Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 939–942

An efficient synthesis of the C_1–C_{14} subunit of (−)-lasonolide A via a target oriented β-*C*-glycoside formation sequence

Kailas B. Sawant, Fei Ding and Michael P. Jennings*

Department of Chemistry, 500 Campus Drive, The University of Alabama, Tuscaloosa, AL 35487-0336, USA

Received 14 November 2005; revised 22 November 2005; accepted 29 November 2005
Available online 19 December 2005

Abstract—An efficient synthesis of the C_1–C_{14} subunit resident in (−)-lasonolide A is reported herein. The key reaction features that were utilized include a Molander–Reformatsky SmI_2 mediated intramolecular aldol reaction followed by a diastereoselective target oriented β-*C*-glycoside formation sequence. Lastly, a chemo- and diastereoselective cross-metathesis of a terminal olefin in the presence of a trisubstituted alkene with acrolein and subsequent olefination of the aldehyde moiety allowed for the completion of the (*E*,*E*)-diene side chain.

Over the past two decades, the construction of α- and β-*C*-glycosides has become increasingly important in the synthesis of biologically active natural products. Along this line, there has been substantial growth in new synthetic methodologies within this area. Such building blocks have been synthesized by using several technologies including the hetero-atom Diels–Alder reaction,[1] Petasis–Ferrier rearrangement,[2] intermolecular silyl-modified Sakurai and Prins cyclizations,[3] *exo*-Pd-mediated allylic etherification,[4] radical cyclization,[5] and intramolecular Michael additions with oxygen nucleophiles.[6] As a complementary procedure to these technologies, our research program is interested in expanding and concomitantly defining a broader scope of Kishi's strategy for the synthesis of β-*C*-glycosides.[7]

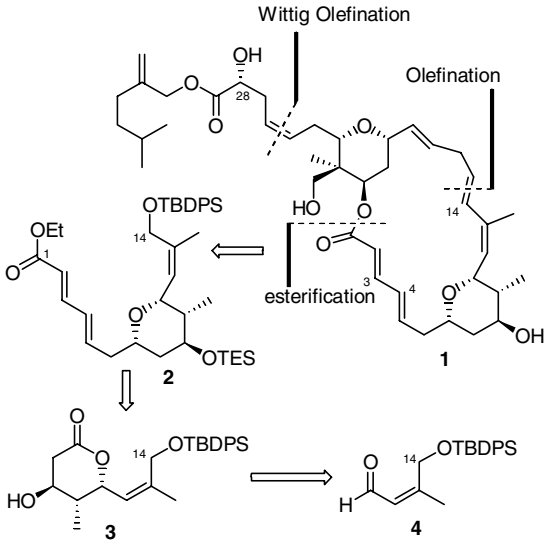
First isolated from *Forcepia* sp. in 1994 by McConnell, (−)-lasonolide A (**1**) represents a potent anti-tumor agent which exhibits significant cytotoxic activity (ng/ml) against P388 murine leukemia, A-549 human lung carcinoma cell lines, and inhibits cell adhesion in the EL-4.IL-2 cell line.[8] In addition to the impressive levels of biological activity, the highly unique structure of **1** makes it an attractive target for total synthesis and an ideal target for testing synthetic methodologies of β-*C*-glycosides. Thus, a variety of synthetic approaches to **1** have been reported[9] with only two total syntheses reported to date.[5,10] Lee and co-workers were the first to disclose the asymmetric total synthesis of **1**, in addition to a structural revision, thus determining both the relative and absolute configuration of natural (−)-lasonolide.[5] Key steps in their synthesis included two radical cyclizations to form both β-*C*-glycoside units followed by a Yamaguchi macrocyclization. Subsequently, Kang and co-workers reported the second total synthesis of **1**, by utilizing a clever desymmetrization followed by an asymmetric allylation en route to the completion of the upper β-*C*-glycoside subunit and then ultimately **1**.[10]

As shown in Scheme 1, our initial approach to the synthesis of **1** was based on a stereoselective reduction of a cyclic oxocarbenium cation mediated by the treatment of an appropriate hemi-ketal with Lewis acid. In turn, the hemi-ketal was envisaged to be derived from a nucleophilic addition of the allyl Grignard reagent to the corresponding lactone **3**. We envisioned a SmI_2 Molander–Reformatsky[11] lactonization sequence for the synthesis of **3**, which would be derived ultimately from the α,β-unsaturated aldehyde **4**.

