Carbohydrate Research, 132 (1984) C1–C4
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Preliminary communication

Simple synthesis of (*S*)-parasorbic acid and other (5*S*)-hydroxy six-carbon synthons from L-rhamnose*

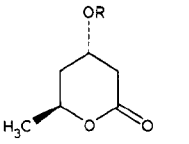
FRIEDER W. LICHTENTHALER, FRANZ D. KLINGLER, and PAN JARGLIS

Institut für Organische Chemie, Technische Hochschule Darmstadt, Petersenstr. 22, D-6100 Darmstadt (West Germany)

(Received March 21st, 1984; accepted for publication, May 3rd, 1984)

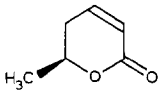
Although (*S*)-(+)-parasorbic acid (**2**) was first obtained 125 years ago by steam distillation of the acidified juice of mountain-ash berries (*Sorbus aucuparia* L.)[2], it took another century for its δ-hexenolactone structure[3] and 5*S* configuration[4,5] to be established and for recognition that it is not present as such in the berries, but as a 3-β-D-glucosyloxy derivative, parasorboside **1**[6]. The isolation of **2** involves a lengthy procedure.

Having only one chiral centre in a C_6-chain suitably functionalised at one end, **2**, as well as the (*S*)-(−)-caprolactone **3** obtained on hydrogenation[7], constitute highly versatile, chiral building-blocks for the synthesis of enantiomerically pure, non-carbohydrate target structures, such as, for example, the C-11/16 unit of prostaglandinoids of the brefeldin A type (**4**).

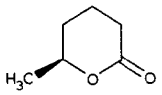


1

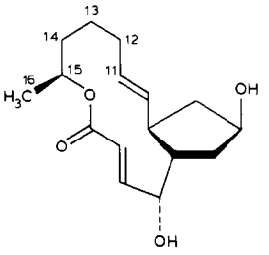
R = β-D-glucosyl



2



3



4

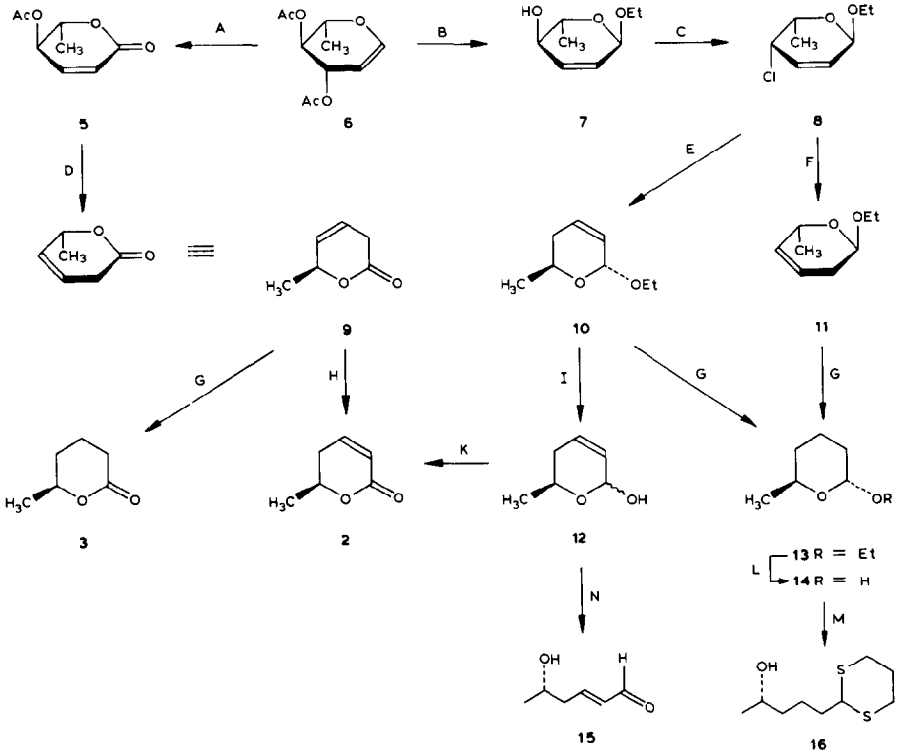
Although several syntheses are available[1] for racemic **2**, there is none for either the 5*S* or the 5*R* enantiomer. We now describe expedient and satisfactory routes from L-rhamnose to the 5*S*-lactones **2** and **3**, as well as to analogues having terminal aldehyde (**10**–**15**) and dithioacetal functionalities (**16**), thus providing several versatile 5*S*-hydroxy C_6-synthons with either a^1, a^3, or d^1 reactivity (for terminology, see ref. 8).

