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Carbohydrate-based approach to four enantiomerically pure 2-naphthylmethyl 3-hydroxy-2-methylbutanoates

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Abstract

Chiral pool approach using D-glucose, L-xylose, and D- and L-arabinoses was used to obtain four stereoisomeric 3-hydroxy-2-methylbutanoic acids with well defined configurations. The acids were isolated as fluorescent 2-naphthylmethyl esters after reaction with 2-naphthyldiazomethane.

The compound (2*E*,10*Z*,12*E*)-20-((3-aminocarboxy)-2-methyl-1-oxybutyl)amino-7-methylene-17-oxo-19-oxy-3,5,15-trimethyl-eicosa-2,10,12-trienoic acid has been isolated from *Pseudomonas batumici*[1] and found to be active against *Staphylococcus aureus*. The compound has five stereogenic centers from which the chirality has not been determined. Here we describe the synthesis of four stereoisomeric 3-hydroxy-2-methylbutanoic acids, isolated in the form of fluorescent 2-napthylmethyl esters, from carbohydrate precursors. These reference compounds are used to solve the chirality of two of the stereogenic centers of the target compound. The target compounds **6**, **14**, **20**, and **23** were obtained as pure enantiomers within accuracy of their ^{1}H 500 MHz measurements.

Optically active 3-hydroxy-2-methylbutanoic acids with variable ee were obtained previously using different versions of the aldol condensation,[2–10] eventually amended by enzymic resolution,[2,3] or by enantioselective reductions of the carbonyl groups[11,12] or acetoxymercuration followed by resolution[13] as the critical steps.

The basic idea of transformation of chirality present in four starting sugar derivatives **1**, **7**, **16**, and **21** into the chirality in targets **6**, **14**, **20**, and **23**, respectively, is shown in Figure 1. In all cases the configurations at the C4 atoms in substrates **1**, **7**, **16**, and **21** and in the intermediate 3,5-dideoxy-3-*C*-methylpentofuranoses **4**, **13**, **19**, and **22**, respectively, were preserved, whereas orientation of the bulky 1,2-*O*-isopropylidene group present in **1**, **7**, **16**, and **21** served as a steric bias to obtain predictably the necessary orientation of the C3 methyl groups in **4**, **13**, **19**, and **22** (see Schemes 1–3). Finally, the stereogenic centers at atoms C3 and C4 in **4**, **13**, **19**, and **22** became those at atoms C2 and C3 in targets **6**, **14**, **20**, and **23**, respectively.

The synthesis of 2-naphthylmethyl-(3*R*)-hydroxy-(2*R*)-methyl-butanoate **6** is shown in Scheme 1. 1,2;5,6-Di-*O*-isopropylidene-α-D-glucofuranose **1** was oxidized with a CrO_3–Py–Ac_2O mixture by analogy to similar transformations,[14,15] followed by the Wittig methylenation and hydrogenation over Adams catalyst to furnish a mixture of the *allo:gluco* epimers in ca. 10:1 proportion.[16,17] Flash chromatography could be used to obtain the necessary more polar *allo* epimer, but it was much more convenient to perform 'dehomologation' by analogy to the other derivatives of D-glucofuranose,[18,19] and subsequent tosylation to obtain 3-deoxy-1,2-*O*-isopropylidene-3*C*-methyl-5-*O*-*p*-toluenesulfonyl-α-D-ribofuranose **3** as a pure stereoisomer by