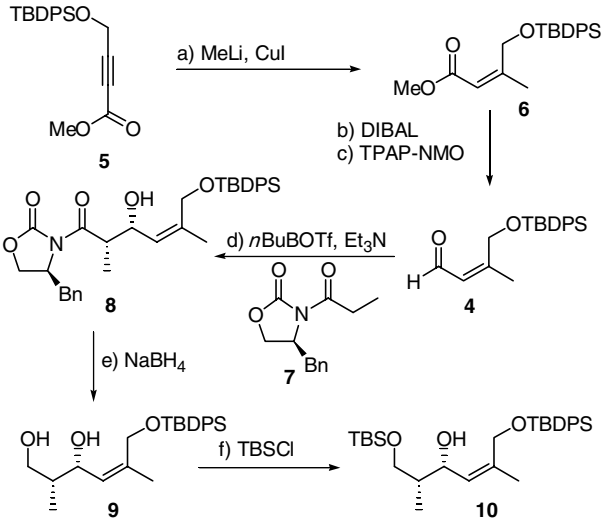
The synthesis of **2** was initiated with the previously reported α,β-acetylenic ester **5**,[12] as shown in Scheme 2. Thus, carbocupration of **5** utilizing the dimethyl Gilman reagent (Me_2Cu^- Li^+) under Corey's conditions[13] allowed for the stereoselective formation of the trisubstituted α,β-unsaturated ester **6** in 91% yield. Subsequent reduction of the ester moiety with DIBAL furnished the primary alcohol, which in turn was oxidized

* Corresponding author. Tel.: +1 205 348 0351; fax: +1 205 348 9104; e-mail: jenningm@bama.ua.edu

0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.11.156

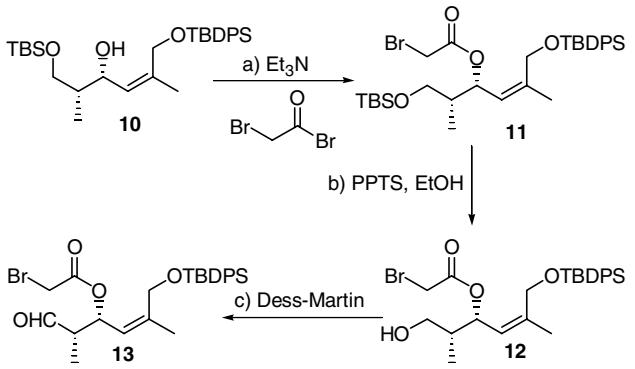


Scheme 1. Retrosynthesis of (−)-lasonolide A.



Scheme 2. Synthesis of intermediate **10**: Reagents and conditions: (a) CuI (1.5 equiv), THF, 0 °C, MeLi (3 equiv), 10 min, then −78 °C, then **5**, 4 h, 91%; (b) DIBAL (2.2 equiv), Et_2O, −78 to 0 °C, 3 h, 92%; (c) TPAP (5 mol %), NMO (2.1 equiv), CH_2Cl_2, 0 °C, 2 h, 96%; (d) **7** (1.15 equiv), CH_2Cl_2, −55 °C, *n*-BuBOTf (1.19 equiv), 30 min, Et_3N (1.3 equiv), 20 min, 0 °C, then **4**, −70 °C, 4 h, 90%; (e) $NaBH_4$ (4 equiv), THF/H_2O: 1/1, rt, 3.5 h, 88%; (f) TBSCl (1.15 equiv), Et_3N (3.1 equiv), DMAP (0.30 equiv), CH_2Cl_2, 12 h, 80%. DIBAL = diisobutyl-aluminum hydride; TPAP = tetrapropylammonium perruthenate; NMO = 4-methyl-morpholine-*N*-oxide; TBSCl = *tert*-butyldimethylsilylchloride; DMAP = 4-dimethylaminopyridine.

