Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 1003–1007
Bioorganic & Medicinal Chemistry Letters

Synthesis of OSW saponin analogs with modified sugar residues and their antiproliferative activities

Pingping Tang,[a] Fatemah Mamdani,[b,c] Xiaoyi Hu,[b,c] Jun O. Liu[b,c] and Biao Yu[a,*]

[a]*State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*
[b]*Department of Pharmacology, Johns Hopkins School of Medicine, 725 North Wolfe Street, Baltimore, MD 21205, USA*
[c]*Department of Neuroscience, Johns Hopkins School of Medicine, 725 North Wolfe Street, Baltimore, MD 21205, USA*

Received 27 September 2006; revised 25 October 2006; accepted 13 November 2006
Available online 15 November 2006

Abstract—Eight monosaccharide analogs of the potent antitumor OSW saponins (**2**–**9**) were synthesized. One analog, 2-*O*-acetyl-α-L-arabinopyranoside **3**, showed antiproliferative activity against the Jurkat cells (IC_{50} = 0.078 μM) comparable to that of the disaccharide derivative (**1**).

About twenty OSW saponins, featuring a 16β,17α-dihydroxycholest-22-one aglycone and an acylated sugar residue attached to the 16β-hydroxyl group (Fig. 1), have been isolated from the bulbs of *Ornithogalum saudersiae* and its taxonomically related plants since 1992.[1] This class of cholestane glycosides have attracted considerable attention due to their extremely potent antitumor activities.[2] OSW-1, for example, showed a mean IC_{50} value of 0.78 nM when tested against the growth of the NCI (the US National Cancer Institute) 60 cell lines, which is 10–100 times lower than those of the clinically used anticancer agents, such as cisplatin, camptothecin, and taxol.[1b] Recent studies have revealed that OSW-1 was able to induce the apoptosis of tumor cells. However, the detailed molecular mechanism of action still remains unknown.[3] Several approaches toward the total synthesis of OSW-1 have been developed,[4,5] which have allowed access to a variety of OSW-1 analogs.[5,6] In particular, we recently found that the steroidal C17-side chain could tolerate certain modifications without significant loss of their antiproliferative potency.[5,6b] In fact, the easily accessible 22-ester analog **1** (Fig. 1) showed slightly stronger inhibitory activity against the growth of some tumor cell lines than OSW-1.[5] The importance of the sugar residue to the antiproliferative activity of OSW saponins has been implicated by changes in activity among the natural congeners and their degradative products. The presence of the 4″-*O*-β-D-glucopyranosyl residue (Fig. 1), the absence of the 2″-*O*-*p*-methoxybenzoyl (MBz) or -cinnamoyl substitution, or the removal of both the 2′-*O*-acetyl and 2″-*O*-*p*-methoxybenzoyl groups on the disaccharide residue of OSW-1 reduced its activity by 10- to 1000-fold.[1b–e]

In an attempt to identify structurally simpler analogs of OSW-1 with full antitumor activity, we turned our attention to the disaccharide moiety. Based on the aforementioned SAR data, we reasoned that truncation of the disaccharide residue in compound **1** into a monosaccharide derivative with the acetyl and *p*-methoxybenzoyl groups retained at their positions like compound **2** would not significantly affect its antiproliferative activity. Should that proven true, it would further simplify the synthesis of this structural class of antitumor agents. Herein we report the synthesis of the monosaccharide derivative **2** and its congeners **3**–**9** and the identification of one potent analog, **3**, that showed activity comparable to OSW-1.

Glycosidic coupling of the 16-OH of a cholestane aglycone with a sugar trichloroacetimidate donor under mild conditions has so far been the only solution to the

Keywords: OSW saponins; Glycosides; Synthesis; Antiproliferative activities.
* Corresponding author. Fax: +86 21 64166128; e-mail: byu@mail.sioc.ac.cn

