Stereoselective Total Synthesis of Stagonolide C and Formal Total Synthesis of Modiolide A

Debendra K. Mohapatra,* Uttam Dash, P. Ramesh Naidu, J. S. Yadav*

Organic Chemistry Division-I, Indian Institute of Chemical Technology (CSIR), Uppal Road, Hyderabad 500007, India
Fax +91(40)27160512; E-mail: mohapatra@iict.res.in

Received 6 May 2009

This paper is dedicated to Dr. A. V. Rama Rao on the occasion of his 74th birthday.

Abstract: The influence of protecting groups at C4 and C7 on a ring-closing metathesis reaction was investigated. Matched induction led to the total synthesis of stagonolide C and the formal total synthesis of modiolide A.

Key words: decanolide, stagonolide C, modiolide A, ring-closing metathesis, Sharpless asymmetric epoxidation

Many naturally occurring ten-membered lactones isolated from fungal metabolites, commonly known as decanolides, have attracted considerable attention from synthetic organic chemists as well as bioorganic chemists, because of their interesting structural features and various biological activities such as plant growth inhibition and antifeedant, anti-fungal and anti-bacterial activities.[1] The main phytotoxic metabolite produced by *S. Cirsii* in liquid culture, named stagonolide (**1**) was isolated and characterized as a new nonenolide.[2] Other metabolites include eight new stagonolides, named stagonolide B to I (**2**–**9**), which were isolated and chemically characterized including their biological properties.[3a,b] These stagonolides were structurally similar to stagonolide (**1**) and were isolated from the same fungus. Another structurally similar ten-membered lactone known as modiolide A (**10**) was isolated by Kobayashi and co-workers[3c] from marine-origin microorganisms and shown to be active against both bacteria and fungi.

Construction of lactones through the formation of a C–C bond and, particularly, by intramolecular ring-closing metathesis[4] reactions remains as a promising tool for the synthesis of decanolides. Recently, Murty et al. reported the total synthesis of stagonolide F following a ring-closing metathesis approach.[5] The influence of the protecting groups on the geometrical outcome of the ring-closing metathesis reaction has been reported previously.[6] During our studies on the total synthesis of nonenolide[6c] (**12**) and decarestrictine[6a] C1 and C2 (**13** and **14**, Figure 1), we observed that complete control of the double bond geometry formed during the ring-closing metathesis reaction was possible through the selection of protecting groups.

As part of an ongoing program aimed at exploring ring-closing metathesis for macrolide synthesis and at generalizing its substrate and protecting group based selectivity, we have investigated the outcome of such ring-closing metathesis reactions on substrates with protecting groups at chiral centers adjacent to both the reacting sites. In this way we hoped to achieve the total synthesis of stagonolide C and the formal total synthesis of modiolide A.

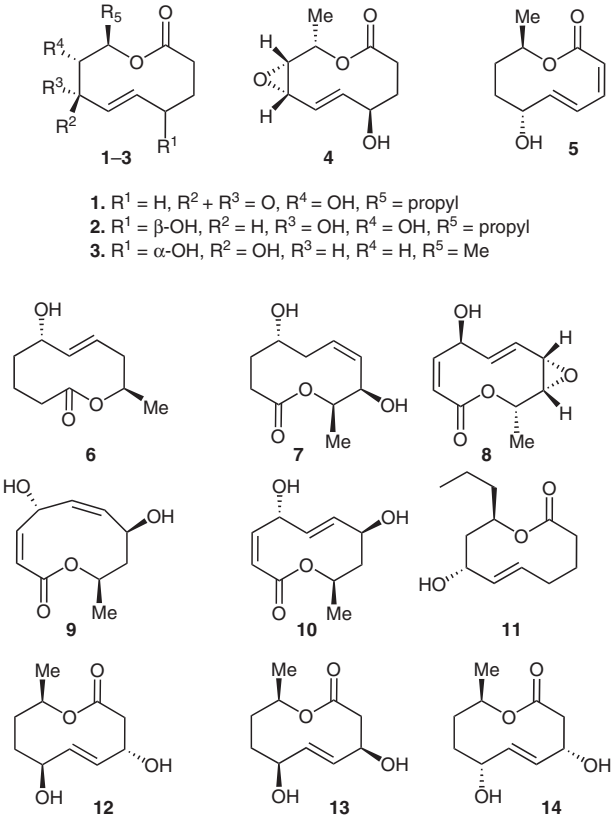
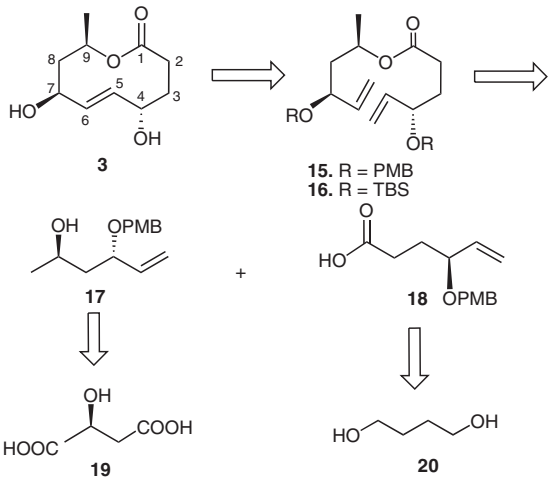