to aldehyde **4** by means of Ley's TPAP reagent[14] with a combined yield of 90% over the two steps from ester **6**. With **4** in hand, our attention was turned to the initial introduction of the *syn*-stereochemistry as required for the completion of **2**. This aspect was uneventfully accomplished by the treatment of aldehyde **4** with the benzyl substituted oxazolidinone **7**. Accordingly, enolization of **7** was achieved under the Evans' protocol[15] utilizing the standard reagents such as *n*-Bu_2BOTf and Et_3N followed by treatment of the pre-formed (*Z*)-boron enolate with aldehyde **4** which provided the

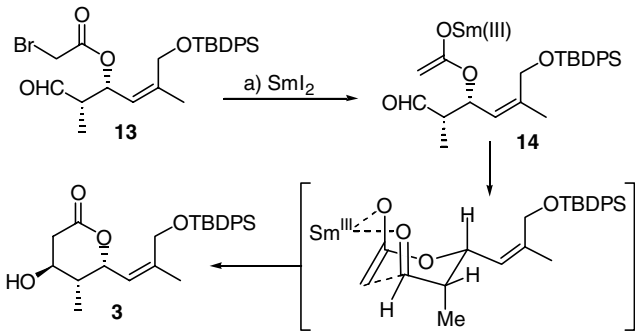


Scheme 3. Synthesis of the bromoacetyl-aldehyde **13**: Reagents and conditions: (a) bromoacetyl bromide (2.0 equiv), Et_3N (2.5 equiv), DMAP (0.03 equiv), CH_2Cl_2, 0 °C, 2 h, 85%; (b) PPTS (0.3 equiv), EtOH, rt, 72 h, 88%; (c) Dess–Martin periodinane (1.5 equiv), CH_2Cl_2, 0 °C, 3 h, 55%. PPTS = pyridinium *p*-toluenesulfonate; Dess–Martin periodinane = 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxo-3-(1*H*)-one.

syn-aldol adduct **8** with a 90% yield and ⩾97:3 dr as determined by ^1H NMR. With the requisite stereochemistry from the aldol product **8** in hand, removal of the Evans' auxiliary was accomplished via treatment of **8** with $NaBH_4$ in a 1/1 THF/H_2O solvent mixture as reported by Prashad[16] to provide the diol **9** in 88% yield. Much to our surprise treatment of **9** with TBSCl and imidazole did not lead to selective silylation of the primary hydroxyl moiety. Finally, discrimination between the primary and secondary alcohol was realized and the silylation was accomplished in 80% yield upon treatment of **9** with TBSCl, Et_3N, and DMAP in CH_2Cl_2 to furnish intermediate **10**.

With the two hydroxyl moieties of **9** differentiated via the selective silylation of the primary alcohol, we turned our attention to the introduction of the bromo-acetate functionality in order to examine the feasibility of the proposed stereoselective intramolecular Reformatsky lactone formation reaction sequence. With this in mind, esterification of the free secondary hydroxyl moiety resident in **10** was accomplished with bromoacetyl bromide, Et_3N, and DMAP in 85% yield as shown in Scheme 3. Subsequent selective TBS desilylation of **11** was achieved by utilizing PPTS in EtOH to afford the free primary hydroxyl intermediate **12**. Unfortunately oxidation of the primary alcohol resident in **12** to the labile aldehyde **13** was problematic. Treatment of **12** with a variety of oxidation protocols such as TEMPO–BAIB, TPAP–NMO, and Swern provided the α,β-unsaturated aldehyde via β-elimination of the bromoacetyl group.[17] Much to our delight, oxidation of **12** readily afforded aldehyde **13** via the Dess–Martin reagent in an acceptable 55% yield.

With **13** in hand, the stage was set for the intramolecular SmI_2 mediated Reformatsky sequence. Molander reported that the treatment of a bromoacetyl moiety with SmI_2 readily allowed for the synthesis of a Sm(III) enolate which subsequently underwent an intramolecular aldol reaction with a pendent aldehyde via a double six-membered transition state to furnish selectively a β-hydroxy lactone with exceptional diastereoselectivity.[11]



Scheme 4. Synthesis of lactone **3**: Reagents and conditions: (a) SmI_2 (2.0 equiv), THF, 0 °C, 2 h, 51%.