0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.11.032

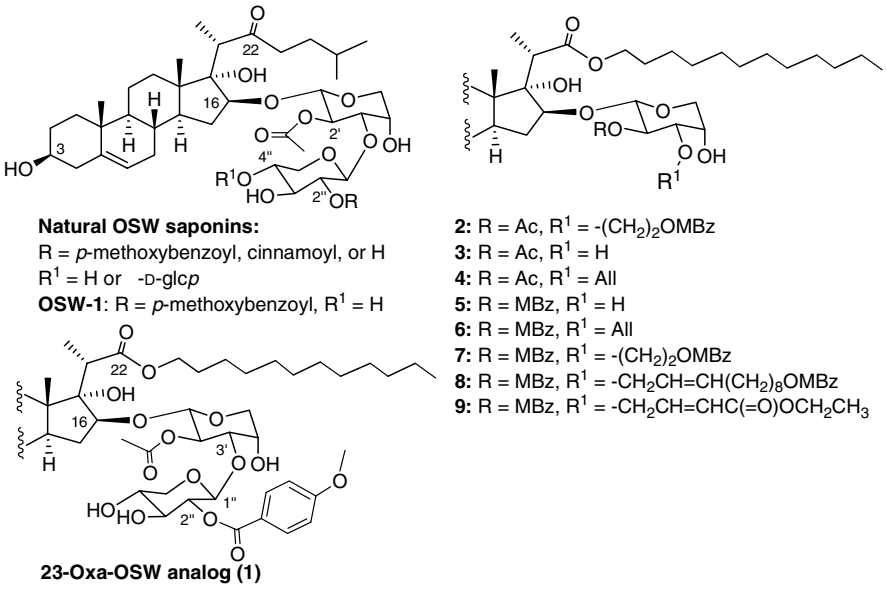


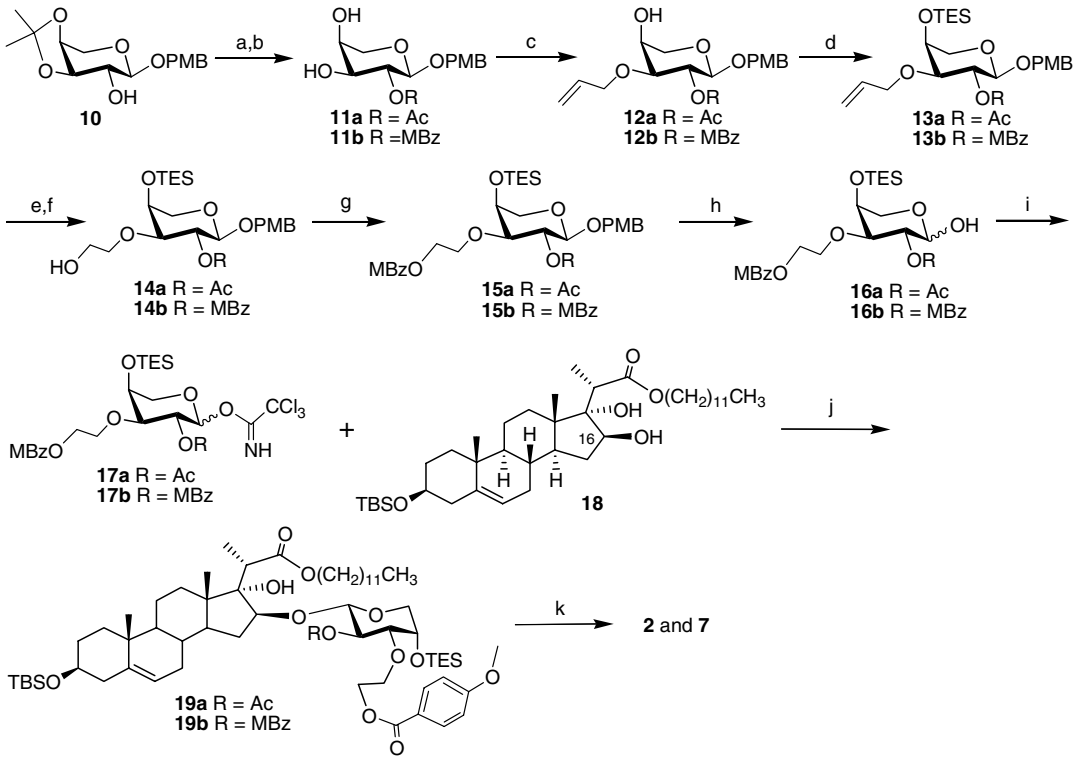
Figure 1. The natural OSW saponins and their synthetic analogs (MBz = *p*-methoxybenzoyl).