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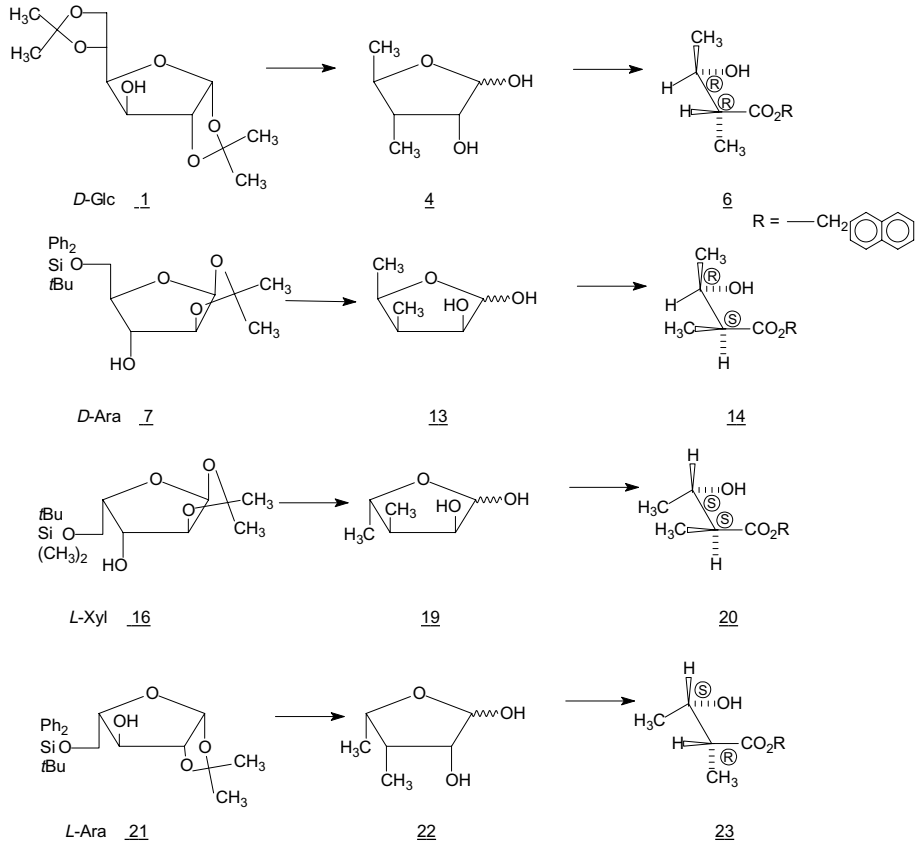
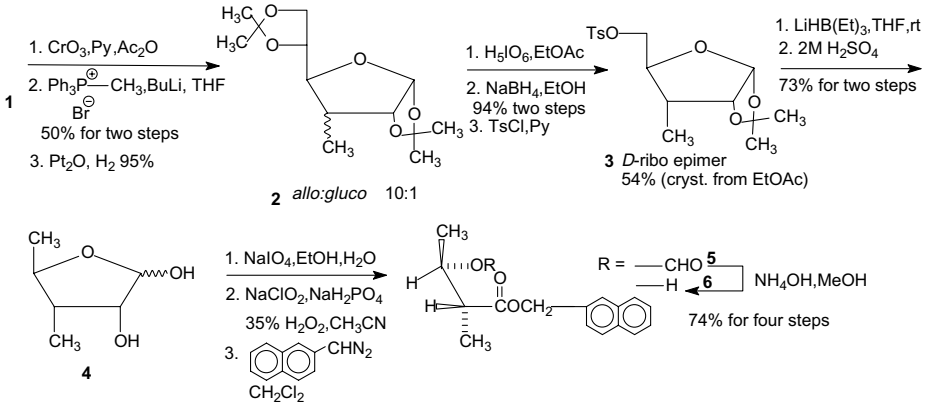


Fig. 1. Synthetic strategy to obtain the four stereoisomeric 3-hydroxy-2-methylbutanoic acids.