Figure 1 Stagonolide (**1**), stagonolide B–I (**2**–**9**), modiolide A (**10**), herbarumin III (**11**), nonenolide (**12**), and decarestrictine C1 and C2 (**13** and **14**)

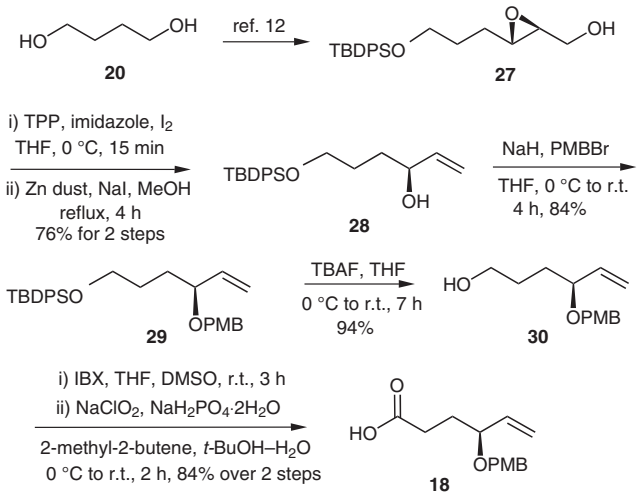
According to our retrosynthetic analysis (Scheme 1), construction of the ten-membered lactone would arise from the formation of the C5–C6 olefinic linkage from the bis-alkene which, in turn, would be prepared via esterification of alcohol **17** and acid **18**; the fragments would be prepared from L-malic acid and butane-1,4-diol, respectively.

The synthesis of fragment **17** began with the known compound **21**,[7] which was subjected to reduction with DIBAL-H at –15 °C in dichloromethane to afford allyl alcohol **22** in 81% yield. Sharpless asymmetric epoxidation[8]

SYNLETT 2009, No. 13, pp 2129–2132
Advanced online publication: 15.07.2009
DOI: 10.1055/s-0029-1217556; Art ID: G10809ST