assembly of OSW saponins.[4b–d,5,6] Thus, the preparation of a relevant monosaccharide trichloroacetimidate (e.g., **17a**) would ensure the attainment of the monosaccharide analog **2** (Scheme 1). Starting from L-arabinose, *p*-methoxybenzyl 3,4-*O*-isopropylidene- α-L-arabinopyranoside (**10**) was prepared by five chemical steps and in 46% yield.[7] Acetylation of the remaining 2-OH followed by removal of the isopropylidene protection provided 3,4-diol **11a**. Selective allyl substitution of the equatorial 3-OH on **11a** was achieved in good yield via a tin-mediated allylation, affording **12a**. The remaining 4-OH was then protected with a TES group. Conversion of the 3-*O*-allyl group into a C2 alcohol met with no difficulty: ozonolysis of the double bond followed by $NaBH_4$ reduction provided 2′-OH derivative **14a** in 83% yield. The nascent 2′-OH was then masked with the MBz group. Finally, the anomeric *p*-methoxybenzyl (PMB) group was selectively cleaved with DDQ, and the resulting lactol was subjected to trichloroacetimidation, providing the desired arabinosyl donor **17a**. Coupling of the aglycone **18**[5] with trichloroacetimidate **17a** under the promotion of a catalytic amount of TMSOTf at low temperature (−40 °C) afforded the expected α-glycoside **19a** in a satisfactory 56% yield. Final removal of the protecting 3-*O*-TBS and 4′-*O*-TES groups was achieved with HF·pyridine, furnishing the designed analog **2**.

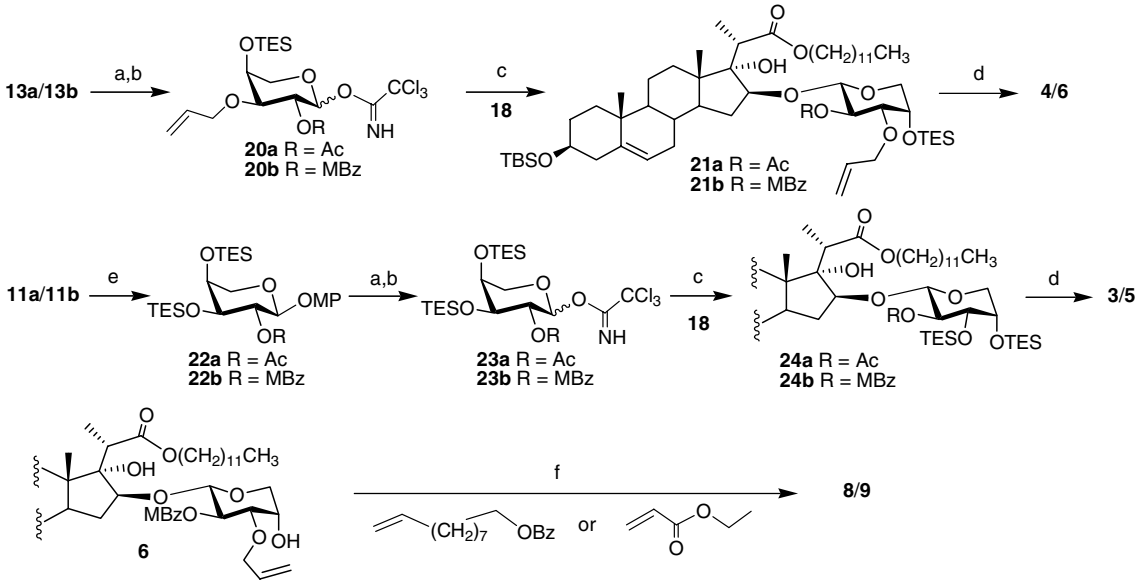
Exploiting the chemistry developed for the synthesis of the monosaccharide analog **2** of OSW saponins, we also managed to obtain quickly a group of structurally related analogs **3**–**9** (Schemes 1and 2). Thus, masking of the 2-OH on **10** with MBz group followed by removal of the 3,4-*O*-isopropylidene group gave **11b**, which was transformed into the 2-*O*-*p*-methoxybenzoyl-L-arabinopyranosyl trichloroacetimidate **17b** successfully employing a similar procedure as that for **11a** → **17a** (Scheme 1). Retaining the 3-*O*-allyl group, compounds **13a/b** were readily converted into the corresponding trichloroacetimidate donors **20a/b** via oxidative cleavage of the anomeric PMB group followed by trichloroacetimidation. Alternatively, the diols **11a/b** were protected with TES group and then converted into the trichloroacetimidate donors **23a/b** (Scheme 2). Glycosylation of the aglycone **18** with the newly prepared trichloroacetimidate donors **17b**, **20a/b**, and **23a/b** under similar conditions employed with donor **17a** afforded the corresponding α-glycosides (**19b**, **21a/b**, and **24a/b**) in comparable yields (~60%). It should be noted that the α-selectivity was ensured by the neighboring participation of the 2-*O*-acetyl and -*p*-methoxylbenzoyl groups in the imidate donors. Final removal of the TBS and TES groups on the coupling products (**19b**, **21a/b**, and **24a/b**) with HF·pyridine afforded the analogs **3**–**7** with varying monosaccharide residues.