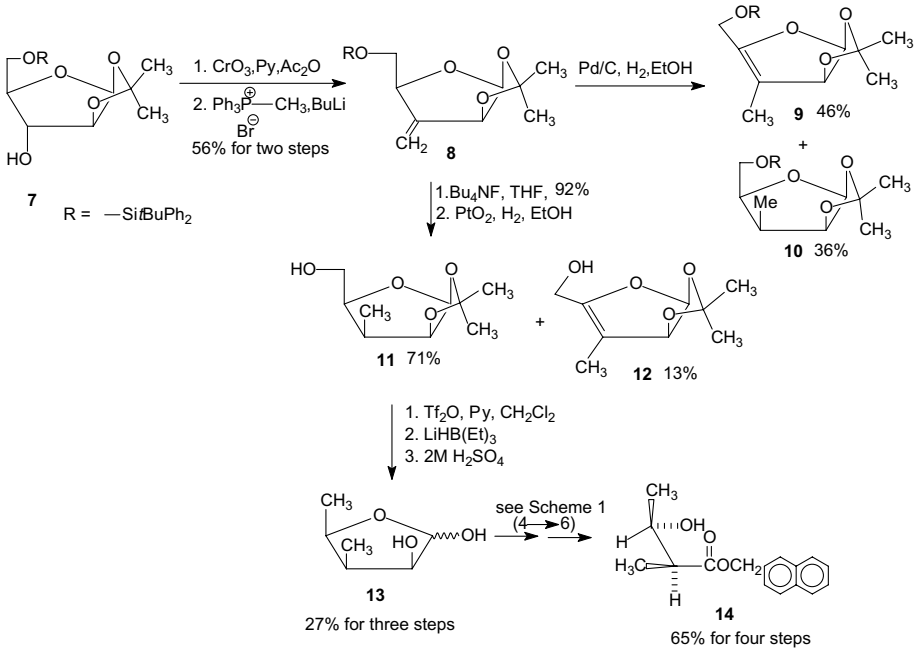


Scheme 1. Synthesis of the (3*R*)-hydroxy-(2*R*)-methyl butanoate.

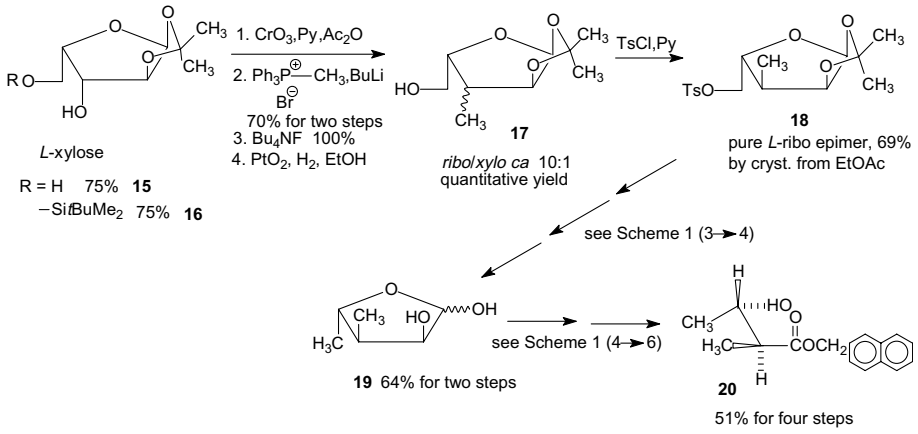
crystallization from EtOAc. The configuration at the C3 atom was confirmed by X-ray analysis.[20]

Treatment with $LiBH(Et)_3$/THF smoothly effected substitution at the C5 position. Hydrolysis of the acetonide function (2 M H_2SO_4–H_2O, rt; $FeCl_3$–$6H_2O$–CH_2Cl_2[21] or I_2–MeOH[22] were totally inefficient) gave diol **4**, which was cleaved with $NaIO_4$ and the formed aldehyde function was oxidized to the carboxyl function using $NaClO_2$–H_2O_2–NaH_2PO_4[23] mixture in CH_3CN for 1–2 h at rt (AgO, THF/H_2O[24] was inefficient). Final esterification with freshly prepared solution of 2-naphthyldiazomethane (obtained by oxidation of 2-naphthylmethylhydrazone[25] with yellow HgO and cat. KOH in CH_2Cl_2, 2 h, by analogy to the other arylhydrazones[26,27]) furnished a mixture of **6** and less polar formate **5**. Both compounds could be separated by flash chromatography, but it was more convenient to perform basic hydrolysis of the formate (NH_4OH–MeOH) and to isolate (3*R*,2*R*) target **6**. ^1H 500 MHz spectrum of this compound showed no traces of epimerisation at C2 by comparison with the spectrum of the 3*R*,2*S* compound **14** (see below).