Scheme 1 Retrosynthetic analysis of stagonolide C

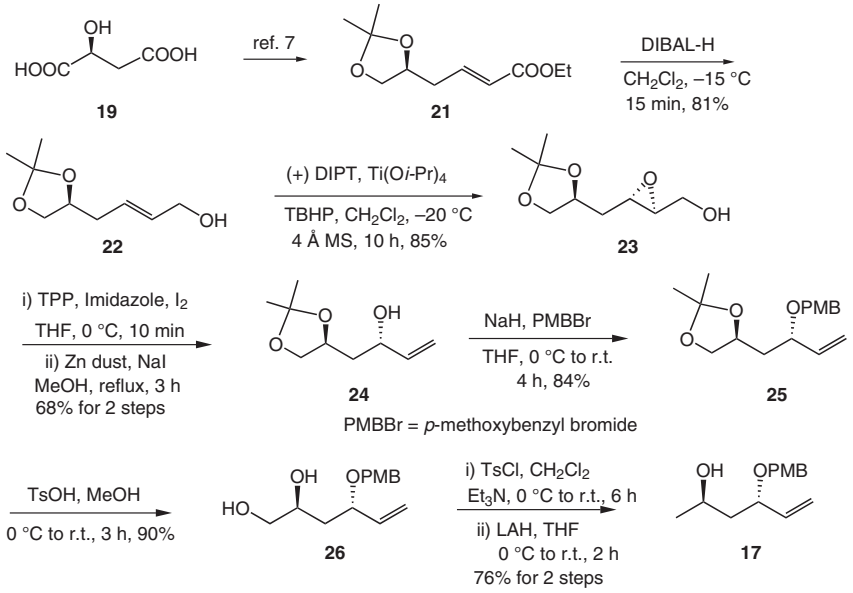


Scheme 3 Synthesis of fragment **18**

of **22** with (+)-DIPT produced 2,3-epoxy alcohol **23** in 85% yield in a 95:5 ratio with the required isomer as the major product (based on ^{1}H and ^{13}C NMR). Conversion of the hydroxy group in **23** into the iodo-derivative with triphenylphosphine, I_2 and imidazole in THF, followed by activated zinc dust mediated elimination,[9] furnished allylic alcohol **24**, which was protected as its *p*-methoxybenzyl ether to afford **25** in 84% yield (Scheme 2). Deprotection of the isopropylidene group with *p*-toluenesulfonic acid in methanol,[10] followed by selective protection of the primary hydroxy group with tosyl chloride and triethylamine and further reduction of the tosyl derivative with lithium aluminum hydride, gave the required alcohol fragment **17**[11] in 76% yield over two steps.

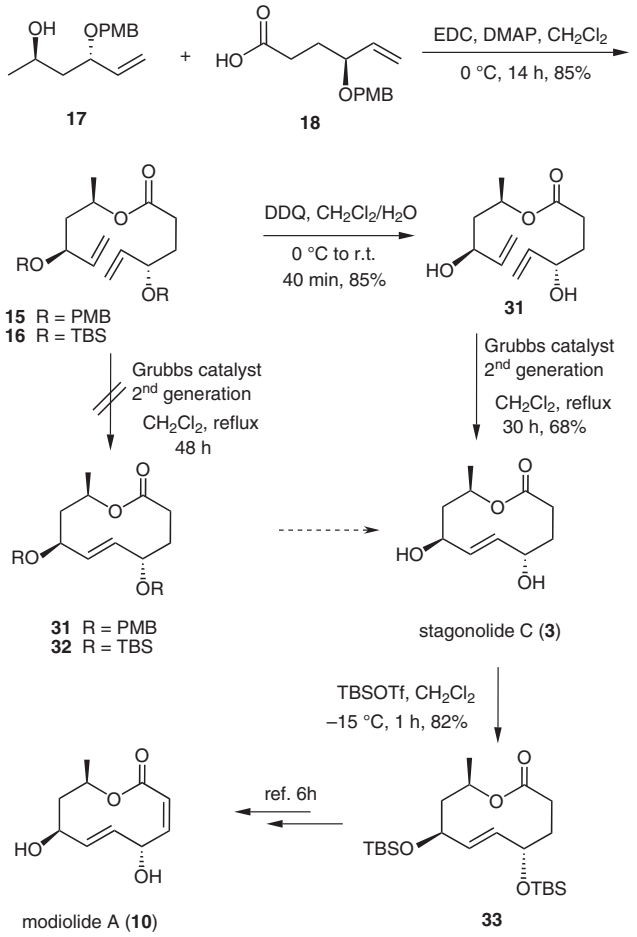
The synthesis of fragment **18** started from the known intermediate **27**,[12] which was prepared from commercially available 1,4-butane diol (**20**), followed by the same sequence of reactions as performed during the preparation of **25**. Treatment of compound **29** with 1 M TBAF solution in THF afforded **30** in 94% yield (Scheme 3). The primary hydroxy group was then oxidized with IBX[13] to afford the corresponding aldehyde; further oxidation[14] with $NaClO_2$ in the presence of NaH_2PO_4 and 2-methyl-2-butene as a scavenger, furnished acid **18**[15] in 84% yield over two steps.

Our next task was to couple the two fragments and investigate the critical ring-closing metathesis reaction. Accordingly, condensation of fragments **17** and **18** was achieved using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC hydrochloride) and 4-(dimethylamino)pyridine (DMAP) to afford the bis-olefinic ester **15** in 85% yield (Scheme 4). As per our earlier report, a 0.001 M solution of **15**[16] and 10 mol% of Grubbs' second-generation catalyst failed to provide the required ten-membered lactone when heated under reflux even up to 48 hours in anhydrous, degassed dichloromethane. The crucial ring-closing metathesis reaction also failed in anhydrous benzene under reflux conditions and by using