Compounds **4/6** bearing an allyl group could be subjected to further derivatization via the powerful olefin cross metathesis reaction.[5b,8] Thus, treatment of the allyl ether **6** with 9-decen-1-yl benzoate (20 equiv) and ethyl acrylate (1.5 equiv) in the presence of the Grubbs (II) catalyst (22 mol%) at refluxing CH_2Cl_2 provided the corresponding coupling products **8** and **9** in 72% and 30% yield, respectively.

The in vitro activities of the synthetic monosaccharide analogs **2**–**9** of OSW saponins,[9] against the proliferation of several human cancer cell lines including RKO (colon carcinoma), Jurkat (human T cell leukemia), and HeLa (human cervical cancer) cell lines, with the 22-ester analog of OSW-1 (**1**) as a positive control,[5] were determined by following the incorporation of [3*H*]-thymidine.[5b] The results are summarized in Table 1. Contrary to our expectations, the designed analog **2**, with the 2′-*O*-acetyl and 2″-*O*-*p*-methoxybenzoyl groups being retained at their positions as in the disaccharide residue in the parent compound **1**, exhibited negligible antiproliferative activity at concentrations up to 10 μM. Neither did compounds **5**–**9**, all of which bear a 2′-*O*-*p*-methoxybenzoyl group, show much activity at 10 μM concentration.



Scheme 1. Reagents and conditions: (a) Ac_2O, pyridine, rt, 88%; (b) 70% HOAc, 40 °C, 85%; (c) Bu_2SnO, toluene, reflux, then AllBr, CsF, DMF, rt, 82%; (d) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 91%; (e) O_3, CH_3OH/CH_2Cl_2, −78 °C; (f) $NaBH_4$, CH_3OH/CH_2Cl_2, 0 °C, 83% (2 steps); (g) MBzCl, pyridine/CH_2Cl_2, rt, 72%; (h) DDQ, H_2O (buffer, pH 7)/CH_2Cl_2, rt, 92%; (i) CCl_3CN, DBU, CH_2Cl_2, rt, 84%; (j) TMSOTf (0.2 equiv), CH_2Cl_2, 4 Å MS, −40 °C, 56%; (k) HF·pyridine, CH_2Cl_2, rt, 80%.



Scheme 2. Reagents and conditions: (a) DDQ, H_2O (buffer, pH 7)/CH_2Cl_2, rt, 95%; (b) DBU, CCl_3CN, CH_2Cl_2, rt, 91%; (c) TMSOTf (0.2 equiv), CH_2Cl_2, 4 Å MS, −40 °C, ~60%; (d) HF·pyridine, CH_2Cl_2, rt, ~94%; (e) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, ~91%; (f) Grubbs II (22 mol%), CH_2Cl_2, reflux, 72% (for **8**), 30% (for **9**).

Interestingly, however, the 2-*O*-acetyl-α-L-arabinopyranoside **3** possessed highly potent activity against the growth of Jurkat cells with an IC_{50} of 78 nM which is comparable to that of the disaccharide derivative **1** (IC_{50} = 15 nM). Surprisingly, compound **3** showed no activity against the RKO cells and a moderate activity against the HeLa cells (IC_{50} = 1.2 μM). Compound **4** bearing an additional 3-*O*-allyl group showed moderate activities against the RKO and HeLa cells (IC_{50} = 1.7 and 1.1 μM, respectively), but was inactive against Jur-

