Tetrahedron Letters 50 (2009) 676–679

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A convenient synthesis of pseudoglycosides via a Ferrier-type rearrangement using metal-free H_3PO_4 catalyst

Bala Kishan Gorityala, Shuting Cai, Rujee Lorpitthaya, Jimei Ma, Kalyan Kumar Pasunooti, Xue-Wei Liu *

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

ARTICLE INFO

Article history:
Received 17 October 2008
Revised 20 November 2008
Accepted 25 November 2008
Available online 30 November 2008

ABSTRACT

A mild and efficient synthesis of pseudoglycals has been developed using a metal-free catalytic system. Phosphoric acid proved to be an excellent catalyst for conversion of 2,4,6-tri-*O*-acetyl-D-glycal to 2,3-unsaturated *O*-glycosides. A wide range of alcohols including naturally bioactive compounds could be coupled with the glycal to give the desired products in good to excellent yields and with high levels of α-selectivity.

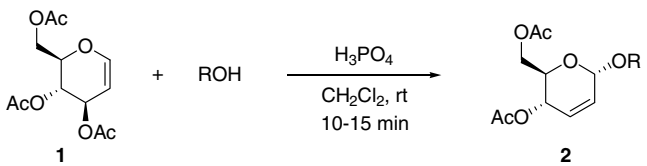
2,3-Unsaturated *O*-glycosides have been recognized as important building blocks in many bioactive molecules[1] and play a substantial role in the synthesis of compounds such as oligosaccharides,[2] uronic acids,[3] biologically active natural products,[4] and antibiotics.[5] Since the Ferrier rearrangement was discovered in 1964,[6] there have been many reports on the development of this direct method to 2,3-unsaturated glycosides. The Ferrier reaction typically involves the allylic rearrangement of glycals with nucleophilic substitution under acidic conditions.[7] This rearrangement is believed to proceed through a cyclic allylic oxocarbonium intermediate that is formed via displacement of the C-3 substituent in a glycal, followed by preferential attack of a nucleophile via the quasi-equatorial orientation.[8]

A pioneering study with $BF_3{\cdot}Et_2O$[9] led to a number of other Lewis acids being used in these reactions. The use of Lewis acids, such as $SnCl_4$,[10] $InCl_3$,[11] $Yb(OTf)_3$,[12] $FeCl_3$,[13] $LiBF_4$,[14] $BiCl_3$,[15] $ZnCl_2$,[16] $Dy(OTf)_3$,[17] $Sc(OTf)_3$,[18] and $ZrCl_4$,[19] has contributed to the advancement of the acid-catalyzed allylic rearrangement of glycal derivatives. However, each catalyst suffers from drawbacks such as low yields, formation of side products, and cost and amount of catalyst. With the objective of developing a viable procedure for the synthesis of 2,3-unsaturated glycosides, we focused on finding a cheap and efficient catalyst that would give high anomeric selectivity and yields. To our best knowledge, phosphoric acid (H_3PO_4) has not been used as a catalyst in this area. H_3PO_4 is used as a catalyst in many reactions, for example, Diels–Alder[20] and oligomerization,[21] and also as a benchmark for other phosphoric acid catalysts.[22] The widespread use of H_3PO_4 as a catalyst can be attributed to the fact that it is cheap and easily available. In the present study, we describe the successful implementation of phosphoric acid (H_3PO_4) as a catalyst in the Ferrier rearrangement for the synthesis of 2,3-unsaturated *O*-glycosides (Scheme 1).

Regarding atom economy, it is crucial to use a low amount of the catalyst. We found that H_3PO_4 could be loaded as low as 0.2 equiv with respect to the starting material. There was no dramatic increase in yield and selectivity, when the amount of H_3PO_4 was increased. Typically, H_3PO_4 was added to the mixture of glycal and alcohol (1 equiv) in dichloromethane at room temperature. When the reaction was complete, the solvent was evaporated, and subsequent purification of the crude product by short-column chromatography gave the desired pseudoglycosides. The structure and stereochemistry of the glycosylated products were elucidated from ^1H, ^{13}C, and 2D NMR spectroscopic data. The results reported in Table 1 show that a variety of alcohols could be utilized and gave the desired 2,3-unsaturated glycosides (**2a–p**) in excellent yields (82–97%). Moreover, the reaction conditions are very mild and rapid, and no side products were formed.

Based on the anomeric ratios obtained from ^1H NMR spectra, it is evident that the catalytic reactions using allyl alcohol, pentan-3-ol, and 2-naphthol as nucleophiles produced α-anomers as the sole products (Table 1, entries 6, 7, and 14). The bulky and long carbon chain nucleophiles were able to give good selectivities (up to 20:1 α/β ratio). Apart from these, anomeric mixtures were formed with the α-anomer being formed predominantly (at least 5:1).