(3*R*,2*S*) Diastereoisomer **14** was obtained as shown in Scheme 2. The *t*-butyldiphenylsilyl-1,2-*O*-isopropylidene-β-D-arabinofuranose **7** was obtained by analogy to its



Scheme 2. Synthesis of the (3*R*)-hydroxy-2(*S*)-methylbutanoate.



Scheme 3. Synthesis of the (3*S*)-hydroxy-(2*S*)-methylbutanoate.

L-enantiomer[28,14,15] and converted to the 3-methylene derivative **8** via oxidation, followed by Wittig reaction (PH_3–PCH_3Br, BuLi, THF; Tebbe reagent or Peterson olefination could also be used by analogy to the L-enantiomer[14]). Hydrogenation over Pd/C furnished a 46:36 mixture of the less polar compound **9** with a migrated C=C bond and the desired 3-*C*-deoxy-3-*C*-*lyxo* product **10**.

Formation of **9** undoubtedly reflected an increased steric congestion in the upper part of the furanosyl ring resulting from the *syn* orientation of the four substituents in **10**. Also, it is known that tetrasubstituted olefins can be quite resistant toward addition of hydrogen,[29] so persistence of **9** under hydrogenation conditions is not unusual. In an attempt to suppress the unwanted migration of the double bond, a steric bulk in the upper part of the furanosyl ring was decreased by desilylation and also the Adams catalyst was used. Platinum is known to favor additions of H_2 to C=C bonds rather to catalyze their migrations.[30] Thus, application of the Adams catalyst permitted to obtain **11** in 71% yield accompanied by the less polar **12** formed in 13% yield. A tosylate derived from **11** was very unreactive toward a substitution by strong nucleophilic ('supernucleophilic') hydride anion coming from $LIBH(Et)_3$, in sharp contrast with a behavior at **3**, but of a corresponding triflate reacted with this reagent even though decomposition was evident by TLC. Hydrolysis of the acetonide function furnished the 3,5-dideoxy-3*C*-methyl-D-lyxofuranose **13**, which was converted to 2-naphthylmethyl-(3*R*)-hydroxy-(2*S*)-methylbutanoate **14** by analogy to the procedure described above for **6**.

A synthesis of the 2-naphthylmethyl (3*S*)-hydroxy-(2*S*)-methylbutanoate **20**, which is an enantiomer of **6**, was

based on relatively cheap L-xylose, rather than on L-glucose. 1,2-*O*-Isopropylidene-α-L-xylofuranose was obtained in a two-step one pot process by analogy to the D-enantiomer,[31] and converted to its 5-*O*-*t*-butyldimethylsilyl ether **16** as described for D-form.[18,32] Oxidation at the C3 position followed by Wittig methylenation, desilylation, and hydrogenation furnished a chromatographically inseparable mixture of the 3-deoxy-1,2-*O*-isopropylidene-3*C*-methyl-α-L-ribofuranose and the corresponding L-xylo epimer in approximate proportion 10:1 in favor of the necessary L-ribo product. Tosylation and crystallization from EtOAc furnished pure L-ribo compound **18**, which was converted to 3,5-dideoxy-3*C*-methyl-L-ribofuranose **19**, and further to **20** by the same procedure as described for **4**.

The last compound, 2-naphthylmethyl-(3*S*)-hydroxy-(2*R*)-methylbutanoate **23** was obtained from L-arabinofuranose **21** by analogy to its D-enantiomer.