As anticipated, treatment of **13** with SmI_2 provided the initial Sm(III) enolate intermediate which quickly underwent cyclization to provide lactone **3** as a single diastereomer as observed by ^1H NMR in 51% yield via the proposed transition state as shown in Scheme 4.[18]

With the key hydroxy-lactone **3** in hand, our attention was initially focused on the allyl β-*C*-glycoside formation followed by final elaboration of the terminal alkene functional group into the final targeted structure **2**. Thus, treatment of lactone **3** with excess allyl magnesium bromide readily afforded the lactol intermediate **15** as a mixture of two diastereomers as observed by ^1H NMR. Immediate addition of TFA to lactol **15** seemingly provided the oxocarbenium intermediate **16**, which was subsequently reduced with Et_3SiH. As observed in our previous synthesis of (−)-dactylolide,[7c] the free secondary hydroxyl group was concomitantly protected as a TES ether under the reductive conditions for the transformation of **16** to **17**. The overall yield of the five transformations (nucleophilic addition, oxocarbenium formation, Et_3SiH reduction of the oxocarbenium cation, active silylating reagent formation, and silylation of the free hydroxyl moiety) was a very respectable 44%. The remaining material balance was the untriethylsilylated compound of pyran **17**. Chemo- and diastereoselective cross-metathesis of the terminal alkene with acrolein utilizing the Grubbs' second-generation carbene catalyst[19] **18** was accomplished with a 15:1 ratio in favor of the predicted and desired (*E*)-α,β-unsaturated aldehyde **19** in 72% yield. The geometry of the two olefins and the β-*C*-glycoside moiety were deduced via the NOE enhancements as shown in Figure 1. In addition to the NOE experiment, the observed coupling constants

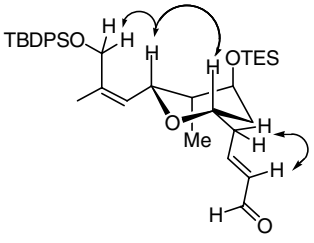
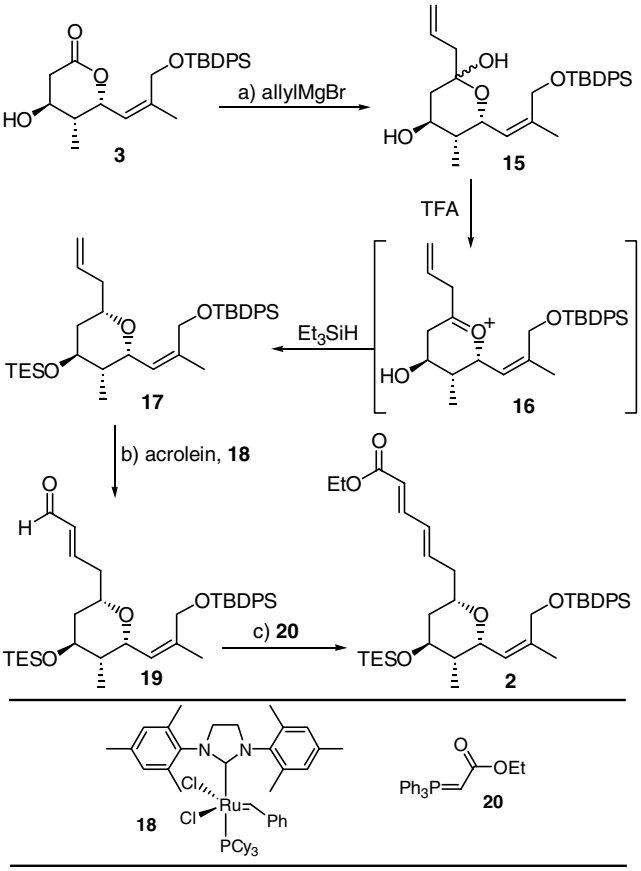


Figure 1. Key NOE enhancements of intermediate **19**.