Encouraged by these results, we next explored the scope of this route for the synthesis of pseudoglycals connected to various biologically important natural products (Table 1, entries 15 and 16).

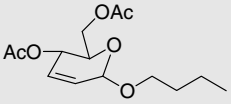
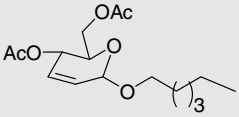
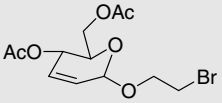
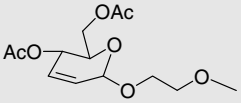
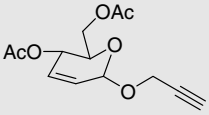
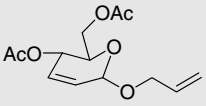
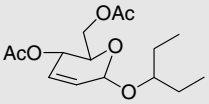
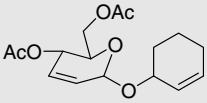
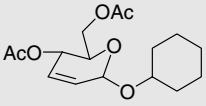
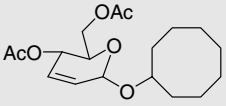
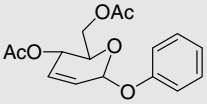
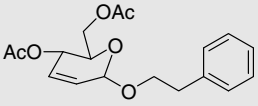


Scheme 1. A synthetic model for the ferrier rearrangement.

* Corresponding author. Tel.: +65 6316 8901; fax: +65 6791 1961.
E-mail address: xuewei@ntu.edu.sg (X.-W. Liu).

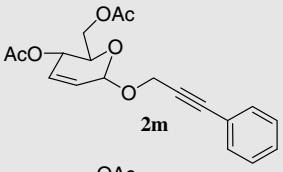
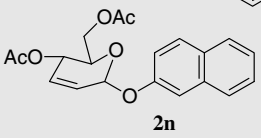
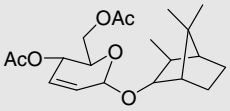
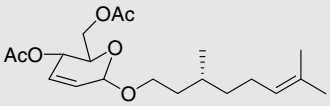
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.11.103

Table 1
Ferrier reaction of 2,3-tri-*O*-acetyl-D-glycal with alcohols in the presence of the H_3PO_4

Entry	Product	Time (min)	Yield (%)	α/β[a]
1	 **2a**	10	93	8:1[26]
2	 **2b**	10	88	10:1
3	 **2c**	15	89	8:1[27]
4	 **2d**	15	85	5:1[28]
5	 **2e**	10	86	10:1[29]
6	 **2f**	10	92	α[26]
7	 **2g**	15	84	α[31]
8	 **2h**	15	97	20:1[32]
9	 **2i**	10	85	20:1[26]
10	 **2j**	10	87	20:1[33]
11	 **2k**	10	93	5:1
12	 **2l**	15	92	8:1[30]

(*continued on next page*)

Table 1 (*continued*)

Entry	Product	Time (min)	Yield (%)	α/β[a]
13	 **2m**	10	89	10:1[34]
14	 **2n**	20	82	α[35]
15	 **2o**	15	87	11:1[36]
16	 **2p**	20	91	6:1[37]

[a] The α/β ratio was determined from the anomeric proton ratio in the ^{1}H NMR spectra.

For example, borneol[23] and citronellol[24] glycosides are challenging targets to study and transform because of their diverse biological activities and their structural complexity. They are generally synthesized by enzymatic[25] as well as Koenigs–Knorr–Zemplen[23] methods, which are expensive, lengthy, and tedious procedures. Under our catalytic conditions, borneol and citronellol pseudoglycosides were obtained in 87% and 91% yields and in anomeric ratios of 11:1 and 6:1, respectively.

In summary, we have demonstrated a practical synthesis of 2,3-unsaturated *O*-glycosides via the Ferrier rearrangement. H_3PO_4 is an effective and viable catalyst in the reaction with various alcohols to furnish many complex pseudoglycals. The simple work-up, rapid reactions, low cost, and the commercial availability of the catalyst are significant advantages of this method.

Acknowledgments

We gratefully thank Nanyang Technological University and the Ministry of Education, Singapore for the financial support.