It is interesting to note that attempts to invert the configuration at the C3 position of **14** (i.e. to get **20** from **14**) via a Mitsunobu process (nBu$_3$P, iPrO$_2$C–N=N–CO$_2$$i$Pr, 2,4-dinitrobenzoic acid, THF) were futile. Secondly, the esterifications with 2-naphthyldiazomethane were instantaneous, and were visually followed by a loss of red-orange color of the reagent and evolution of nitrogen. In situ generated aryldiazomethanes are in general less than 85% pure[33] and by coincidence the impurities present in 2-naphthyldiazomethane used throughout this work interfered with the isolation of the transiently formed formates, for example, **5**. For this reason, only in the case of glucose such intermediate was isolated. Additional advantage of using 2-naphthylmethyl esters besides their fluorescence is that they are easily detectable on TLC since they form characteristic brownish-red spots upon spraying with 2% solution of CrO_3 in 10% aq H_2SO_4 and heating. In contrast, underivatized 3-hydroxy-2-methylbutanoic acids form faint yellow spots on blue background using acid–base indicator bromocresol green, albeit the sensitivity of this method is rather low.[34,35]

The compounds presented here were characterized by 300 MHz or 500 MHz NMR and by high resolution mass measurement.[36]

In summary, all four stereoisomeric 3-hydroxy-2-methylbutanoic acids were obtained starting from easily accessible derivatives of D-glucose, L-xylose, and D- and L-arabinose. The target acids were isolated as fluorescent[37] 2-naphthylmethyl esters.