Scheme 2 Synthesis of fragment **17**

protecting groups such as PMB ethers and TBS ethers. Finally, reaction with diol **31** (0.001 M in CH_2Cl_2) and 10 mol% Grubbs' second-generation catalyst afforded the required ten-membered lactone **3**[17] (stagonolide C) as the sole product in 68% yield. The geometry of the newly formed double bond was unequivocally assigned by detection of the olefinic J_{trans} coupling constant (15.6 Hz between the protons at δ = 5.41 and 5.58 ppm, respectively). The constitution and configuration of the assigned structure was unambiguous since the spectral and analytical data were in excellent accord with the proposed structure and perfectly matched with those reported in the literature.[3a] In addition, computational analysis of both isomers showed the *E*-isomer to be 6 kcal/mol less in energy than the *Z*-isomer, signifying that the *E*-isomer in this case is more stable than the *Z*-isomer (Figure 2).



Scheme 4 Total synthesis of stagonolide C (**3**) and formal total synthesis of modiolide A (**10**)

As the RCM reaction failed with both the TBS-protected and PMB-protected bis-olefins, we proceeded with the advanced intermediate for the total synthesis of modiolide A. The free hydroxy groups present at C4 and C7 in **3** were protected as their TBS ethers with TBSOTf in dichloromethane at –15 °C, to afford the bis-TBS compound **33**,[18] whose spectral and analytical data were in good agreement with the reported values.[6h]

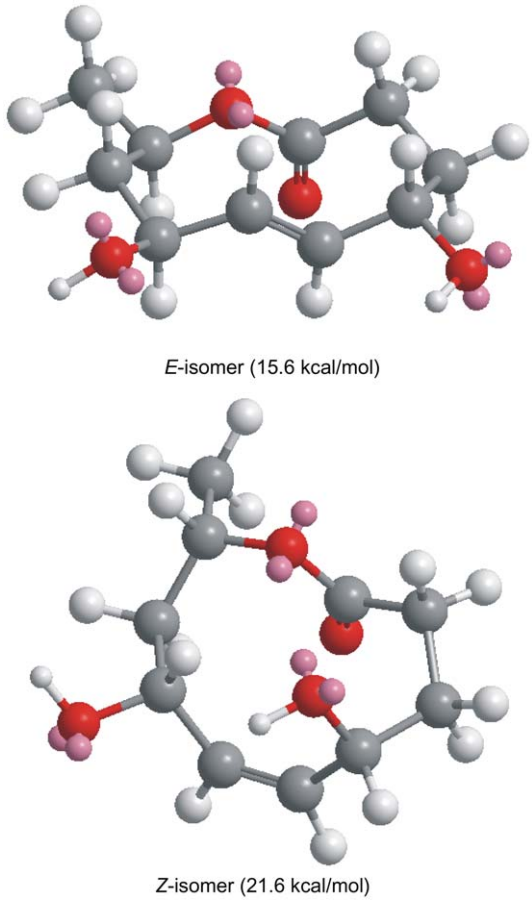


Figure 2 Minimum energy conformers calculated for the *E*- and *Z*-isomers of stagonolide C

In conclusion, the first stereoselective total synthesis of stagonolide C and the formal total synthesis of modiolide A were achieved starting from commercially available L-malic acid and 1,4-butane diol. The key reactions involved were Sharpless asymmetric epoxidation, activated zinc dust mediated reductive elimination and ring-closing metathesis.

Acknowledgment

U.D. and P.R.N. thank CSIR, New Delhi, India, for the financial assistance in the form of fellowships.

References and Notes

(1) For reviews on synthetic, biosynthetic, and pharmacological aspects of decanolides, see: (a) Dräger, G.; Kirschning, A.; Thiericke, R.; Zerlin, M. *Nat. Prod. Rep.* **1996**, *13*, 365. (b) Ferraz, H. M. C.; Bombonato, F. I.; Longo, L. S. Jr. *Synthesis* **2007**, 3261. (c) Riatto, V. B.; Pilli, R. A.; Victor, M. M. *Tetrahedron* **2008**, *64*, 2279.

(2) Yuzikhin, O.; Mitina, G.; Berestetskiy, A. *J. Agric. Food Chem.* **2007**, *55*, 7707.

