Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 5943–5947
Tetrahedron Letters

Double intramolecular oxymercuration: stereoselective synthesis of highly substituted bis-tetrahydrofuran

Debendra K. Mohapatra,* Seetaram Mohapatra and Mukund K. Gurjar

Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune 411 008, India

Received 3 May 2006; revised 31 May 2006; accepted 8 June 2006
Available online 30 June 2006

Abstract—Stereoselective intramolecular oxymercuration has been demonstrated as the key reaction for the efficient preparation of mono- and dihydroxylated unsymmetrical bis-tetrahydrofuran skeletons present in naturally occurring biologically active acetogenins using carbohydrates. These trans- and *syn*-selective intramolecular oxymercurations were explored in an enantioselective synthesis of the bis-tetrahydrofuran skeleton of mucoxin.

In recent years, the Annonaceous acetogenins have been the focus of extensive synthetic efforts[1] as a result of their remarkable range of biological properties such as antitumor, antiprotozoal, antifeedant, immunosuppressive, pesticidal, anthelmintic and microbial.[2] In particular, the 2,5-disubstituted bis-tetrahydrofuran (classical acetogenins **1**–**5**) sub-group of this family has been found to inhibit the growth of human tumor cells at sub-micromolar levels. A large proportion of such compounds are also cytotoxic to tumor cells that are resistant to typical chemotherapeutic agents.[3] Mucoxin **6**, a nonclassical acetogenin, is the first of its kind found to contain a trisubstituted hydroxylated tetrahydrofuran ring (Fig. 1).[4] Recently, asimitrin **7** a ring-hydroxylated unsymmetrical bis-tetrahydrofuran acetogenin was isolated from the seeds of *Asimina triloba*.[5] This class of compound showed cytotoxic selectivity with 100–10,000 times the potency compared to the classical acetogenins. Because of their diverse array of biological activities and by virtue of their extremely limited availability in Nature, these compounds have attracted the attention of synthetic organic chemists worldwide.

Stereocontrolled construction of the tetrahydrofuran unit plays a pivotal role in the total synthesis of Annonaceous acetogenins. Among the more successful approaches for bis-tetrahydrofuran ring formation are the cyclization of hydroxy-epoxides,[6] hydroxy-alkenes,[7] and variations of the Williamson ether synthesis.[8] Protocols based on Sharpless epoxidation and dihydroxylation,[9] addition of chiral allenyltin reagents to aldehydes,[10] and elaboration of natural enantiopure materials,[11] have been employed for the synthesis of the tetrahydrofuran precursors.

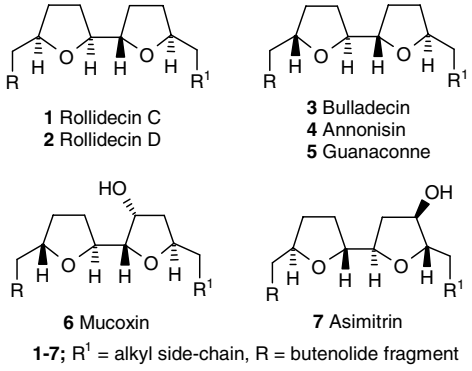


Figure 1. Classical and non-classical acetogenins.

We have previously reported intramolecular oxymercuration as an efficient method for stereoselective formation of the tetrahydrofuran ring during an enantioselective synthesis of the C12–C29 fragment of amphidinolide E.[12] Such ring closures have been earlier pioneered by Evans' and Hannessian's groups.[13] Prompted by the hydroxylated tetrahydrofuran core present in non-classical acetogenins as well as their

Keywords: Acetogenins; Intramolecular oxymercuration; Wittig reaction; Unsymmetrical bis-tetrahydrofuran; Demercuration; Barton–McCombie deoxygenation.
* Corresponding author. Tel.: +91 20 25902627; fax: +91 20 25902629; e-mail: dk.mohapatra@ncl.res.in

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.06.049

pronounced activity, we became intrigued with the possibility of using an intramolecular oxymercuration strategy for an efficient preparation of mono- and dihydroxylated bis-tetrahydrofuran systems which could be used to synthesize sufficient amounts of naturally occurring acetogenins and/or their derivatives and congeners with various side-chains, for the evaluation of biological activity (SARs).

