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.

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The compound (2E,10Z,12E)-20-((3-aminocarboxy)-2-methyl-1-oxybutyl)amino-7-methylene-17-oxo-19-oxo-3,5,15-trimethyl-eicosa-2,10,12-trienoic acid has been isolated from Pseudomonas batumici 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-naphthylmethyl 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 1H 500 MHz measurements.

Optically active 3-hydroxy-2-methylbutanoic acids with variable ee were obtained previously using different versions of the aldol condensation, eventually amended by enzymic resolution, or by enantioselective reductions of the carbonyl groups or acetoxymercuration followed by resolution 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-di-deoxy-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-(3R)-hydroxy-(2R)-methyl-butanoate 6 is shown in Scheme 1. 1,2;5,6-Di-O-isopropylidene-α-D-glucofuranose 1 was oxidized with a CrO3–Py–Ac2O mixture by analogy to similar transformations, followed by the Wittig methylation and hydrogenation over Adams catalyst to furnish a mixture of the allo:gluco epimers in ca. 10:1 proportion. 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 α-glucofuranose, 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
crystallization from EtOAc. The configuration at the C3 atom was confirmed by X-ray analysis. Treatment with LiBH(Et)₃/THF smoothly effected substitution at the C5 position. Hydrolysis of the acetonide function (2 M H₂SO₄–H₂O, rt; FeCl₃–6H₂O–CH₂Cl₂ or I₂–MeOH)22 were totally inefficient) gave diol 4, which was cleaved with NaIO₄ and the formed aldehyde function was oxidized to the carboxyl function using NaClO₂–H₂O₂–NaH₂PO₄ mixture in CH₃CN for 1–2 h at rt (AgO, THF/H₂O24 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 CH₂Cl₂, 2 h, by analogy to the other arylhydrazones26,27) 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 (NH₄OH–MeOH) and to isolate (3R,2R) target 6. ¹H 500 MHz spectrum of this compound showed no traces of epimerisation at C2 by comparison with the spectrum of the 3R,2S compound 14 (see below).

(3R,2S) Diastereoisomer 14 was obtained as shown in Scheme 2. The β-butyldiphenylsilyl-1,2-O-isopropylidene-β-D-arabinofuranose 7 was obtained by analogy to its...
L-enantiomer and converted to the 3-methylene derivative via oxidation, followed by Wittig reaction (PH3–PCH3Br, BuLi, THF; Tebbe reagent or Peterson olefination could also be used by analogy to the L-enantiomer). Hydrogenation over Pd/C furnished a 46:36 mixture of the less polar compound with a migrated C=C bond and the desired 3-C-deoxy-3-C-lyxo product.

Formation of 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, so persistence of 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 H2 to C=C bonds rather to catalyze their migrations. 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, but of a corresponding tri-flate 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, which was converted to 2-naphthylmethyl-(3R)-hydroxy-(2S)-methylbutanoate by analogy to the procedure described above for 6.

A synthesis of the 2-naphthylmethyl (3S)-hydroxy-(2S)-methylbutanoate, 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 α-enantiomer,\textsuperscript{13} and converted to its α-butyldimethylsilyl ether 16 as described for α-form.\textsuperscript{18,32} Oxidation at the C3 position followed by Wittig methylation, desilylation, and hydrogenation furnished a chromatographically inseparable mixture of the 3-deoxy-1,2-O-isopropylidene-3C-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-(3S)-hydroxy-(2R)-methylbutanoate 23 was obtained from L-arabinofuranose 21 by analogy to its α-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 (nBu3P, iPr2O2C–N=N–CO2iPr, 2,4-dinitrobenzoic acid, THF) were futile. Secondly, the esterifications with 2-naphthyldiazomethane are in general less than 85%\textsuperscript{2} and by coincidence the impurities present in 2-naphthyl methyl esters are easily detectable on TLC since they form characteristic brownish-red spots upon spraying with 2% solution of 2,4-dinitrobenzoic acid, THF) were futile. Secondly, the esterifications with 2-naphthyldiazomethane were instanta-