Table 1. The antiproliferative activity of the synthetic OSW-1 analogs (**1**–**9**) against tumor cells

	IC_{50} (μM)				
	1	**2**	**3**	**4**	**5–9**
RKO	0.0007	ND	ND	1.7	ND
Jurkat	0.015	ND	0.078	ND	ND
HeLa	0.071	ND	1.2	1.1	ND

ND, IC_{50} not determined. These compounds did not show considerable inhibitory activities at a concentration of 10 μM.

kat cells. The differential sensitivity of different cell lines to the same compound is also seen with the OSW-1 disaccharide analog **1** and is therefore not unique for the monosaccharide analogs. It is intriguing that analog **1** is about 100-fold more potent against RKO than HeLa cells, while analog **4** has a similar potency against both cell lines. Similarly, analogs **3** and **4** are equally potent against HeLa cells, but for Jurkat T cells, they differ dramatically in their activity. The precise molecular mechanism underlying these disparities in potency among this class of OSW-1 analogs remains to be elucidated.

In summary, based on the previous SAR data on the highly potent antitumor OSW saponins, we rationally designed and synthesized an analog bearing a truncated sugar residue (**2**). The synthesis was achieved in 16 steps and 6% overall yield starting from L-arabinose; and the synthetic approach was adaptable to the quick elaboration of the related compounds. Thus, the monosaccharide analogs **3**–**9** were also prepared. Although the designed analog **2**, along with compounds **5**–**9**, did not show antiproliferative activity against cancer cell lines tested, one monosaccharide analog, 2-*O*-acetyl-α-L-arabinopyranoside **3**, showed activity comparable to that of the disaccharide derivative (**1**) against the Jurkat cells (IC_{50} = 0.078 μM). These results suggest that the sugar moiety in the OSW saponins is essential for their potent antitumor activity.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (20372070 and 20321202), the Chinese Academy of Sciences (KGCX2-SW-209), and the Committee of Science and Technology of Shanghai (04DZ14901).