Our retrosynthetic analysis for the dihydroxylated bis-tetrahydrofuran ring system is illustrated in Scheme 1. The stereocontrolled off-template construction of the first tetrahydrofuran ring was planned to utilize an intramolecular oxymercuration protocol on 4-alkenol derivative **11** followed by a second one on **9** to lead to the target compound **8**.

The known[14] intermediate **11** was prepared from D-glucose by a slight modification of the earlier protocol, wherein the Grignard reaction was carried out in ether by reverse addition of the Grignard reagent at 0 °C to improve the diastereoselectvity (9:1) in favor of **11**. Compound **11** was isolated from the crude reaction mixture by crystallization from hexane in 80% yield. The intramolecular oxymercuration[15] reaction of **11** with mercuric chloride in water at room temperature gave a cis–trans mixture of tetrahydrofuran derivatives with 3:1 selectivity, which was conveniently separated by flash silica gel column chromatography to obtain the pure *cis*- and *trans*-tetrahydrofurans **13** and **14**. The stereochemistry of **13** was unambiguously confirmed by single-crystal X-ray crystallography. It is noteworthy that treatment of compound **11** with mercury(II) acetate in THF led to the formation of compound **14**, exclusively. As previously suggested,[16] in THF, coordination-controlled mercurium ion formation followed by intramolecular nucleophilic attack by the C-5 hydroxyl group from the opposite face would lead to formation of the trans-isomer as the sole product (Fig. 2). In the presence of H_2O, the coordination is prevented leading to a mixture of *cis*- and *trans*-tetrahydrofuran ring systems. The demercuration[17] was then carried out under a stream of oxygen in the presence of sodium borohydride to afford the primary alcohol, which on benzylation gave **10** (Scheme 2). Our next concern was to construct the second tetrahydrofuran ring with substitution at C-3 and C-4 from the carbohydrate moiety, thus, compound **10** was treated with 20% acetic acid in the presence of a catalytic amount of sulfuric acid under reflux to afford the hemiacetal, which after purification by silica gel column chromatography was subjected to one-carbon homologation[18] with $Ph_3P{=}CH_2$ to produce the olefin **9**.

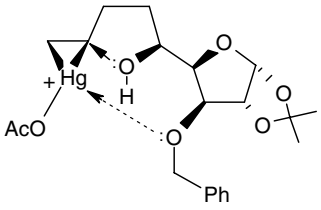
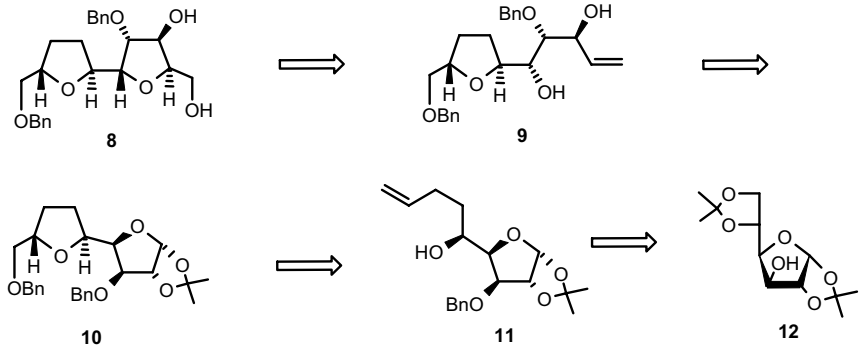


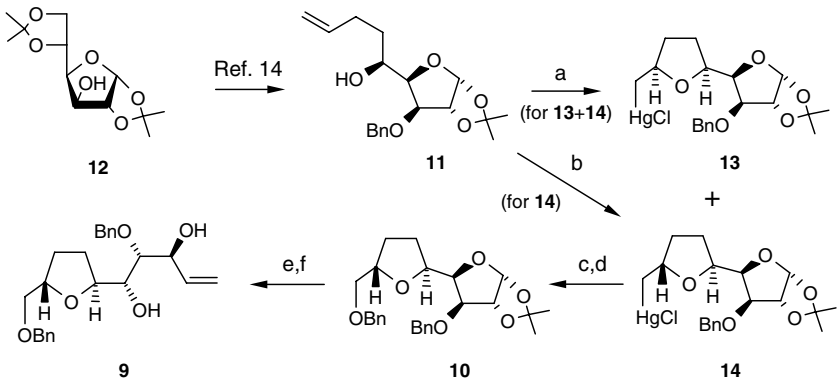
Figure 2. Proposed mechanism.