Scheme 5. Completion of subunit **2**. Reagents and conditions: (a) (i) allylMgBr (2.5 equiv), THF, −78 °C, 1 h, (ii) TFA (6 equiv), Et_3SiH (6 equiv), CH_2Cl_2, −78 °C, 2 h, 44%; (b) acrolein (2.0 equiv), **18** (5 mol %), CH_2Cl_2, 50 °C, 16 h, 72%; (c) **20** (2 equiv), THF, 0 °C to rt, 4 h, 82%. TFA = trifluoroacetic acid.

(14 Hz) of the unsaturated aldehyde protons provided further geometrical proof of compound **19**. Final elaboration of the aldehyde moiety to the (*E*,*E*)-α,β-unsaturated ester was accomplished upon treatment of **19** with the stabilized Wittig reagent **20** to ultimately furnish **2** in an 82% yield (Scheme 5).[20]

In conclusion, we have completed the synthesis of the C_1–C_{14} subunit resident in (−)-lasonolide A. The key reaction features that were utilized included a Molander–Reformatsky SmI_2 mediated intramolecular aldol reaction followed by a diastereoselective target oriented β-*C*-glycoside formation sequence. Lastly, a chemo- and diastereoselective cross-metathesis of a terminal olefin in the presence of a trisubstituted alkene with acrolein and subsequent olefination of the aldehyde moiety allowed for the completion of the (*E*,*E*)-diene side chain of **1**. Studies toward the total synthesis of **1** are ongoing and will be reported in due course.

Acknowledgements

Support was provided by the University of Alabama and the NSF (CHE-0115760), for the departmental NMR facility.