3,4-Di-O-acetyl-L-rhamnal (**6**), which is accessible from L-rhamnose by a one-pot procedure[9], was smoothly converted into the L-*erythro*-enelactone **5** by BF_3-induced

*Sugar-derived Chiral Building Blocks, Part II. For Part I, see ref. 1.

0008-6215/84/$03.00

peroxidation[10]. On exposure to zinc amalgam and hydrogen chloride in ether[11], **5** smoothly underwent reductive cleavage of the allylic acetoxyl group with concomitant shift of the double bond into the unconjugated position, to give 89% of isoparasorbic acid **9**** {oil, b.p. 110°/8 Torr, $[\alpha]_D^{20}$ +88° (*c* 1, chloroform)}. On brief exposure of **9** to base, however, the olefinic double-bond was transposed quantitatively into conjugation with the carbonyl function to yield **2** {b.p. 98–100°/10 Torr, $[\alpha]_D^{20}$ +209° (*c* 1.2, ethanol); lit.[3] b.p. 104–105°/14 Torr, $[\alpha]_D$ +210° (ethanol)}. Raney nickel-promoted hydrogenation of either **9** or **2** afforded 5*S*-δ-caprolactone **3** {b.p. 100–102°/10 Torr, $[\alpha]_D^{20}$ −51° (*c* 1, ethanol); data in accord with those reported[3]}.



Key: A *m*-chloroperbenzoic acid/BF_3-etherate (0.2 equiv.), CH_2Cl_2, 20 min, −40° (89%); B EtOH/BF_3-etherate (1.6 and 0.4 equiv., respectively), benzene, 30 min, 25°, then MeOH–H_2O–Et_3N (3:2:1), 5 h, 25° (81%); C tosyl chloride–pyridine, 6 h, 50° (84%); D zinc amalgam (10 equiv.)–dry HCl in ether, 2 h, 0° (87%); E $NiCl_2$–$NaBH_4$ in ethanol, 5 min (66%); F $LiAlH_4$–tetrahydrofuran, 5 h, 65° (93%); G Raney Ni/H_2 (90%); H diazabicyclo[5.4.0]undecene (0.1 equiv.), tetrahydrofuran, 4 h, 25° (91%); I M HCl–acetone (1:1), 10 min, 20° (88%); K MnO_2–CH_2Cl_2, 14 h, 20° (35%); L Amberlite IR-120 (H^+) resin–water, 3 h, reflux (80%); M propane-1,3-dithiol/conc. HCl, 3 h, 25° (90%); N distillation (b.p. 95–98°/2 Torr).

Products **9–**16** were chromatographically homogeneous syrups that were characterised by ^{1}H-n.m.r. spectroscopy (300 MHz) and field-desorption mass spectrometry; compounds for which the b.p. (bath) and $[\alpha]_D$ value are recorded gave satisfactory elemental analyses.