References and notes

1. (a) Fraser-Reid, B. *Acc. Chem. Res.* **1985**, *18*, 347; (b) Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem.* **1969**, *24*, 199; (c) Toshima, K.; Tatsuda, K. *Chem. Rev.* **1993**, *93*, 1503; (d) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576; (e) Feher, M.; Schmidt, J. M. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 218; (f) Dorgan, B. J.; Jackson, R. F. W. *Synlett* **1996**, 859; (g) Schmidt, R. R.; Angerbauer, R. *Carbohydr. Res.* **1981**, *89*, 159; (h) Schmidt, R. R.; Angerbauer, R. *Carbohydr. Res.* **1981**, *89*, 193; (i) Schmidt, R. R.; Angerbauer, R. *Carbohydr. Res.* **1979**, *72*, 272; (j) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed.* **1996**, *35*, 1380; (k) Liu, Z. J. *Tetrahedron: Asymmetry* **1999**, *10*, 2119.
2. Bussolo, V. D.; Kim, Y. J.; Gin, D. Y. *J. Am. Chem. Soc.* **1998**, *120*, 13515.
3. (a) Schmidt, R. R.; Angerbauer, R. *Carbohydr. Res.* **1981**, *89*, 159; (b) Angerbauer, R.; Schmidt, R. R. *Carbohydr. Res.* **1981**, *89*, 193.
4. Tolstikov, A. G.; Tolstikov, G. A. *Russ. Chem. Rev.* **1993**, *62*, 579.
5. Williams, N. R.; Wander, J. D. In *The Carbohydrates in Chemistry and Biochemistry*; Academic Press: New York, 1980.
6. Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 570.
7. Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455.
8. (a) Ferrier, R. J.; Sankey, G. H. *J. Chem. Soc. C* **1966**, 2345; (b) Wieczorek, B.; Thiem, J. *J. Carbohydr. Chem.* **1998**, *17*, 785; (c) Levy, D. E.; Tang, C. In *The Chemistry of C-Glycosides*; Pergamon Press: Tarrytown, NY, 1995; (d) Postema, M. H. D. In *C-Glycosides Synthesis*; CRC Press: Boca Raton, FL, 1995; (e) Csuk, R.; Shaade, M.; Krieger, C. *Tetrahedron* **1996**, *52*, 6397.
9. (a) Descotes, G.; Martin, J. C. *Carbohydr. Res.* **1977**, *56*, 168; (b) Klaffke, W.; Pudlo, P.; Springer, D.; Thiem, J. L. *Ann. Chem.* **1991**, *6*, 509.
10. Bhate, P.; Harton, D.; Priebe, W. *Carbohydr. Res.* **1985**, *144*, 331.
11. (a) Babu, B. S.; Balsubramanian, K. K. *Tetrahedron Lett.* **2000**, *41*, 1271; (b) Das, S. K.; Reddy, K. A.; Roy, J. *Synlett* **2003**, 1607.
12. Takhi, M.; Rahman, A.; Schmidt, R. R. *Tetrahedron Lett.* **2001**, *42*, 4053.
13. Masson, C.; Soto, J.; Besodes, M. *Synlett* **2000**, 1281.
14. Yadav, J. S.; Reddy, B. V. S.; Chandraiah, L.; Reddy, K. S. *Carbohydr. Res.* **2001**, *332*, 221.
15. Swamy, N. R.; Venkateswarlu, A. *Synthesis* **2002**, 598.
16. Bettadaiah, B. K.; Srinivas, P. *Tetrahedron Lett.* **2003**, *44*, 7257.
17. Yadav, J. S.; Reddy, B. V.; Reddy, J. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2390.
18. Yadav, J. S.; Reddy, B. V.; Murthy, C. V.; Kumar, G. M. *Synlett* **2000**, 1450.
19. Smitha, G.; Reddy, S. C. *Synthesis* **2004**, 834.
