidene group and treatment of the resulting diol with NaH and TsCl afforded the epoxide **8**.[15] Copper-catalyzed epoxide ring-opening with allylmagnesium bromide in the presence of CuCN furnished alcohol **9** in 81% yield (Scheme 2).[16] Intramolecular oxymercuration of alcohol **9** with mercury(II) acetate in dichloromethane gave a trans–cis mixture of



Scheme 2. Synthesis of **5** and **10**.

tetrahydrofuran derivatives with 8:2 selectivity. Flash silica gel column chromatography was used to obtain pure *trans*- and *cis*-tetrahydrofurans **5** and **10**. The ^{1}H

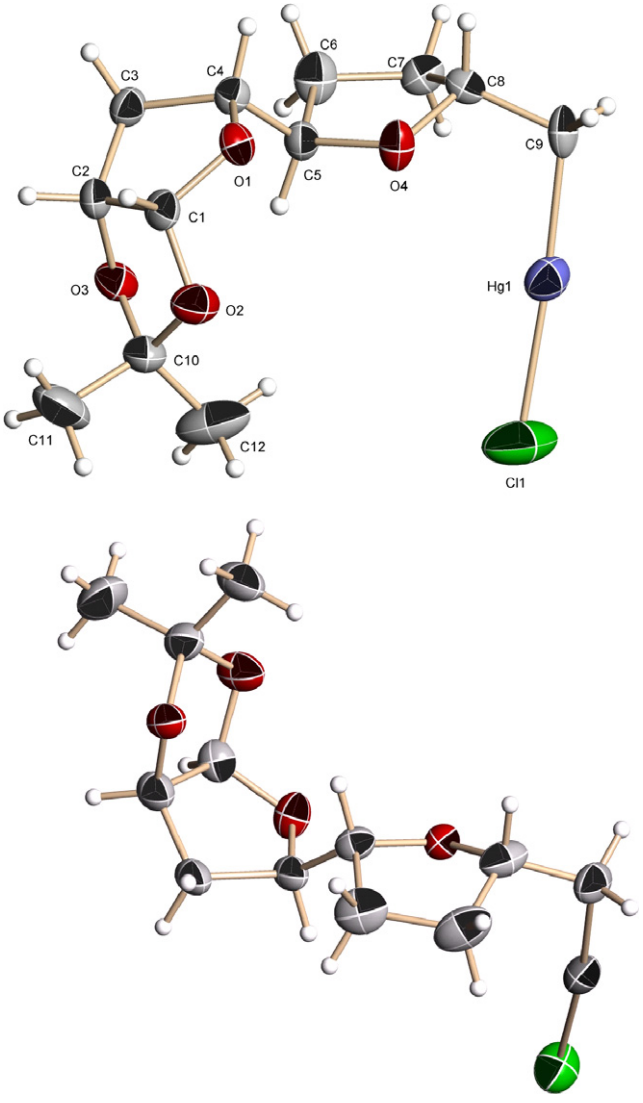
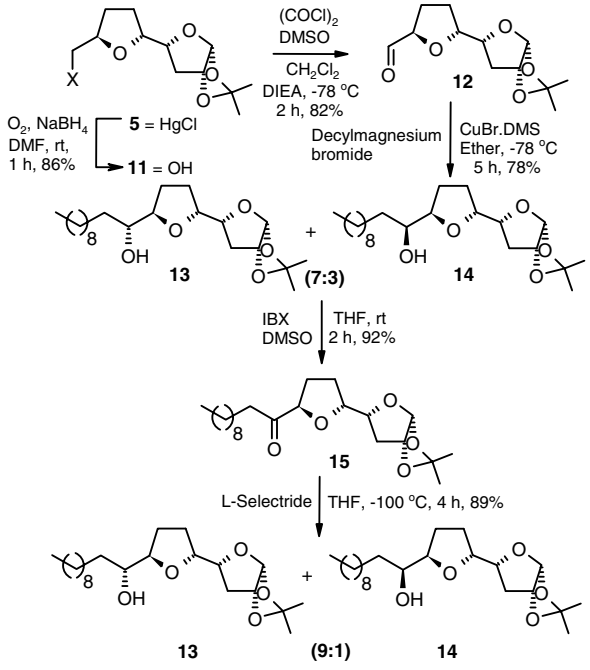


Figure 2. ORTEP diagrams of **5** and **10**.

and ^{13}C NMR of compounds **5** and **10** were in good agreement with the assigned structures.[17] The relative stereochemistry was ascertained by NOE experiments. The structures and absolute stereochemistry were unambiguously confirmed by single-crystal X-ray crystallography (Fig. 2).[18]