(3) (a) Evidente, A.; Cimmino, A.; Berestetskiy, A.; Mitina, G.; Andolfi, A.; Motta, A. *J. Nat. Prod.* **2008**, *71*, 31. (b) Evidente, A.; Cimmino, A.; Berestetskiy, A.; Andolfi, A.; Motta, A. *J. Nat. Prod.* **2008**, *71*, 1897. (c) Tsuda, M.; Mugishima, T.; Komatsu, K.; Sone, T.; Tanaka, M.;

Mikami, Y.; Kobayashi, J. *J. Nat. Prod.* **2003**, *66*, 412.
(4) (a) Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (c) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (d) Prunet, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 2826. (e) Love, J. A. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, **2003**, 296. (f) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (g) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012. (h) Maier, M. E. *Angew. Chem. Int. Ed.* **2000**, *39*, 2073. (i) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (j) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (k) Gerlach, K.; Quitschalle, M.; Kalesse, M. *Tetrahedron Lett.* **1999**, *40*, 3553. (l) Nevalainen, M.; Koskinen, A. M. P. *Angew. Chem. Int. Ed.* **2001**, *40*, 4060.
(5) Perepogu, A. K.; Raman, D.; Murty, U. S. N.; Rao, V. J. *Bioorg. Chem.* **2009**, *37*, 46.
(6) (a) Mohapatra, D. K.; Sahoo, G.; Ramesh, D. K.; Sastry, G. N. *Chem. Eur. J.* **2009**, submitted. (b) Ghosh, S.; Rao, R. V. *Tetrahedron Lett.* **2007**, *48*, 6937. (c) Mohapatra, D. K.; Ramesh, D. K.; Giardello, M. A.; Chorghade, M. S.; Gurjar, M. K.; Grubbs, R. H. *Tetrahedron Lett.* **2007**, *48*, 2621. (d) Fürstnet, A.; Nagano, T.; Müller, C.; Seidel, G.; Müller, O. *Chem. Eur. J.* **2007**, *13*, 1452. (e) Prasad, K. R.; Penchalaiah, K.; Choudhary, A.; Anbarsan, P. *Tetrahedron Lett.* **2007**, *48*, 309. (f) Sharma, G. V. M.; Cherukupalli, G. R. *Tetrahedron: Asymmetry* **2006**, *17*, 1081. (g) Garćia-Fortanet, J.; Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *J. Org. Chem.* **2005**, *70*, 9822. (h) Matsuda, M.; Yamazaki, T.; Fuhshuku, K.; Sugai, T. *Tetrahedron* **2007**, *63*, 8752. (i) Gurjar, M. K.; Karmakar, S.; Mohapatra, D. K. *Tetrahedron Lett.* **2004**, *45*, 4525. (j) Salaskar, A.; Sharma, A.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **2006**, *17*, 325. (k) Boruwa, J.; Gogoi, N.; Barua, N. C. *Org. Biomol. Chem.* **2006**, *4*, 3521. (l) Nanda, S. *Tetrahedron Lett.* **2005**, *46*, 3661. (m) Arai, M.; Morita, N.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2000**, *41*, 1199.
(7) (a) Guindon, Y.; Yoakim, C.; Bernstein, M. A.; Morton, H. E. *Tetrahedron Lett.* **1985**, *26*, 1185. (b) Takemura, T.; Nishi, Y.; Takahashi, S.; Kobayashi, J.; Nakata, T. *Tetrahedron* **2002**, *58*, 6359; and references therein.
(8) Gao, Y.; hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(9) Reddy, L. V. R.; Sagar, R.; Shaw, A. K. *Tetrahedron Lett.* **2006**, *47*, 1753.
(10) Rama Rao, A. V.; Murthy, V. S.; Sharma, G. V. M. *Tetrahedron Lett.* **1995**, *36*, 139.
(11) Analytical and spectral data of **17**: $[\alpha]_D^{27}$ –30.4 (*c* 1.8, $CHCl_3$); IR (KBr): 3456, 2922, 2853, 1616, 1513, 1247 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.16 (d, *J* = 9.0 Hz, 2 H), 6.73 (d, *J* = 9.0 Hz, 2 H), 5.80–5.68 (m, 1 H), 5.23–5.14 (m, 2 H), 4.51–4.48 (m, 1 H), 4.48 (d, *J* = 11.3 Hz, 1 H), 4.19 (d, *J* = 11.3 Hz, 1 H), 4.01–3.94 (m, 1 H), 3.73 (s, 3 H), 1.67–1.50 (m, 2 H), 1.07 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 138.1, 129.4, 128.6, 117.1, 113.8, 77.6, 69.9, 64.6, 55.2, 43.5, 23.3; MS (ESI): *m*/*z* = 237 $[M + H]^+$, 259 $[M + Na]^+$; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{20}O_3Na$: 259.1310; found: 259.1318.