Acknowledgments

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References and notes

1. Smirnov, V. V.; Churkina, L. N.; Perepnikhatka, V. I.; Mukvich, N. S.; Garagulya, A. D.; Kiprianova, E. A.; Kravets, A. N.; Dovzhenko, S. A. *Appl. Biochem. Microbiol.* **2000**, *36*, 46.
2. Neri, C.; Williams, J. M. J. *Adv. Synth. Catal.* **2003**, *345*, 835.
3. Neri, C.; Williams, J. M. J. *Tetrahedron Lett.* **2002**, *43*, 4257.
4. Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A.; Scheidt, K. A. *J. Org. Chem.* **2002**, *67*, 4275.
5. Vicario, J. L.; Badía, D.; Dominguez, E.; Rodríguez, M.; Carrillo, L. *J. Org. Chem.* **2000**, *65*, 3754.
6. Harris, R. C.; Cutter, A. L.; Weissman, K. J.; Hanefeld, U.; Timoney, M. C.; Staunton, J. *J. Chem. Res.* **1998**, 283.
7. Lützen, A.; Köll, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1193.
8. Raimundo, B. C.; Heathcock, C. H. *Synlett* **1995**, 1213.
9. Hoffmann, R. W.; Dresely, S. *Chem. Ber.* **1989**, *122*, 903.
10. Davis, S. G.; Dordor-Hedgecock, J. M.; Warner, P. *Tetrahedron Lett.* **1985**, *26*, 2125.
11. Tai, A.; Morimoto, N.; Yoshikawa, M.; Uehara, K.; Sugimura, T.; Kikukawa, T. *Agric. Biol. Chem.* **1990**, *54*, 1753.
12. Tai, A.; Imaida, M. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1114.
13. Maskens, K.; Polgar, N. *J. Chem. Soc., Perkin Trans. 1* **1973**, 109.
14. Doboszewski, B.; Herdewijn, P. *Tetrahedron* **1996**, *52*, 1651.
15. Dahlman, O.; Garegg, P. J.; Mayer, H.; Schramek, S. *Acta Chem. Scand. B* **1986**, *40*, 15.
16. Dang, H.-S.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1161.
17. Martin, O. R.; Nabinger, R. C.; Ali, Y.; Vyas, D. M.; Szarek, W. A. *Carbohydr. Res.* **1983**, *121*, 302.
18. Robins, M. J.; Doboszewski, B.; Timoshchuk, V. A.; Peterson, M. A. *J. Org. Chem.* **2000**, *65*, 2939.
19. Xie, M.; Berges, D. A.; Robins, M. J. *J. Org. Chem.* **1996**, *61*, 5178.
20. de Armas, H. N.; Doboszewski, B.; Herdewijn, P.; Blaton, N. *Acta Crystallogr. Sect. E* **2007**, *63*, 2678.
21. Sen, S. E.; Roach, S. L.; Boggs, J. K.; Ewing, G. J.; Magrath, J. *J. Org. Chem.* **1997**, *62*, 6684.
22. Szarek, W. A.; Zamojski, A.; Tiwari, K. N.; Ison, E. R. *Tetrahedron Lett.* **1986**, *27*, 3827.
23. Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.
24. Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.
25. Asis, S. E.; Bruno, A. M.; Martinez, A. R.; Sevilla, M. W.; Gaozza, C. H.; Romano, A. M.; Coussio, J. D.; Ciccia, G. *Il Farmaco* **1999**, *54*, 517–523.
26. Miller, J. B. *J. Org. Chem.* **1959**, *25*, 560.
27. Gutsche, C. D.; Jason, E. F. *J. Am. Chem. Soc.* **1956**, *78*, 1184.
28. Martin, O. R.; Rao, S. P.; El-Shenawy, H. A.; Kurz, K. G.; Cutler, A. B. *J. Org. Chem.* **1988**, *53*, 3287.
29. Smith, M. B.; March, J. In *March's Advanced Organic Chemistry*, 6th ed.; Wiley-Interscience: New Jersey, 2007; p 1053.
30. Keith, J. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon, 1995; p 71.
31. Moravcová, J.; Capková, J.; Staněk, J. *Carbohydr. Res.* **1994**, *263*, 61.
32. Yoshimura, Y.; Sano, T.; Matsuda, A.; Ueda, T. *Chem. Pharm. Bull.* **1988**, *36*, 162.
33. Smets, G.; Boutemburg, A. *J. Polym. Sci. A1* **1970**, *8*, 3251.
34. Touchstone, J. C.; Dobbins, M. F. In *Practice of Thin Layer Chromatography*, 2nd ed.; Wiley Interscience: New York, 1983; p 163.
35. Krebs, K. G.; Heusser, D.; Wimmer, H. In *Thin-Layer Chromatography. A Laboratory Handbook*; Stahl, E., Ed.; Springer Verlag: Berlin, 1969; p 854.
36. *Selected data of intermediates* **4** *and* **13**, *and targets* **6** *and* **14** *derived from them*: **4**: $[\alpha]_D$ +13.2 (initial); +27.9 (after 30 min), *c* 5.7, $CHCl_3$; ^{1}H (500 MHz, $CDCl_3$): 5.38 (d, $J_{12} = 3.8$ Hz) and 5.19 (s) H1; 5.11 (br s, exchangeable, OH); 4.04 (*t*, $J_{23} = J_{21} = 4.5$ Hz) and 3.94 (d, $J_{23} = 4.3$ Hz) H2; 3.89 (dq, $J_{H-Me} = 6.0$ Hz, $J_{43} = 10.2$ Hz) and 3.86 (dq, $J_{H-Me} = 6.1$ Hz, $J_{43} = 10.3$ Hz) H4; 3.70 and 3.28 (two br s,

exchangeable, OH); 2.01 (m of 14 lines, $J_{H-Me} = 6.9$ Hz, J_{34} ca. 9.6 Hz, $J_{32} = 4.3$ Hz) and 1.71 (m of 14 lines, $J_{H-Me} = 6.6$ Hz, $J_{34} = 9.6$ Hz, J_{32} ca. 5.5 Hz) H3; 1.28 (d, $J_{Me-H} = 6.2$ Hz) and 1.18 (d, $J_{Me-H} = 6.1$ Hz) terminal Me; 1.00 (d, $J_{Me-H} = 7.0$ Hz) and 0.99 (d, $J_{Me-H} = 6.9$ Hz) terminal C2 Me.

^{13}C (75 MHz, $CDCl_3$): 102.29, 97.13, 80.91, 78.81, 75.51, 73.58, 44.84, 42.28, 20.68, 18.82, 9.73, 9.16.

Exact mass (EI, 50 eV) calculated for $C_6J_{12}O_3$–OH = 115.07589, found 155.07717.