Although aldehyde analogues of **2** and **3**, such as **12** and **14**, in principle may be generated by reduction of the lactone groupings with hydride reagents (as was shown with racemic **2**[12] and **3**[13]), the four-step approach from 3,4-di-*O*-acetyl-L-rhamnal (**6**) was more efficient. In adapting a known procedure[14], treatment of **6** with ethanol/BF_3-etherate and subsequent *O*-deacetylation readily gave the 2,3-unsaturated ethyl glycoside **7**, $[\alpha]_D^{20}$ −51° (*c* 0.6, chloroform), which, with toluene-*p*-sulfonyl chloride–pyridine at −20°, gave the 4-*O*-tosyl derivative {m.p. 112°, $[\alpha]_D^{20}$ −21° (*c* 0.8, chloroform)}. In contrast, tosylation of **7** at 50° resulted in displacement of the highly reactive, allylic sulfonate group to afford the 4-chloroglycoside **8** {m.p. 39–41°, $[\alpha]_D^{20}$ +286° (*c* 0.6, chloroform)} in high yield. Dechlorination of **8** with nickel chloride–sodium borohydride at −30° afforded (2*R*,6*S*)-2-ethoxy-6-methyl-5,6-dihydropyranone {**10**, b.p. 80°/10 Torr, $[\alpha]_D^{22}$ +46° (*c* 0.8, chloroform)*} in high yield, whereas, with lithium aluminium hydride in refluxing tetrahydrofuran, the 2,3-dihydro isomer **11** {b.p. 80°/10 Torr, $[\alpha]_D^{20}$ −58° (*c* 1, chloroform)} was obtained. Hydrolysis of **10** (M HCl, 10 min, 20°) afforded, on work-up at room temperature, a syrupy 6:1 mixture of the cyclic acetals **12** (1:1 αβ-ratio) and the *trans*-hydroxyaldehyde **15**, as evidenced by the ^{1}H-n.m.r. data†. Work-up of the reaction mixture at >40° shifted the composition of the mixture towards **15**, which, on distillation, was essentially (>95%) the sole product {b.p. 95–98°/2 Torr, $[\alpha]_D^{20}$ +21° (*c* 0.7, chloroform)}. The readily inducible, thermal *cis* → *trans*-rearrangement (**12** → **15**) also accounted for the low yield obtainable on oxidation of *in situ*-hydrolysed **10**, oxidation products of **15** being formed together with sorbinaldehyde and sorbic acid. Such complications were not observed with the hydrogenation product of **10**, *i.e.* **13** {b.p. 60°/12 Torr††, $[\alpha]_D^{22}$ −139° (*c* 0.8, chloroform); lit.[13] for the (+)-parasorbic acid-derived *O*-methyl analogue, $[\alpha]_D$ −144° (ethanol)}, which, on BF_3-catalysed peroxidation, readily afforded the caprolactone **3** (85%). Acid hydrolysis of **13** gave the hemiacetal **14** [b.p. 75–78°/12 mmHg, ~3:2 αβ-mixture without detectable (^{1}H-n.m.r.) hydroxyaldehyde], or, when followed by treatment with propane-1,3-dithiol, the dithioacetal **16** {syrup, $[\alpha]_D^{22}$ +7° (*c* 1, chloroform)} as an acyclic form of (5*S*)-hydroxyhexanal with d^1-reactivity.

The synthetic potential of the above (5*S*)-hydroxy C_6-synthons is demonstrated by the conversion of **14**, by reaction with methyl dimethylphosphonoacetate in methanolic sodium methoxide (conditions and work-up as reported by Maurer *et al.*[16] for racemic **14**), into the methyl ester (**18**) of (*S*,*S*)-6-methyltetrahydropyran-2-ylacetic acid {67%, b.p. 90°/10 Torr, $[\alpha]_D^{22}$ +35° (*c* 0.5, chloroform); lit.[17] $[\alpha]_D^{21}$ +32° (benzene)}. This approach to enantiomerically pure **18**, a glandular secretion product from civet[16], compares favorably with its construction from (*S*)-propylene oxide[17]. Similarly, the C11/16-portion of (+)-brefeldin A (**4**) may be elaborated most advantageously from **14**,

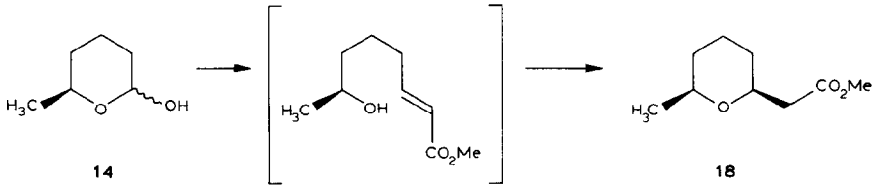
---

*An $[\alpha]_D^{16}$ value of −48° (chloroform) has been reported[15] for the enantiomeric 2-methoxy analogue of **10**.

† ^{1}H-N.m.r. data (300 MHz in $CDCl_3$): **15**, δ 9.53 (d, H-1), 6.95 (dt, H-3), 6.21 (ddt, H-2), 2.45 (m, H-4,4), 4.05 (dt, H-5), 1.25 (d, CH_3), $J_{1,2}$ 7.9, $J_{2,3}$ 15.7, $J_{2,4}$ 1.4, $J_{3,4}$ 7.1, $J_{4,5}$ 6.2, $J_{5,6}$ 6.3 Hz; **12** (less well-resolved), δ 5.7 and 5.6 (2 m, H-2,3), 5.38 (dd, $J_{1,2}$ 3.6, $J_{1,3}$ 1.1 Hz, H-1, β-L isomer), 5.02 (dd, $J_{1,2}$ 8.1, $J_{1,3}$ 3.2 Hz, H-1), α-*L* isomer), 4.45 (bm, H-5), and 2.20 (bm, H-4,4).