References and notes

1. (a) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246; (b) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398.
2. (a) Smith, A. B.; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102; (b) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, *37*, 141.
3. (a) Hoye, T. R.; Hu, M. *J. Am. Chem. Soc.* **2003**, *125*, 9576; (b) Mekhalfia, A.; Marko, I. E.; Adams, H. *Tetrahedron Lett.* **1991**, 4783; (c) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420.
4. (a) Burke, S. D.; Jiang, L. *Org. Lett.* **2001**, *3*, 1952; (b) Graening, T.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2580.
5. (a) Lee, E.; Song, H. Y.; Kang, J. W.; Kim, D. S.; Jung, C. K.; Joo, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 384; (b) Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K.; Lee, E. *J. Am. Chem. Soc.* **2002**, *124*, 14655; (c) Lee, E.; Song, H. Y.; Joo, J. M.; Kang, J. W.; Kim, D. S.; Jung, C. K.; Hong, C. Y.; Jeong, S. W.; Jeon, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3519; (d) Song, H. Y.; Joo, J. M.; Kang, J. W.; Kim, D. S.; Jung, C. K.; Kwak, H. S.; Park, J. H.; Lee, E.; Hong, C. Y.; Jeong, S. W.; Jeon, K.; Park, J. H. *J. Org. Chem.* **2003**, *68*, 8080.
6. White, J. D.; Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 8593.
7. (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976; (b) Jennings, M. P.; Clemens, R. T. *Tetrahedron Lett.* **2005**, *46*, 2021; (c) Ding, F.; Jennings, M. P. *Org. Lett.* **2005**, *7*, 2321.
8. Horton, P. A.; Koehn, F. E.; Longley, R. E.; McConnell, O. J. *J. Am. Chem. Soc.* **1994**, *116*, 6015.
9. (a) Gurjar, M. K.; Kumar, P.; Rao, B. V. *Tetrahedron Lett.* **1996**, *37*, 8617; (b) Nowakowski, M.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1997**, *38*, 1001; (c) Gurjar, M. K.; Chakrabarti, A.; Rao, B. V.; Kumar, P. *Tetrahedron Lett.* **1997**, *38*, 6885; (d) Beck, H.; Hoffmann, H. M. R. *Eur. J. Org. Chem.* **1999**, 2991; (e) Misske, A. M.; Hoffmann, H. M. R. *Chem. Eur. J.* **2000**, *6*, 3313; (f) Hart, D. J.; Patterson, S.; Unch, J. P. *Synlett* **2003**, 1334; (g) Kang, S. H.; Choi, H. W.; Kim, C. M.; Jun, H. S.; Kang, S. Y.; Jeong, J. W.; Youn, J. H. *Tetrahedron Lett.* **2003**, *44*, 6817; (h) Deba, T.; Yakushiji, F.; Shindo, M.; Shishido, K. *Synlett* **2003**, 1500; (i) Joo, J. M.; Kwak, H. S.; Park, J. H.; Song, H. Y.; Lee, E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1905–1908; (j) Dalgard, J. E.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1589.
10. (a) Kang, S. H.; Kang, S. Y.; Kim, C. M.; Choi, H.; Jun, H. S.; Lee, B. M.; Park, C. M.; Jeong, J. W. *Angew. Chem., Intl. Ed.* **2003**, *42*, 4779; (b) Kang, S. H.; Kang, S. Y.; Choi, H.; Kim, C. M.; Jun, H. S.; Youn, J. H. *Synthesis* **2004**, 1102.
11. Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P. J. *J. Am. Chem. Soc.* **1991**, *113*, 8036.
12. Nakada, M.; Kojima, E.; Ichinose, H. *Synth. Commun.* **2000**, *30*, 863.
13. Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.
14. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
15. Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109.
16. Prashad, M.; Har, D.; Kim, H.-Y.; Repic, O. *Tetrahedron Lett.* **1998**, *39*, 7067.
17. De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.
18. Data for lactone **3**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.7 (m, 4H), 7.4 (m, 6H), 5.3 (dd, $J = 9$, 1 Hz, 1H), 5.2 (dd, $J = 9$, 3 Hz, 1H), 4.2 (s, 2H), 3.9 (dd, $J = 9.5$, 4.5 Hz, 1H), 2.8 (dd, $J = 18$, 5.5 Hz, 1H), 2.4 (dd, $J = 18$, 3.5 Hz, 1H), 1.7 (m, 1H), 1.9 (s, 3H), 1.1 (s, 9H), 0.9 (d, $J = 7$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 140.7, 135.6, 133.2, 129.8, 127.9, 121.8, 74.6, 68.1, 62.6, 39.2, 36.0, 26.8, 21.3, 19.3, 10.8. IR (neat) 3450, 1721, 1428, 1112, 1062 cm^{-1}. $R_f = 0.2$, 40% EtOAc in hexanes. HRMS (EI) calculated for $C_{26}H_{34}O_4Si$ (M^+): 438.2226, found: 438.2229.
19. (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953; (b) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
20. Data for β-*C*-glycoside **2**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.7 (m, 4H), 7.4 (m, 6H), 7.2 (dd, $J = 15.5$, 4.5 Hz, 1H), 6.2 (dd, $J = 15$, 11 Hz, 1H), 6.1 (m, 1H), 5.8 (d, $J = 15$ Hz, 1H), 5.3 (d, $J = 7.5$ Hz, 1H), 4.5 (d, $J = 7.5$ Hz, 1H), 4.3 (dd, $J = 12.5$, 3.5 Hz, 1H), 4.2 (q, $J = 7$ Hz, 2H), 4.1 (d, $J = 7.5$ Hz, 1H), 3.7 (m, 2H), 2.2 (m, 1H), 2.25 (m, 1H), 1.9 (s, 3H), 1.5 (m, 1H), 1.3 (t, $J = 7$ Hz, 3H), 1.2 (m, 2H), 1.1 (s, 9H), 0.85 (d, $J = 7$ Hz, 3H), 0.81 (q, 9H), 0.43 (dt, $J = 16$, 8 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 144.8, 140.3, 135.6, 132.6, 130.2, 129.5, 127.6, 125.6, 119.7, 71.2, 70.8, 70.5, 62.6, 60.2, 40.3, 39.6, 35.5, 29.9, 26.8, 22.0, 14.3, 11.3, 6.8, 4.8. IR (neat) 3055, 2984, 1616, 1440, 1268 cm^{-1}. $R_f = 0.52$, 15% EtOAc in hexanes. HRMS (EI) calculated for $C_{40}H_{60}O_5Si_2$ (M^+): 676.3979, found: 676.3978.