20. Takagi, R.; Kondo, A.; Ohkata, K. *J. Mol. Catal. A: Chem.* **2007**, *1*, 120.
21. Klerk, A. D.; Leckel, D. O.; Prinsloo, N. M. *Ind. Eng. Chem. Res.* **2006**, *45*, 6127.
22. Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909.
23. Mastalic, J.; Jerkovic, I.; Vinkovic, M.; Dzolic, Z.; Vikic-Topic, D. *Croat. Chem. Acta* **2004**, *77*, 491.
24. Oka, N.; Ikegami, A.; Ohki, M.; Sakata, K.; Yagi, A.; Watanabe, N. *Phytochemistry* **1998**, *47*, 1527.
25. Yamauchi, T.; Hara, M.; Mihashi, K. *Phytochemistry* **1972**, *1*, 3345.
26. Zhang, G.; Liu, Q.; Shi, L.; Wang, J. *Tetrahedron* **2008**, *64*, 339.
27. Ferrier, R. J.; Petersen, P. M. *Tetrahedron* **1990**, *46*, 1.
28. Surya Kiran, N.; Malla Reddy, S.; Srinivasulu, M.; Venkateswarlu, Y. *Synth. Commun.* **2008**, *38*, 170.
29. Yadav, J. S.; Subba Reddy, B. V.; Sunder Reddy, J. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2390.
30. Das, S. K.; Reddy, K. A.; Roy, J. *Synlett* **2003**, 1607.
31. *Typical experimental procedure*: To a mixture of 2,4,6-tri-*O*-acetyl-D-glycal (100 mg, 0.37 mmol) and pentan-3-ol (1 equiv) in dichloromethane (1 ml) was added 0.2 equiv of phosphoric acid at room temperature. The mixture was stirred for the appropriate amount of time (Table 1, entry 7), and the extent of reaction was monitored by TLC analysis. The reaction mixture was then filtered and rinsed with dichloromethane. Evaporation of the solvent under reduced pressure, followed by purification of the residue by silica gel column chromatography, gave the desired 2,3-unsaturated glycoside (**2g**): $[\alpha]_D^{24}$ +313.9 (*c* 0.2 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (d, *J* = 10.5 Hz, 1H), 5.80 (d, *J* = 10.5 Hz, 1H), 5.25 (dt, *J* = 9.3, 1.4 Hz, 1H), 5.09 (s, 1H), 4.20 (dd, *J* = 12.1, 5.7 Hz, 1H), 4.16–4.11 (m, 2H), 3.55 (pent, *J* = 5.9 Hz, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 1.57–1.48 (m, 4H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.3, 128.7, 128.2, 93.4, 81.2, 66.9, 65.3, 63.1, 27.1, 26.1, 20.9, 20.7, 10.0, 9.3; IR (NaCl neat) ν 1743, 1369, 1230, 1033 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ Calcd for $C_{15}H_{24}O_6Na$ 323.1471, found 323.1462.
32. *Cyclohex-2-enyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside* (**2h**): obtained as a mixture of two diastereomers; $[\alpha]_D^{24}$ +38.7 (*c* 0.5 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87–5.81 (m, 3H), 5.76 (m, 1H), 5.29 (d, *J* = 8.8 Hz, 1H), 5.19 (d, *J* = 17.4 Hz, 1H), 4.25–4.16 (m, 4H), 2.09 (s, 3H), 2.08 (s, 3H), 2.03 (m, 1H), 1.97–1.92 (m, 2H), 1.83–1.72 (m, 2H), 1.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 170.3, 131.5, 128.9, 128.7, 128.4, 128.3, 94.0, 72.7, 66.8, 65.4, 63.1, 30.1, 25.0, 20.9, 19.2; IR (NaCl neat) ν 1743, 1371, 1230,