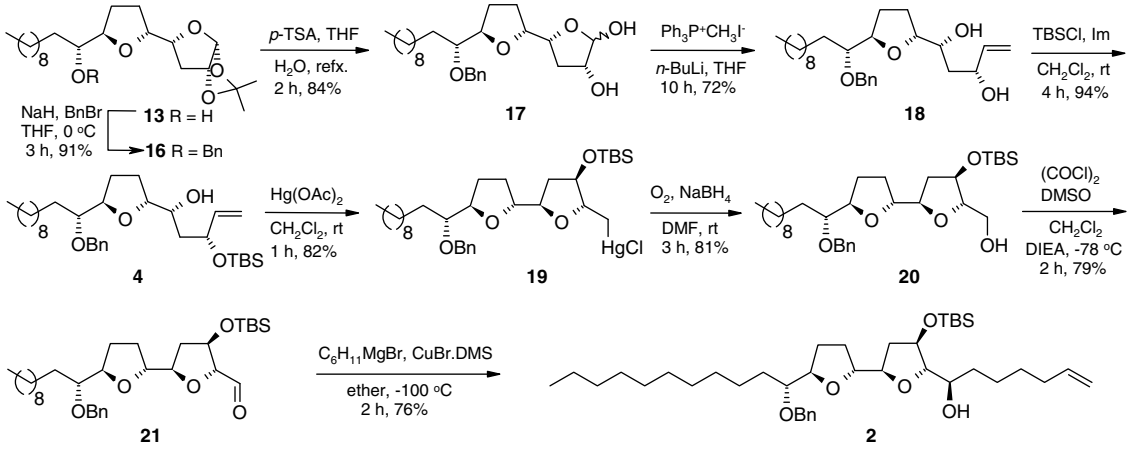
Demercuration of **5** was carried out under a stream of oxygen in the presence of sodium borohydride to afford the primary alcohol **11**. Our next concern was to introduce the alkyl side chain. To this end, the primary hydroxyl group of **11** was oxidized under Swern conditions[19] to afford aldehyde **12**. Treatment of **12** with decylmagnesium bromide in the presence of CuBr·DMS gave **13** and **14** containing a secondary hydroxyl group flanking the THF ring with a 7:3 preponderance of the desired isomer **13**.[20] To improve the selectivity, the secondary hydroxyl group was oxidized with IBX[21] in DMSO to the keto derivative **15**, which on treatment with L-Selectride[22] afforded compounds **13** and **14** in a 9:1 ratio. These were separated by flash silica gel column chromatography (Scheme 3). The chirality of the newly created secondary hydroxyl group bearing center was confirmed by a modified Mosher's method.[23] With **13** in hand, our next aim was to construct the trisubstituted tetrahydrofuran ring with requisite stereochemistry derived from the carbohydrate moiety. At this point, it was necessary to protect the hydroxyl functionality with a protecting group that would withstand the 1,2-acetonide deprotection conditions. Thus, treatment of compound **13** with BnBr in the presence of NaH afforded the benzyl ether derivative **16** in 91% yield. Compound **16** was then treated with *p*-TSA in the presence of THF and H_2O (7:3) under reflux to afford the hemiacetal, which after purification by silica gel column chromatography was subjected to one-carbon homologation[24] with $Ph_3P{=}CH_2$ to produce olefin **18** in 72% yield. The allylic hydroxyl group was selectively protected as its TBS-ether **4** in 94% yield. The requisite structural skeleton was now set for the second intramolecular oxymercuration reaction. Treatment of compound **4** with mercury(II) acetate in dichloromethane afforded **19** as a single diastereoisomer (Scheme 4). The structure of compound **19** was confirmed by ^1H, ^{13}C NMR, and elemental analysis and the stereochemistry around the tetrahydrofuran ring was assigned by NOE experiments.[25]



Scheme 3. Synthesis of **13** and **14**.

Demercuration of **19** was carried out using a fast flow of oxygen in the presence of sodium borohydride to obtain **20** in 81% yield. Finally, Swern oxidation followed by Grignard reaction with hexenylmagnesium bromide in the presence of CuBr·DMS at −100 °C afforded **2** with the secondary hydroxyl group with the required stereochemistry as the exclusive product.[26] The configuration of the newly created hydroxyl center at C15 of **2** was assigned following the modified Mosher's method.

In summary, commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose was elaborated via a double stereoselective intramolecular oxymercuration reaction sequence developed in our laboratories, to the C10–C34 fragment of asimitrin in a simple and efficient stereocontrolled manner. Total synthesis of the target molecule is underway and will be reported in due course.



Scheme 4. Synthesis of segment **2** of asimitrin.