Now, the requisite structural skeleton was set for the second intramolecular oxymercuration. Treatment of compound **9** with mercury(II) acetate in dichloromethane or THF afforded **16** as the major product, while in the presence of H_2O, compound **15** was the major product (Scheme 3). Hence, a study of the influence of H_2O was performed and Table 1 summarizes the results of stereoselective intramolecular oxymercuration under different reaction conditions. The stereoisomers could be separated easily by silica gel column chromatography and their purities and structures were confirmed by ^1H, ^{13}C NMR, elemental analysis, and the relative stereochemistries were ascertained using NOESY experiments.[19]

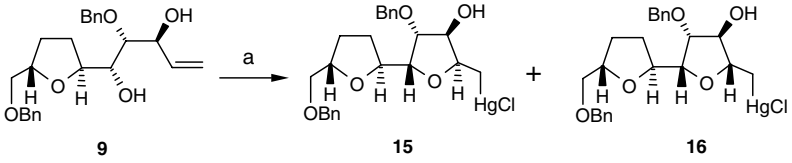
Application of this efficient protocol to the asymmetric synthesis of the hydroxylated tetrahydrofuran skeleton present in naturally occurring biologically active mucoxin **6** from compound **15** is illustrated in Scheme 4. Demercuration of **15** under a stream of oxygen in the presence of sodium borohydride, followed by selective protection of the primary hydroxyl group as its TBS ether afforded compound **18**. With **18** in hand, it was then obligatory to remove the secondary oxygen function from C-4 of the tetrahydrofuran moiety following the Barton–McCombie protocol via the xanthate **19** and treatment with tributylstannane to produce **20** in excellent yield. Cleavage of the silyl ether using TBAF



Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) $HgCl_2$, H_2O, rt, 1 h, (**13**:**14** = 3:1), (90%); (b) $Hg(OAc)_2$, THF, rt, 2 h, only **14**, (87%); (c) O_2, $NaBH_4$, DMF, rt, 4 h (81%); (d) NaH, BnBr, rt, 3 h (94%); (e) 20% CH_3COOH, H_2SO_4 (cat.), 80 °C, 7 h (78%) and (f) $Ph_3P{=}CH_2$, THF, rt, 4 h (88%).

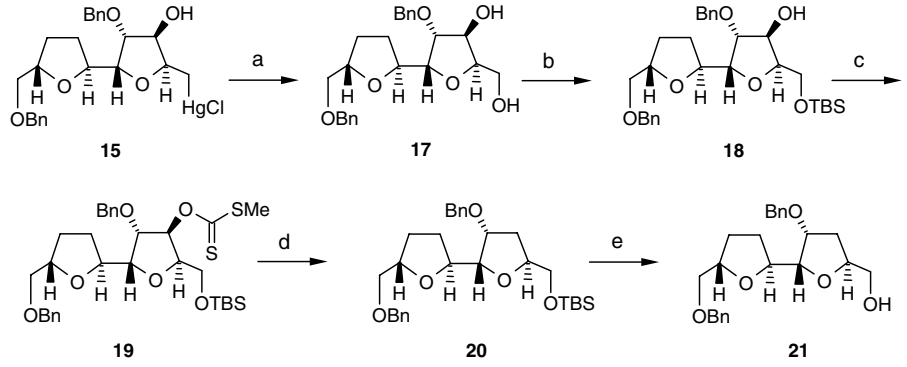


Scheme 3. Second stereoselective oxymercuration under different reaction conditions (Table 1).