†† Higher vacuum substantially reduced the yield due to the pronounced volatility of **13**.

particularly when compared with previous efforts for the construction of this segment from (*R*)-glutamic acid[18], (*S*)-propylene oxide[19], or from a methylcyclohexenone *via* microbial reduction[20].



14 17 18

An analogous set of (5*R*)-building blocks, *i.e.*, the enantiomers of **9**–**16**, has been obtained[21] from D-glucose.

ACKNOWLEDGMENTS

The authors thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support.

REFERENCES

1 F. W. Lichtenthaler, in Atta-ur-Rahman (Ed.), *Proc. Int. Symp. Nat. Prod. Chem., First, Karachi (Pakistan)*, 1984 in press.
2 A. W. Hofmann. *Justus Liebigs Ann. Chem.*, 110 (1859) 129–140; O. Doebner, *Ber.*, 27 (1894) 344–351.
3 R. Kuhn and D. Jerchel, *Ber.*, 76 (1943) 413–419.
4 R. Kuhn and K. Kum, *Chem. Ber.*, 95 (1962) 2009–2011.
5 R. Lukeš, J. Jarý, and J. Němec, *Collect. Czech. Chem. Commun.*, 27 (1962) 735–741.
6 R. Tscheche, H.-J. Hoppe, G. Snatzke, G. Wulff, and H.-W. Fehlhaber, *Chem. Ber.*, 104 (1971) 1420–1428.
7 L. J. Haynes and E. R. H. Jones, *J. Chem. Soc.*, (1946) 954–957; R. Joly and G. Amiard, *Bull. Soc. Chim. Fr.*, (1947) 139–140; K. Torsell and M. P. Tyagi, *Acta Chem. Scand., Ser. B*, 31 (1977) 7–10; W. H. Pirkle and P. E. Adams, *J. Org. Chem.*, 45 (1980) 4117–4121.
8 D. Seebach, *Angew. Chem.*, 91 (1979) 259–278; *Angew. Chem, Int. Ed. Engl.*, 18 (1979) 239–258.
9 B. Iselin and T. Reichstein, *Helv. Chim. Acta*, 27 (1944) 1146–1149; W. Roth and W. Pigman, *Methods Carbohydr. Chem.*, 2 (1963) 405–408.
10 P. Jarglis and F. W. Lichtenthaler, *Tetrahedron Lett.*, (1982) 3781–3784.
11 I. Elphimoff-Felkin and P. Sarda, *Tetrahedron Lett.*, (1972) 725–728; *Org. Syn.*, 56 (1977) 101–107.
12 K. Torsell and M. P. Tyagi, *Acta Chem. Scand., Ser. B*, 31 (1977) 297–301.
13 B. W. Babcock, D. R. Dimmel, D. P. Graves, and R. D. McKelvey, *J. Org. Chem.*, 46 (1981) 736–742.
14 J. S. Brimacombe, L. W. Doner, and A. J. Rollins, *J. Chem. Soc., Perkin Trans. 1*, (1972) 2977–2979.
15 K. Tatsuta, T. Yamaguchi, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, 51 (1978) 3035–3038.
16 B. Maurer, A. Grieder, and W. Thommen, *Helv. Chim. Acta*, 62 (1979) 44–47.
17 D. Seebach and M. Pohmakotr, *Helv. Chim. Acta*, 62 (1979) 843–846.
18 K. Mori, *Tetrahedron*, 31 (1975) 3011–3012; T. Kitahara, K. Mori, and M. Matsui, *Tetrahedron Lett.*, (1979) 3021–3024.
19 H.-J. Gais and T. Lied, *Angew. Chem.*, 96 (1984) 143–145; *Angew. Chem., Int. Ed. Engl.*, 23 (1984) 145–146.
20 C. Le Drian and A.E. Greene, *J. Am. Chem. Soc.*, 104 (1982) 5473–5483.
21 F.-D. Klingler and F. W. Lichtenthaler, unpublished data.