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References and notes

1. Jolad, S. D.; Hoffmann, J. J.; Schram, K. H.; Cole, J. R.; Tempesta, M. S.; Kriek, G. R.; Bates, R. B. *J. Org. Chem.* **1982**, *47*, 3151–3153.
2. Bermejo, A.; Figadere, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269–303, and references cited therein.
3. Oberlies, N. H.; Croy, V. L.; Harrison, M. L.; McLaughlin, J. L. *Cancer Lett.* **1997**, *115*, 73–79.
4. Oberlies, N. H.; Chang, C. J.; McLaughlin, J. L. *J. Med. Chem.* **1997**, *40*, 2102–2106.
5. Ahammadsahib, K. I.; Hollingworth, R. M.; McGovern, J. P.; Hui, Y. H.; McLaughlin, J. L. *Life Sci.* **1993**, *53*, 1113–1120.
6. He, K.; Zeng, L.; Ye, Q.; Shi, G. E.; Oberlies, N. H.; Zhao, G. X.; Njoku, J.; McLaughlin, J. L. *Pestic. Sci.* **1997**, *49*, 372–378.
7. Londershausen, M.; Leicht, W.; Lieb, F.; Moeschler, H.; Weiss, H. *Pestic. Sci.* **1991**, *33*, 427–438.
8. Lewis, M. A.; Arnason, J. T.; Philogene, B. J. R.; Rupprecht, J. K.; McLaughlin, J. L. *Pestic. Biochem.Physiol.* **1993**, *45*, 15–23.
9. Morre, D. J.; Decabo, R.; Farley, C.; Oberlies, N. H.; McLaughlin, J. L. *Life Sci.* **1994**, *56*, 343–348.
10. Weiss, H.; Friedrich, T.; Hofhaus, G.; Preis, D. *Eur. J. Biochem.* **1991**, *197*, 563–576.
11. Shi, G.; Kozlowski, J. F.; Schwedler, J. T.; Wood, K. V.; MacDougal, M.; McLaughlin, J. L. *J. Org. Chem.* **1996**, *61*, 7988–7989.
12. Kim, E. J.; Suh, K. M.; Kim, D. H.; Jung, E. J.; Seo, C. S.; Son, J. K.; Woo, M. H.; McLaughlin, J. L. *J. Nat. Prod.* **2005**, *68*, 194–197.
13. Mohapatra, D. K.; Mohapatra, S.; Gurjar, M. K. *Tetrahedron Lett.* **2006**, *47*, 5943–5947.
14. Horton, D.; Roski, J. P.; Norris, P. *J. Org. Chem.* **1996**, *61*, 3783–3793.
15. *Analytical and spectral data of* **8**. $[\alpha]_D^{25}$ −37.77 (*c* 1.0, CH_2Cl_2); IR ($CHCl_3$) 1597, 1495, 1454 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.83 (d, $J = 3.7$ Hz, 1H), 4.75 (ddd, $J = 1.2$, 3.7, 5.3 Hz, 1H), 3.82 (ddd, $J = 3.0$, 7.3, 10.3 Hz, 1H), 3.35 (m, 1H), 2.81 (t, $J = 4.0$ Hz, 1H), 2.58 (dd, $J = 2.6$, 4.8 Hz, 1H), 2.22 (dd, $J = 5.6$, 8.5 Hz, 1H), 2.14 (m, 1H), 1.57 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 112.3, 106.7, 82.4, 80.3, 53.6, 44.5, 34.1, 27.0, 25.9; Anal. Calcd for $C_9H_{14}O_4$: C, 58.06; H, 7.52. Found: C, 58.32; H, 7.74.
16. Reddy, P. P.; Yen, K.-F.; Uang, B.-J. *J. Org. Chem.* **2002**, *67*, 1034–1035.
17. *Analytical and spectral data of* **5**. $[\alpha]_D^{25}$ −16.5 (*c* 0.6, CH_2Cl_2); IR ($CHCl_3$): 3017, 1637, 1383, 1374, 1215, 1031 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.75 (d, $J = 3.9$ Hz, 1H), 4.71 (m, 1H), 4.40 (m, 1H), 4.32 (q, $J = 7.7$ Hz, 1H), 3.95 (m, 1H), 2.39 (dd, $J = 5.5$, 12.0 Hz, 1H), 2.23–2.07 (m, 5H), 1.88 (m, 1H), 1.71 (s, 1H), 1.56 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) 112.8, 106.2, 82.5, 80.6, 77.8, 38.0, 36.6, 33.6, 29.1, 27.6, 26.5; Anal. Calcd for $C_{12}H_{19}O_4HgCl$: C, 31.16; H, 4.11. Found: C, 31.38; H, 4.25. Analytical and spectral data of **10**. $[\alpha]_D^{25}$ +21.4 (*c* 0.9, CH_2Cl_2); IR ($CHCl_3$): 3024, 1639, 1392, 1376, 1217, 1044 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.77 (d, $J = 4.0$ Hz, 1H), 4.70 (m, 1H), 4.39 (m, 1H), 4.11 (q, $J = 7.5$ Hz, 1H), 4.01 (m, 1H), 2.39 (m, 1H), 2.21–2.11 (m, 3H), 1.89 (m, 1H), 1.84 (m, 1H), 1.74 (s, 1H), 1.57 (s, 3H), 1.41 (m, 1H), 1.31 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) 112.7, 106.3, 83.1, 81.4, 80.5, 78.6, 38.5, 34.9, 34.1, 28.2, 27.4, 26.3; Anal. Calcd for $C_{12}H_{19}O_4HgCl$: C, 31.16; H, 4.11. Found: C, 31.24; H, 4.17.
18. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 645458 for **5** and CCDC 645459 for **10**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 0 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
19. Mancuso, A. J.; Huang, S.-L.; Swern, D. J. *J. Org. Chem.* **1978**, *43*, 2480–2482.
20. Mead, K.; Macdonald, T. T. *J. Org. Chem.* **1985**, *50*, 422–424.
21. Frigeno, M.; Santogostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.
22. (a) Wittmann, S.; Schoenecker, B. *J. Prakt. Chem./Chem.-Ztg.* **1996**, *338*, 759–762; (b) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567–607.
23. (a) Ohtani, I.; Kusumi, J.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096; (b) Yoshida, W. Y.; Bryan, P. J.; Baker, B. J.; McClintok, J. B. *J. Org. Chem.* **1995**, *60*, 780–782.
24. Freeman, F.; Robarge, K. D. *Carbohydr. Res.* **1986**, *154*, 270–274.
25. *Analytical and spectral data of* **19**. $[\alpha]_D^{25}$ −8.86, (*c* 1.3, CH_2Cl_2); IR ($CHCl_3$): 3059, 3025, 1869, 1802, 1747, 1668, 1601, 1583, 1492, 979, 964, 748 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.25–7.14 (m, 5H), 4.65 (d, $J = 11.6$ Hz, 1H), 4.49 (d, $J = 11.6$ Hz, 1H), 4.22–4.13 (m, 2H), 4.05–3.89 (m, 2H), 3.74 (m, 1H), 3.54 (m, 1H), 2.24–2.03 (m, 2H), 1.94–1.77 (m, 3H), 1.72–1.51 (m, 3H), 1.15 (s, 18H), 0.85 (s, 9H), 0.79 (t, $J = 5.5$ Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 139.3, 128.2, 127.9, 127.3, 82.8, 81.1, 80.8, 80.5, 80.4; 73.6, 73.5, 38.7, 31.9, 29.7, 29.6, 29.4, 28.7, 26.3, 25.9, 25.9, 22.7, 18.5, 14.2, −4.4; Anal. Calcd for $C_{33}H_{57}O_4SiHgCl$: C, 50.76; H, 7.30. Found: C, 50.82; H, 7.48.
26. *Analytical and spectral data of* **2**. $[\alpha]_D^{25}$ −10.94 (*c* 0.4, CH_2Cl_2); IR ($CHCl_3$): 3480, 2976, 2940, 1640, 1598 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–7.29 (m, 4H), 7.23 (m, 1H), 5.79 (m, 1H), 4.97 (m, 1H), 4.90 (m, 1H), 4.72 (d, $J = 11.6$ Hz, 1H), 4.58 (d, $J = 11.6$ Hz, 1H), 4.43 (q, $J = 6.2$ Hz, 1H), 4.09–4.04 (m, 2H), 3.82 (m, 1H), 3.75 (m, 1H), 3.62 (ddd, $J = 3.6$, 6.8, 11.0 Hz, 2H), 2.15 (m, 1H), 2.07–2.03 (m, 2H), 2.00–1.87 (m, 3H), 1.82 (m, 1H), 1.68 (m, 1H), 1.52–1.37 (m, 7H), 1.30–1.22 (m, 17H), 0.90 (s, 9H), 0.88 (t, $J = 6.8$ Hz, 3H), 0.08 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 139.3, 139.0, 128.2, 127.8, 127.3, 114.2, 83.7, 82.9, 81.1, 80.3, 79.5, 73.4, 73.2, 70.4, 38.0, 33.9, 33.5, 32.0, 31.9, 29.7, 29.6, 29.4, 29.2, 28.8, 26.0, 25.9, 25.8, 25.5, 22.7, 18.0, 14.1, −4.3, −5.0; Anal. Calcd for $C_{39}H_{68}O_5Si$: C, 72.67; H, 10.55. Found: C, 72.83; H, 10.37.