References and notes

1. (a) Kubo, S.; Mimaki, Y.; Terao, M.; Sashida, Y.; Nikaido, T.; Ohmoto, T. *Phytochemistry* **1992**, *31*, 3969; (b) Mimaki, Y.; Kuroda, M.; Kameyama, A.; Sashida, Y.; Hirano, T.; Oka, K.; Maekawa, R.; Wada, T.; Sugita, K.; Beutler, J. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 633; (c) Kuroda, M.; Mimaki, Y.; Yokosuka, A.; Sashida, Y. *Chem. Pharm. Bull.* **2001**, *49*, 1042; (d) Kuroda, M.; Mimaki, Y.; Yokosuka, A.; Sashida, Y.; Beutler, J. A. *J. Nat. Prod.* **2001**, *64*, 88; (e) Kuroda, M.; Mimaki, Y.; Yokosuka, A.; Hasegawa, F.; Sashida, Y. *J. Nat. Prod.* **2002**, *65*, 1417.
2. Rouhi, A. M. *Chem. Eng. News* **1995**, *11*, 28.
3. (a) Zhu, J.; Xiong, L.; Yu, B.; Wu, J. *Mol. Pharm.* **2005**, *68*, 1831; (b) Zhou, Y.; Garcia-Prieto, C.; Carney, D. A.; Xu, R. H.; Pelicano, H.; Kang, Y.; Yu, W.; Lou, C.; Kondo, S.; Liu, J.; Harris, D. M.; Estrov, Z.; Keating, M. J.; Jin, Z.; Huang, P. *J. Natl. Cancer Inst.* **2005**, *97*, 1781.
4. (a) Guo, C.; Fuchs, P. L. *Tetrahedron Lett.* **1998**, *39*, 1099; (b) Deng, S.; Yu, B.; Lou, Y.; Hui, Y. *J. Org. Chem.* **1999**, *64*, 202; (c) Morzycki, J. W.; Gryszkiewicz, A.; Jastrzebska, I. *Tetrahedron Lett.* **2000**, *41*, 3751; (d) Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2001**, *123*, 3369; (e) Morzycki, J. W.; Wojtkielewicz, A. *Carbohydr. Res.* **2002**, *337*, 1269; (f) Xu, Q.; Peng, X.; Tian, W. *Tetrahedron Lett.* **2003**, *44*, 9375.
5. (a) Shi, B.; Wu, H.; Yu, B.; Wu, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 4324; (b) Shi, B.; Tang, P.; Hu, X.; Liu, J. O.; Yu, B. *J. Org. Chem.* **2005**, *70*, 10354.
6. (a) Ma, X.; Yu, B.; Hui, Y.; Miao, Z.; Ding, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2153; (b) Deng, L.; Wu, H.; Yu, B.; Jiang, M.; Wu, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2781; (c) Morzycki, J. W.; Wojtkielewicz, A.; Gryszkiewicz, A.; Wolczynski, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3323.
7. Ple, K.; Chwalek, M.; Voutquenne-Nazabadioko, L. *Eur. J. Org. Chem.* **2004**, *7*, 1588.
8. (a) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58; (b) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
9. Analytical data for the monosaccharide analogs **2**–**9**. Compound **2**: $[\alpha]_D^{24} = 13.7$ (*c* 0.47, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.33 (br s, 1H), 4.91 (d, *J* = 1.9 Hz, 1H), 4.54 (m, 1H), 4.38 (m, 2H), 4.26 (m, 1H), 4.14 (m, 1H), 3.90–3.71 (m, 9H), 3.64 (m, 1H), 3.50 (m, 2H), 2.89 (q, *J* = 7.5 Hz, 1H), 2.61 (m, 1H), 2.30–2.20 (m, 3H), 2.06 (s, 3H), 0.98 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.9, 169.5, 166.2, 163.6, 140.6, 131.7, 122.2, 121.4, 113.7, 99.9, 90.4, 84.7, 71.7, 68.3, 64.9, 63.9, 63.5, 55.4, 49.5, 48.2, 45.7, 40.8, 36.4, 31.9, 31.8, 31.6, 29.6, 29.5, 29.5, 29.3, 29.2, 28.5, 25.8, 22.7, 20.8, 19.3, 14.1, 13.3, 12.9. HRMS (ESI) calcd for $C_{51}H_{78}O_{13}Na$ ($M+Na^+$): 921.5382; found: 921.5335. Compound **3**: $[\alpha]_D^{25} = 27.5$ (*c* 0.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.45 (d, *J* = 3.6 Hz, 1H), 4.80 (dd, *J* = 3.0, 2.4 Hz, 1H), 4.44 (d, *J* = 2.7 Hz, 1H), 4.33–4.24 (m, 1H), 4.01–3.83 (m, 5H), 3.72 (dd, *J* = 11.7, 8.1 Hz, 1H), 3.65–3.48(m, 2H), 3.05 (d, *J* = 8.4 Hz, 1H), 2.89 (q, *J* = 7.5 Hz, 1H), 2.48–2.40 (m, 1H), 2.40–2.20 (m, 3H), 2.11 (s, 3H), 1.36 (d, *J* = 7.5 Hz, 3H), 1.07 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.8, 169.8, 140.7, 121.3, 99.9, 90.9, 84.5, 71.7, 70.7, 68.9, 65.1, 64.9, 61.1, 49.5, 48.1, 45.9, 42.2, 40.9, 37.2, 36.4, 34.5, 32.1, 31.9, 31.8, 31.6, 29.6, 29.5, 29.5, 29.3, 29.2, 28.4, 25.8, 22.6, 20.8, 20.5, 19.3, 14.1, 13.6, 13.0; HRMS (ESI) calcd for $C_{41}H_{68}O_{10}Na$ ($M+Na^+$): 743.4707; found: 743.4705. Compound **4**: $[\alpha]_D^{19} = -30.5$ (*c* 0.66, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.99–5.81 (m, 1H), 5.34–5.21 (m, 3H), 4.93 (br s, 1H), 4.36–4.25 (m, 3H), 4.05–3.71 (m, 6H), 3.58–3.48 (m, 3H), 2.93 (q, *J* = 7.5 Hz, 1H), 2.43–2.19 (m, 4H), 2.09 (s, 3H), 1.36 (d, *J* = 7.5 Hz, 3H), 1.01 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.0, 169.5, 140.6, 133.9, 121.5, 117.6, 99.9, 90.5, 84.7, 74.6, 71.7, 70.5, 68.1, 61.9, 63.9, 60.8, 49.5, 48.3, 45.7, 42.3, 40.7, 37.1, 36.4, 34.5, 32.2, 31.9, 31.8, 31.6, 29.7, 29.6, 29.5, 29.5, 29.3, 29.2, 28.5, 25.8, 22.6, 20.8, 20.6, 19.3, 14.1, 13.4, 12.9; HRMS (ESI) calcd for $C_{44}H_{72}O_{10}Na$ ($M+Na^+$): 783.5022; found: 783.5018. Compound **5**: $[\alpha]_D^{19} = -8.4$(*c* 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 5.34 (br s, 1H), 4.98 (br s, 1H), 4.64 (m, 1H), 4.22 (m, 1H), 4.11–4.04 (m, 4H), 3.87 (s, 3H), 3.70 (m, 2H), 3.60–3.50 (m,