13: $[\alpha]_D$ +44.8 (initial); +32.3 (after 25 min), *c* 1.6, $CHCl_3$; ^{1}H (500 MHz, $CDCl_3$): 5.28 (d, $J_{12} = 4.6$ Hz) and 5.27 (d, $J_{12} = 1.6$ Hz) H1; 4.42 (m of five lines, $J_{4\text{-Me}} = J_{34} = 6.6$ Hz) and 4.12 (m of five lines, $J_{4\text{-Me}} = J_{43} = 6.5$ Hz) H4; 4.10 (dd, $J_{21} = 5.1$ Hz, $J_{23} = 6.4$ Hz) and 4.08 (dd, $J_{21} = 1.5$ Hz, $J_{23} = 5.4$ Hz) H2; 2.46 (multiplet of 10 lines, $J_{32} = 5.5$ Hz, $J_{34} = 7.3$ Hz, $J_{3\text{-Me}} = 7.3$ Hz) and 2.28 (m of six lines, $J = 7.0$ Hz) H3; 1.22 (d, $J_{Me-H} = 6.6$ Hz) and 1.17 (d, $J_{Me-H} = 6.6$ Hz) terminal Me; 1.02 (d, $J_{Me-H} = 7.3$ Hz) and 0.98 (d, $J_{Me-H} = 7.3$ Hz) C2–Me.

^{13}C (75 MHz, $CDCl_3$): 101.57, 96.46, 79.06, 77.14, 76.52, 73.52, 73.48, 38.99, 38.24, 17.86, 17.59, 8.23, 7.53.

HRMS (EI, 50 eV) calculated for $C_6H_{12}O_3$–CH_3 = 117.05516, found 117.05431.

6: $[\alpha]_D$ −24.1, *c* 5, $CHCl_3$; ^{1}H (500 MHz, $CDCl_3$): 7.85–7.82 (m, 4H) and 7.51–7.44 (m, 3H) H aromatic; 5.32 (s, 2H, –OCH_2–); 3.92 (m of five broadened lines, $J = 6.3$ Hz, 1H, H3); 2.64 (br s, exchangeable, –OH); 2.54 (m of five lines, $J = 7.2$ Hz, H2); 1.22 (d, $J = 6.4$ Hz, 3H, terminal Me); 1.21 (d, $J = 7.2$ Hz, 3H, C2–Me).

^{13}C (75 MHz, $CDCl_3$): 175.66, 133.14, 133.09, 128.42, 127.95, 127.68, 127.29, 126.32, 126.29, 125.69, 69.44, 66.49, 47.06, 20.71, 14.05.

HRMS (electrospray): calculated for $C_{16}H_{18}O_3$+Na^+ = 281.11483, found 281.11465.

14: $[\alpha]_D$ ~+0.5, *c* 6, $CHCl_3$; ^{1}H (500 MHz, $CDCl_3$ after D_2O exchange): 7.84–7.81 (m, 4H) and 7.50–7.43 (m, 3H) H aromatic, 5.30 (s, 2H, –OCH_2–), 4.09 (dq, $J_{32} = 4.0$ Hz, $J_{3\text{-Me}} = 6.3$ Hz, 1H, H3), 2.62 (br s, residual OH), 2.57 (dq, $J_{23} = 3.9$ Hz, $J_{2\text{-Me}} = 7.2$ Hz, 1H, H2), 1.22 (d, $J_{Me\text{-}2} = 7.3$ Hz, 3H, C2–Me), 1.17 (d, $J_{Me\text{-}3} = 6.4$ Hz, 3H, terminal Me).

^{13}C (125 MHz, $CDCl_3$): 175.70, 133.10, 133.07, 128.43, 127.93, 127.67, 127.35, 126.32, 126.30, 125.70, 67.95, 66.50, 45.57, 19.80, 10.98.

HRMS (electrospray) calculated for $C_{16}H_{18}O_3$+Na^+ = 281.11483, found 281.11477.

37. Matthees, D. P.; Purdy, W. C. *Anal. Chim. Acta* **1979**, *109*, 61.