Table 1. Results from the intramolecular oxymercuration under different reaction conditions

Entry	**9** (equiv)	Conditions	Ratio **15**:**16**	Yield[a] (%)
1	1.0	$Hg(OAC)_2$ (1.5 equiv), CH_2Cl_2, rt, 3 h	5:95	92
2	1.0	$Hg(OAC)_2$ (1.5 equiv), THF, rt, 4 h	5:95	89
3	1.0	$Hg(OAC)_2$ (1.5 equiv), H_2O–THF (2:1), rt, 3 h	85:15	90
4	1.0	$HgCl_2$ (1.5 equiv), H_2O–THF (2:1), rt, 2 h	87:13	87
5	1.0	$HgCl_2$ (1.5 equiv), H_2O, rt, 2 h	95:5	92
6	1.0	$HgCl_2$ (1.5 equiv), THF, rt, 2 h	14:86	91

[a] Isolated yield.



Scheme 4. Reagents and conditions: (a) O_2, $NaBH_4$, DMF, rt, 4 h (86%); (b) imidazole, TBSCl, rt, 5 h (92%); (c) NaH, CS_2, MeI, THF, 0 °C, 2 h (93%); (d) Bu_3SnH, AIBN, toluene, 90 °C, 3 h (94%) and (e) TBAF, THF, rt, 3 h (89%).

in THF at room temperature afforded the target unsymmetrical bis-tetrahydrofuran with requisite stereochemistry and functionality. This substance is now ready for connecting to the other subunits of mucoxin **6**.

In conclusion, starting from D-glucose, we have demonstrated an efficient stereocontrolled routes for the preparation of various functionalized bis-tetrahydrofuran derivatives, which are subunits of polyether antibiotics and acetogenins, using a strategy involving stereoselective intramolecular oxymercuration as the key step. An application of the strategy has been demonstrated by synthesizing the unsymmetrical bis-tetrahydrofuran skeleton of mucoxin with appropriate stereochemistry

and functionality starting from compound **12** in fifteen steps with 17% overall yield. Following the present protocol, the total syntheses of acetogenins are underway and will be reported in due course.

Acknowledgments

S.M. thanks CSIR, New Delhi, for financial support in the form of a research fellowship. We thank Dr. P. R. Rajmohan for providing the NMR data.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.049.