References and notes

36. Selected data of intermediates 4 and 13, and targets 6 and 14 derived from them: 4: \[\delta_2^1H +13.2 \text{ (initial)} +27.9 \text{ (after 30 min),} \text{ e}5.7 \text{, CHCl}_3, \]

\[1^H \text{ (500 MHz, CDCl}_3): 5.38 \text{ (d, } J_{2,3} = 3.8 \text{ Hz and } 5.19 \text{ (s) H1, 5.11 (br s, exchangeable, OH)}; 4.04 \text{ (t, } J_{3,4} = 4.5 \text{ Hz) and } 3.94 \text{ (d, } J_{3,4} = 4.3 \text{ Hz)} H2; 3.89 \text{ (dq, } J_{4,5} = 6.0 \text{ Hz, } J_{4,3} = 10.2 \text{ Hz and } 3.86 \text{ (dq, } J_{5,6} = 6.1 \text{ Hz, } J_{4,3} = 10.3 \text{ Hz) H4; 3.70 and 3.28 (two br s,}

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

\(^{13}\text{C} (75 \text{ MHz}, \text{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 \(\text{C}_6\text{H}_1\text{O}_3–\text{OH} = 115.07589\), found 155.07717.

\(\text{a} [\delta]_D +44.8\) (initial); \(+32.3\) (after 25 min), c 1.6, CHCl₃; \(^1\text{H} (500 \text{ 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, \(J_{3,4} = 6.6\) Hz) and 4.12 (m of five lines, \(J_{3,4} = 6.5\) Hz) H4; 4.10 (dd, \(J_{23} = 5.1\) Hz, \(J_{23} = 6.4\) Hz) and 4.08 (dd, \(J_{23} = 1.5\) Hz, \(J_{23} = 5.4\) Hz) H2; 2.46 (multiplet of 10 lines, \(J_{3,4} = 5.5\) Hz, \(J_{3,4} = 7.3\) Hz, \(J_{3,4} = 7.3\) Hz) and 2.28 (m of six lines, \(J = 7.0\) Hz) H3; 1.22 (d, \(J_{3,4} = 6.6\) Hz) and 1.17 (d, \(J_{3,4} = 6.6\) Hz) terminal Me; 1.02 (d, \(J_{3,4} = 7.3\) Hz) and 0.98 (d, \(J_{3,4} = 7.3\) Hz) C2–Me.

\(^{13}\text{C} (75 \text{ MHz}, \text{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 \(\text{C}_6\text{H}_1\text{O}_3–\text{CH}_3 = 117.05789\), found 117.05781.

6: \([\delta]_D –24.1, c 5, \text{CHCl}_3; \(^1\text{H} (500 \text{ MHz, CDCl}_3): 7.85–7.82 (m, 4\text{H}) and 7.51–7.44 (m, 3\text{H}) \text{H aromatic}; 5.32 (s, 2\text{H}, –OCH}_2–\); 3.92 (m of five broadened lines, \(J = 6.3\) Hz, 1\text{H}, 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, 3\text{H}, terminal Me); 1.21 (d, \(J = 7.2\) Hz, 3\text{H}, C2–Me).

\(^{13}\text{C} (75 \text{ 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 \(\text{C}_{16}\text{H}_{18}\text{O}_3+\text{Na}^+ = 281.11483\), found 281.11465.

13: \([\delta]_D –44.8\) (initial); \(+32.3\) (after 25 min), c 1.6, CHCl₃; \(^1\text{H} (500 \text{ 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, \(J_{3,4} = 6.6\) Hz) and 4.12 (m of five lines, \(J_{3,4} = 6.5\) Hz) H4; 4.10 (dd, \(J_{23} = 5.1\) Hz, \(J_{23} = 6.4\) Hz) and 4.08 (dd, \(J_{23} = 1.5\) Hz, \(J_{23} = 5.4\) Hz) H2; 2.46 (multiplet of 10 lines, \(J_{3,4} = 5.5\) Hz, \(J_{3,4} = 7.3\) Hz, \(J_{3,4} = 7.3\) Hz) and 2.28 (m of six lines, \(J = 7.0\) Hz) H3; 1.22 (d, \(J_{3,4} = 6.6\) Hz) and 1.17 (d, \(J_{3,4} = 6.6\) Hz) terminal Me; 1.02 (d, \(J_{3,4} = 7.3\) Hz) and 0.98 (d, \(J_{3,4} = 7.3\) Hz) C2–Me.

\(^{13}\text{C} (75 \text{ 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 \(\text{C}_{16}\text{H}_{18}\text{O}_3+\text{Na}^+ = 281.11483\), found 281.11477.