(12) Ravelo, J. L.; Rodriguez, C. M.; Martin, V. S. *J. Organomet. Chem.* **2006**, *691*, 5326; and references therein.
(13) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.
(14) (a) Balkrishna, S. B.; Childers, W. E. Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091. (b) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.
(15) Analytical and spectral data of **18**: $[\alpha]_D^{27}$ –30.5 (*c* 2.7, $CHCl_3$); IR (KBr): 3426, 2929, 2865, 1709, 1610, 1513, 1455, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.16 (d, *J* = 8.7 Hz, 2 H), 6.8 (d, *J* = 8.7 Hz, 2 H), 5.77–5.65 (m, 1 H), 5.25–5.2 (m, 2 H), 4.51 (d, *J* = 11.4 Hz, 1 H), 4.25 (d, *J* = 11.4 Hz, 1 H), 3.77 (s, 3 H), 3.77–3.70 (m, 1 H), 2.41 (t, *J* = 7.3 Hz, 2 H), 1.91–1.78 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.4, 159.0, 138.0, 130.2, 129.3, 117.6, 113.6, 78.7, 69.7, 55.1, 30.0, 29.9; MS (ESI): *m*/*z* = 273 $[M + Na]^+$; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{18}O_4Na$: 273.1102; found: 273.1101.
(16) Analytical and spectral data of **15**: $[\alpha]_D^{27}$ –55.3 (*c* 1.9, $CHCl_3$); IR (KBr): 2923, 2853, 1729,1613, 1513, 1377, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.24 (m, 4 H), 6.91–6.85 (m, 4 H), 5.80–5.68 (m, 2 H), 5.29–5.13 (m, 5 H), 4.54 (d, *J* = 11.5 Hz, 1 H), 4.51 (d, *J* = 11.3 Hz, 1 H), 4.27 (d, *J* = 11.3 Hz, 1 H), 4.21 (d, *J* = 11.5 Hz, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 3.80–3.72 (m, 2 H), 2.41–2.18 (m, 2 H), 1.96–1.67 (m, 4 H), 1.21 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8, 159.0, 138.5, 138.3, 130.5, 130.3, 129.6, 129.3, 117.5, 117.0, 113.7, 79.1, 76.3, 69.9, 69.8, 67.6, 55.2, 42.2, 30.5, 30.4, 20.5; MS (ESI): *m*/*z* = 491 $[M + Na]^+$; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{36}O_6Na$: 491.2409; found: 491.2413.
(17) Analytical and spectral data of **3**: $[\alpha]_D^{27}$ +46.2 (*c* 1.0, $CHCl_3$); IR (KBr): 3443, 2923, 2855, 1717, 1647, 1448, 1368, 1243 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.58 (dd, *J* = 15.6, 9.2 Hz, 1 H), 5.41 (dd, *J* = 15.6, 9.0 Hz, 1 H), 5.14 (dq, *J* = 11.1, 6.4 Hz, 1 H), 4.15–4.05 (m, 2 H), 2.32–2.25 (m, 1 H), 2.04 (m, 3 H), 1.92–1.71 (m, 2 H), 1.22 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.6, 135.8, 132.8, 74.3, 71.8, 67.8, 43.2, 34.3, 31.5, 21.3; MS (ESI): *m*/*z* = 223 $[M + Na]^+$.
(18) Analytical and spectral data of **33**: $[\alpha]_D^{27}$ +14.7 (*c* 1.4, EtOH); IR (KBr): 2931, 2859, 1731, 1645, 1461, 1370, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.45 (dd, *J* = 15.8, 9.0 Hz, 1 H), 5.30 (dd, *J* = 15.8, 8.6 Hz, 1 H), 5.14–5.03 (m, 1 H), 4.08–3.97 (m, 2 H), 2.26–2.20 (m, 1 H), 2.05–1.96 (m, 2 H), 1.95–1.84 (m, 1 H), 1.78–1.71 (m, 2 H), 1.18 (d, *J* = 6.6 Hz, 3 H), 0.86 (s, 9 H), 0.85 (s, 9 H), 0.04 (s, 6 H), 0.02 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4, 135.1, 132.4, 75.3, 73.0, 67.5, 44.8, 35.5, 31.5, 25.7, 21.4, 18.1, –4.3, –4.4, –4.7; MS (ESI): *m*/*z* = 429 $[M + H]^+$; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{44}O_4NaSi_2$: 451.2675; found: 451.2675.