References and notes

1. Bermejo, A.; Figadere, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269–303, and references therein.
2. (a) Tormo, J. R.; Gallardo, T.; Gonzalez, M. C.; Bermenjo, A.; Cabedon, N.; Andrew, I.; Estornell, W. *Curr. Top. Phytochem.* **1999**, *2*, 69–90; (b) Johnson, H. A.; Oberlies, N. H.; Alali, F. Q.; McLaughlin, J. L. *Bio. Act. Nat. Prod.* **2000**, 173–183.
3. (a) Oberlies, N. H.; Croy, V. L.; Harrison, M. L.; McLaughlin, J. L. *Cancer Lett.* **1997**, *115*, 73–79; (b) Oberlies, N. H.; Chang, C.-J.; McLaughlin, J. L. *J. Med. Chem.* **1997**, *40*, 2102–2106.
4. Narayan, R. S.; Borhan, B. *J. Org. Chem.* **2006**, *71*, 1416–1429.
5. 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.
6. THF's from hydroxy epoxides: (a) Hoye, T. R.; Tan, L. *Tetrahedron Lett.* **1995**, *36*, 1981–1984, and references cited therein for the earlier work; (b) Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419–4427; (c) Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 7067–7073.
7. THF's from hydroxyalkenes: (a) Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1997**, *119*, 12014–12015, and references cited therein for the earlier work; (b) Hu, Y.; Brown, R. C. D. *Chem. Commun.* **2005**, 5636–5637, and references cited therein for the earlier work.
8. THF's via Williamson type etherification: (a) Yazbak, A.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1998**, *63*, 5863–5868; (b) Emde, U.; Koert, U. *Eur. J. Org. Chem.* **2000**, 1889–1904.
9. Recent reviews on the synthesis of THF acetogenins: (a) Figadere, B. *Acc. Chem. Res.* **1995**, *28*, 359–365; (b) Koert, U. *Synthesis* **1995**, 115–132; (c) Hoppe, R.; Scharf, H.-D. *Synthesis* **1995**, 1447–1464; (d) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G.; Appendino, G. *Chemtracts: Org. Chem. 1998, 11*, 803–827.
10. Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1999**, *64*, 971–975.
11. THF's from enantiopure natural precursors: (a) Koert, U. *Tetrahedron Lett.* **1994**, *35*, 2517–2520; (b) Yao, Z.-J.; Wu, Y. L. *J. Org. Chem.* **1995**, *60*, 1170–1176.
12. Gurjar, M. K.; Mohapatra, S.; Phalgune, U. D.; Puranik, V. G.; Mohapatra, D. K. *Tetrahedron Lett.* **2004**, *45*, 7899–7902.
13. (a) Hanessian, S.; Cooke, N. G.; Dettoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276–5290; (b) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290–5313.
14. Bertrand, P.; Sukkari, H. E.; Gesson, J. P.; Renoux, B. *Synthesis* **1999**, 330–335.
15. (a) Speziale, V.; Roussel, J.; Lattes, A. *J. Heterocycl. Chem.* **1974**, *11*, 771–775; (b) Vincens, M.; Dumont, C.; Vidal, M. *Can. J. Chem.* **1979**, *57*, 2314–2318.
16. (a) Thaisrivongs, S.; Seebach, D. *J. Am. Chem. Soc.* **1983**, *105*, 7407–7413; (b) Giese, B.; Bartmann, D. *Tetrahedron Lett.* **1985**, *26*, 1197–1200; (c) Garavelas, A.; Mavropoulos, I.; Perlmutter, P.; Westman, G. *Tetrahedron Lett.* **1995**, *36*, 463–466; (d) Bratt, K.; Garavelas, A.; Perlmutter, P.; Westmann, G. *J. Org. Chem.* **1996**, *61*, 2109–2117.
17. Sih, J. C.; Graber, D. R. *J. Org. Chem.* **1982**, *47*, 4919–4927.
18. Freeman, F.; Robarge, K. D. *Carbohydr. Res.* **1986**, *154*, 270–274.