1033 cm^{-1}; HRMS (ESI) *m*/*z* [M+Na]$^+$ Calcd for $C_{16}H_{22}O_6Na$ 323.1314, found 323.1310.

33. *Cyclooctanyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside* (**2j**): $[\alpha]_D^{24}$ +156.7 (*c* 1.0 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (d, *J* = 10.2 Hz, 1H), 5.78 (dt, *J* = 10.2, 2.3 Hz, 1H), 5.26 (dd, *J* = 9.6, 1.4 Hz, 1H), 5.11 (s, 1H), 4.21 (d, *J* = 12.1 Hz, 1H), 4.12 (m, 2H), 3.83 (hept, *J* = 4.2 Hz, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 1.76 (m, 1H), 1.71–1.69 (m, 4H), 1.59–1.40 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 170.3, 128.65, 128.63, 92.8, 78.6, 66.8, 65.5, 63.2, 53.4, 33.0, 31.3, 27.3, 27.2, 25.2, 22.9, 20.9, 20.7; IR (NaCl neat) *v* 1743, 1373, 1234, 1036 cm^{-1}; HRMS (ESI) *m*/*z* [M+Na]$^+$ calcd for $C_{18}H_{28}O_6Na$ 363.1784, found 363.1771.
34. *3-Phenylprop-2-ynyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside* (**2m**): $[\alpha]_D^{24}$ +196.0 (*c* 0.5 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.46–7.42 (m, 2H), 7.32–7.28 (m, 3H), 5.93 (d, *J* = 17.5 Hz, 1H), 5.87 (d, *J* = 17.5 Hz, 1H), 5.33 (s, 2H), 4.53 (s, 2H), 4.26 (dd, *J* = 12.1, 5.1 Hz, 1H), 4.18 (dd, *J* = 12.1, 2.4 Hz, 1H), 4.14 (m, 1H), 2.09 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 170.2, 131.8, 129.6, 128.6, 128.3, 127.4, 122.3, 92.7, 86.5, 84.3, 67.2, 65.2, 62.8, 55.8, 51.4, 20.9, 20.7; IR (NaCl neat) *v* 1743, 1371, 1234, 1037 cm^{-1}; HRMS (ESI) *m*/*z* [M+H]$^+$ calcd for $C_{19}H_{21}O_6$ 345.1338, found 345.1339.
35. *2-Naphthyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside* (**2n**): $[\alpha]_D^{24}$ +151.5 (*c* 1.0 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.77 (m, 1H), 7.76–7.66 (m, 2H), 7.48 (m, 1H), 7.46 (m, 1H), 7.10 (t, *J* = 8.9 Hz, 1H), 6.30 (m, 1H), 5.98 (dt, *J* = 10.2, 1.6 Hz, 1H), 5.96 (dt, *J* = 10.2, 1.6 Hz, 1H), 5.66 (ddd, *J* = 6.47, 2.83, 1.88 Hz, 1H), 4.36–4.34 (m, 2H), 4.08 (dt, *J* = 9.2, 3.0 Hz, 1H), 2.14 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 170.1, 154.0, 129.13, 129.10, 128.9, 127.0, 126.9, 124.6, 123.1, 120.8, 119.9, 112.8, 75.2, 64.2, 62.4, 21.0, 20.8; IR (NaCl neat) *v* 1747, 1226, 1039 cm^{-1}; HRMS (ESI) *m*/*z* [M+Na]$^+$ calcd for $C_{20}H_{20}O_6Na$ 379.1158, found 379.1147.
36. *(+)-Borneol 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside* (**2o**): $[\alpha]_D^{24}$ +72.6 (*c* 0.8 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.84–5.79 (m, 2H), 5.27 (d, *J* = 9.8 Hz, 1H), 4.99 (s, 1H), 4.21 (dd, *J* = 12.2, 5.6 Hz, 1H), 4.12 (dd, *J* = 12.2, 2.2 Hz, 1H), 4.10–4.09 (m, 1H), 3.82 (dt, *J* = 6.6, 2.1 Hz, 1H), 2.24–2.22 (m, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 1.96–1.90 (m, 1H), 1.70–1.64 (m, 2H), 1.59 (t, *J* = 4.5 Hz, 1H), 1.23–1.17 (m, 2H), 0.94–0.82 (s, 3H), 0.81(s, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 170.2, 128.4, 128.2, 96.1, 85.8, 66.8, 66.7, 64.1, 48.8, 47.7, 46.6, 38.9, 28.2, 28.2, 26.6, 20.9, 20.7, 19.7, 13.6; IR (NaCl neat) *v*1747, 1369, 1230, 1041 cm^{-1}; HRMS (ESI) *m*/*z* [M+Na]$^+$ calcd for $C_{20}H_{30}O_6Na$ 389.1940, found 389.1938.
37. *(S)-(−)-β-Citronellol 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside* (**2p**): $[\alpha]_D^{24}$ +41.5 (*c* 0.5 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.86 (d, *J* = 10.4 Hz, 1H), 5.87 (d, *J* = 10.4 Hz, 1H), 5.29 (dd, *J* = 9.6, 1.1 Hz, 1H), 5.08 (t, *J* = 7.0 Hz, 1H), 5.01 (s, 1H), 4.23 (dd, *J* = 12.1, 5.4 Hz, 1H), 4.16 (dd, *J* = 12.1, 2.2 Hz, 1H), 4.10–4.07 (m, 1H), 3.82 (dd, *J* = 7.4, 2.2 Hz, 1H), 3.55–3.50 (m, 1H), 2.08 (s, 3H), 2.07 (s, 3H), 1.99–1.93 (m, 2H), 1.67–1.65 (m, 4H), 1.59–1.55 (m, 4H), 1.41–1.30 (m, 2H), 1.17–1.12 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 170.3, 131.2, 128.9, 127.9, 124.7, 94.3, 67.0, 66.9, 65.3, 63.1, 37.2, 36.5, 29.4, 25.7, 25.4, 20.9, 20.8, 19.3, 17.6; IR (NaCl neat) *v* 1743, 1371, 1232, 1035 cm^{-1}; HRMS (ESI) *m*/*z* [M+Na]$^+$ calcd for $C_{20}H_{32}O_6Na$ 391.2097, found 391.2089.