1H), 3.18–2.91 (m, 1H), 1.01 (s, 3H), 0.87 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 164.3, 163.4, 140.2, 131.4, 120.9, 120.7, 113.2, 99.3, 90.8, 84.0, 71.1, 69.7, 67.9, 64.9, 63.8, 59.6, 54.9, 48.9, 47.6, 45.4, 41.7, 40.3, 36.6, 35.9, 33.9, 31.5, 31.4, 31.2, 31.1, 29.2, 29.1, 29.0, 28.8, 28.7, 27.8, 25.2, 22.1, 20.0, 18.8, 13.5, 13.3, 12.4; HRMS (MALDI) calcd for $C_{47}H_{72}O_{11}Na$ ($M+Na^+$): 835.4997; found: 835.4967. Compound **6**: $[\alpha]_D^{21} = -17.5$ (*c* 1.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 5.94 (m, 1H), 5.37 (m, 2H), 5.24 (m, 1H), 5.13 (br s, 1H), 4.55 (br s, 1H), 4.43 (m, 1H), 4.23 (m, 1H), 4.11–4.04 (m, 2H), 3.87 (s, 3H), 3.60–3.50 (m, 2H), 2.98 (m, 1H), 1.02 (s, 3H), 0.88 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.1, 164.7, 163.8, 140.6, 134.0, 131.8, 121.6, 121.4, 117.6, 113.7, 107.8, 99.8, 90.6, 84.8, 74.3, 71.7, 70.6, 67.9, 65.1, 63.8, 55.4, 49.5, 48.3, 45.7, 42.3, 40.7, 36.4, 34.5, 31.9, 31.8, 29.7, 29.6, 29.5, 29.3, 29.2, 28.4, 25.8, 22.6, 19.4, 14.1, 13.5, 12.8; HRMS (MALDI) calcd for $C_{50}H_{76}O_{11}Na$ ($M+Na^+$): 875.5279; found: 875.5279. Compound **7**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99–7.95 (m, 4H), 6.92–6.87 (m, 4H), 5.34 (br s, 1H), 5.10 (br s, 1H), 4.54 (m, 2H), 4.42 (m, 1H), 4.25–4.18 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.56 (m, 2H), 2.93 (m, 1H), 2.63 (m, 1H), 1.10 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H), 0.88 (s, 3H). Compound **8**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, J = 8.3 Hz, 2H), 7.97 (d, J = 8.8 Hz, 2H), 7.56–7.43 (m, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.78 (m, 1H), 5.56 (m, 1H), 5.35 (br s, 2H), 5.11 (d, J = 2.0 Hz, 2H), 4.53 (br, 1H), 4.36–4.29 (m, 3H), 4.21 (m, 1H), 4.07–3.89 (m, 3H), 3.86 (s, 3H), 3.81–3.73 (m, 3H), 3.53 (m, 2H), 3.00 (q, J = 7.5 Hz, 1H), 1.01 (s, 3H); HRMS (MALDI) calcd for $C_{65}H_{96}O_{13}Na$ ($M+Na^+$): 1107.6764; found: 1107.6743. Compound **9**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, J = 9.0 Hz, 2H), 7.06–6.91 (m, 3H), 6.15–6.09 (m, 0.5H), 5.36 (br s, 1.5H), 5.10 (m, 1H), 4.64 (m, 1H), 4.56 (br s, 1H), 4.32–4.22 (m, 4H), 4.02 (m, 2H), 3.88 (s, 3H), 3.83–3.56 (m, 5H), 2.91–2.88 (m, 1H), 1.02 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H), 0.86 (s, 3H).