19. Analytical and spectral data of compound **9**: $[\alpha]_D^{25}$ −10.7 (*c* 2.4, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.34–7.25 (m, 10H), 5.97 (qd, 1H, $J = 5.6$, 10.5 Hz), 5.39 (dt, 1H, $J = 1.6$, 17.2 Hz), 5.22 (dt, 1H, $J = 1.6$, 10.5 Hz), 4.69 (s, 2H), 4.54 (s, 2H), 4.41–4.32 (m, 1H), 4.28–4.14 (m, 2H), 3.59 (t, 1H, $J = 3.8$ Hz), 3.47–3.43 (m, 3H), 2.11–1.72 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.1, 137.9, 128.3, 128.2, 128.0, 127.7, 127.6, 127.5, 127.4, 116.2, 82.2, 78.9, 78.4, 74.3, 73.2, 72.6, 72.5, 72.1, 28.4, 28.0. Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59%. Found: C, 72.30; H, 7.52%. Analytical and spectral data of compound **15**: $[\alpha]_D^{25}$ −23.1 (*c* 2.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.26 (m, 10H), 4.67 (d, 1H, $J = 12.4$ Hz), 4.53 (d, 2H, $J = 2.3$ Hz), 4.45 (d, 1H, $J = 12.4$ Hz), 4.27 (q, 1H, $J = 7.8$ Hz), 4.23–418. (m, 2H), 3.85 (dd, 1H, $J = 4.1$, 7.8 Hz), 3.76–3.71 (m, 2H), 3.57 (dd, 1H, $J = 5.9$, 10.1 Hz), 3.46 (dd, 1H, $J = 4.6$, 10.1 Hz), 2.19 (dd, 1H, $J = 6.8$, 11.9 Hz), 2.10 (dd, 1H, $J = 3.2$, 11.9 Hz), 1.97–1.91 (m, 1H), 1.82–1.76 (m, 1H), 1.68–1.60 (m, 1H), 1.42–1.33 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 137.1, 128.7, 128.6, 128.4, 128.3, 127.9, 127.7, 85.1, 84.7, 83.1, 81.6, 78.2, 78.0, 73.4, 72.7, 71.6, 29.7, 28.6, 28.0. Anal. Calcd for $C_{24}H_{29}O_5HgCl$: C, 45.50; H, 4.61%. Found: C, 45.64; H, 4.59%. Analytical and spectral data of compound **16**: $[\alpha]_D^{25}$ −19.4 (*c* 1.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.24 (m, 10H), 4.61–4.55 (m, 2H), 4.52 (s, 2H), 4.43 (d, 1H, $J = 11.9$ Hz), 4.28 (q, 1H, $J = 7.6$ Hz), 4.24–4.17 (m, 1H), 4.13–4.07 (m, 2H), 3.87 (d, 1H, $J = 4.0$ Hz), 3.55 (dd, 1H, $J = 5.8$, 10.1 Hz), 3.46 (dd, 1H, $J = 4.27$, 10.1 Hz), 3.12 (br s, 1H), 2.05 (dd, 1H, $J = 7.0$, 12.0 Hz), 2.02–1.93 (m, 2H), 1.78 (dd, 1H, $J = 3.7$, 12.0 Hz), 1.74–1.62 (m, 2H), 1.52–1.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 137.7, 128.5, 128.4, 127.9, 127.7, 127.5, 85.3, 82.7, 79.4, 78.6, 77.9, 74.2, 73.4, 72.8, 72.3, 28.7, 28.0, 27.9. Anal. Calcd for $C_{24}H_{29}O_5HgCl$: C, 45.50; H, 4.61%. Found: C, 45.57; H, 4.72%. Analytical and spectral data of compound **17**: $[\alpha]_D^{25}$ −13.6 (*c* 2.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.26 (m, 10H), 4.65 (d, 1H, $J = 11.9$ Hz), 4.53 (s, 2H), 4.41 (d, 1H, $J = 11.9$ Hz), 4.32 (br s, 1H), 4.29 (q, 1H, $J = 8.3$ Hz), 4.19 (m, 1H), 3.92 (dd, 1H, $J = 4.6$, 7.8 Hz), 3.89 (q, 1H, $J = 4.1$ Hz), 3.83 (dd, 1H, $J = 1.8$, 4.1 Hz), 3.78 (dd, 1H, $J = 3.7$, 12.0 Hz), 3.71 (dd, 1H, $J = 4.1$, 11.6 Hz), 3.53 (dd, 1H, $J = 5.0$, 10.1 Hz), 3.46 (dd, 1H, $J = 5.0$, 10.1 Hz), 3.25 (br s, 1H), 3.06 (br s, 1H), 2.04–1.95 (m, 2H), 1.76–1.68 (m, 1H), 1.56–1.49 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 137.5, 128.4, 128.3, 127.9, 127.8, 127.6, 127.5, 86.2, 85.2, 83.0, 78.1, 75.4, 73.3, 72.5, 71.4, 62.6, 28.6, 28.2. Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30%. Found: C, 69.46; H, 7.24%. Analytical and spectral data of

compound **21**: $[\alpha]_D^{25}$ −45.9 (*c* 2.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 10H), 4.59 (d, 1H, $J = 11.6$ Hz), 4.55 (s, 2H), 4.36 (dt, 1H, $J = 6.5$, 9.8 Hz), 4.29 (d, 1H, $J = 11.6$ Hz), 4.26–4.16 (m, 2H), 4.04–4.01 (m, 1H), 3.84 (dd, 1H, $J = 2.5$, 11.6 Hz), 3.67 (dd, 1H, $J = 4.0$, 7.8 Hz), 3.60–3.54 (m, 2H), 3.48 (dd, 1H, $J = 5.3$, 9.8 Hz), 2.54 (br s, 1H), 2.20–2.07 (m, 3H), 2.03–1.96 (m, 1H), 1.82–1.73 (m, 1H), 1.59–1.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 137.5, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 85.5, 79.1, 78.9, 78.4, 78.1, 73.4, 72.6, 70.7, 64.4, 32.2, 28.8, 28.5. Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59%. Found: C, 72.30; H, 7.66%.