Acta Chemica Scandinavica, 1995: 49: 297–300
Printed in Belgium – all rights reserved

ACTA
CHEMICA SCANDINAVICA
ISSN 0904–213X

Synthesis of Optically Active Glyceric Acid Derivatives from Ascorbic Acids

Per H. J. Carlsen,[†,a] Kristin Misund[b] and Johan Røe[c]

[a]Institute of Organic Chemistry, University of Trondheim-NTH, N-7034 Trondheim, Norway, [b]Research and Development, Borregard Fine Chemicals, N-1701 Sarpsborg, Norway and [c]Weiders Farmasøytiske AS, Hausmannsgt. 6, N-0133 Oslo, Norway

Carlsen, P. J. H., Misund, K. and Røe, J., 1995. Synthesis of Optically Active Glyceric Acid Derivatives from Ascorbic Acids. – Acta Chem. Scand. 49: 297–300 © Acta Chemica Scandinavica 1995.

The synthesis of acetals and ketals of L-ascorbic acid and D-isoascorbic acid has been studied. A convenient and inexpensive method involving reflux in acetone in the presence of an acidic ion-exchange resin was developed. In a perruthenate-catalyzed oxidative degradation reaction using sodium hypochlorite as the stoichiometric oxidant at pH 8.0, acetals or ketals of L-ascorbic acid were converted in high yields into the corresponding acetals or ketals of (*S*)-glyceric acid as their sodium salts. D-Isoascorbic acid similarly gave the (*R*)-glyceric acid derivatives.

Optically active glyceric acid derivatives are versatile C_3-building blocks for synthesis of chiral pharmaceutical products,[1] lipids,[2] amino alcohol synthetic intermediates and pharmacologically active compounds, *e.g.*, β-adrenergic blocking agents,[3] amino acids,[4] β-lactams,[5] antibiotics,[6] side-chain modified steroids[7] and chiral natural products.[8]

Synthesis of salts and esters of optically active glyceric acids has been accomplished by oxidation of D-mannitol or intermediates derived from ascorbic acid.[9] They have also been obtained by oxidation of the corresponding alcohols and aldehydes.[7,10] Synthesis and properties have recently been reviewed for (*R*)- and (*S*)-2,3-*O*-isopropylideneglyceraldehyde[11] and also reported for the corresponding alcohols.[12] These compounds have found considerable use as intermediates in the synthesis of natural products and in the pharmaceutical chemistry. The optically active glyceric acids have also been prepared from D- or L-serine[13] or by enzymatic resolution of the racemic acid.[14]

As part of a program dealing with the synthesis of optically pure, biologically active compounds, we searched for inexpensive and easily accessible sources and precursors for both enantiomers of glyceric acid, preferably as the acetals or ketals, (*R*)-**1** and (*S*)-**1**.

Most of the previously reported syntheses normally involved long and tedious procedures, even where optically active precursors were used, resulting in low overall yields and partial racemization. Alternatives routes applying asymmetric synthesis and achiral precursors are, *e.g.*, the Sharpless epoxidation[15] or hydroxylation[16] procedures, which yield products of high e.e., often in the range 90–98%. However, even these high values may not satisfy the requirement for the synthesis of, *e.g.*, chiral pharmaceutical products. We therefore turned our attention to the chiral pool from which essentially optically pure synthons can be obtained. L-Ascorbic acid and D-isoascorbic acid are abundant, inexpensive and of high optical purity and became therefore our choice of starting materials for the preparation of (*R*)-**1** and (*S*)-**1**.

We now report a short and inexpensive procedure for the preparation of ketals and acetals of **2** and **3**, and their transformation into products (*S*)-**1** and (*R*)-**1**, respectively.

(*R*)-1 (*S*)-1

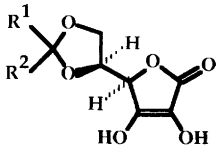
a: $R^1 = R^2 = CH_3$

b: R^1, R^2 = cyclohexyl

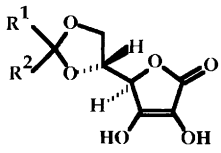
c: $R^1 = H$, R^2 = Ph

Fig. 1.

[†] To whom correspondence should be addressed.



2 (a-c)



3 (a-c)

Fig. 2.

Results and discussion

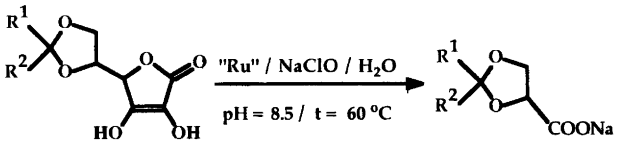
The synthesis of acetals and ketals **2a–c** and **3a–c**, were studied. 5,6-*O*-Isopropylidene-L-ascorbic acid, **2a**, was obtained by the acetyl chloride catalyzed reaction between L-ascorbic acid and acetone as described by Jung *et al.*[4] and Jackson *et al.*[17] The corresponding 5,6-*O*-isopropylidene-D-isoascorbic acid, **3a**, was prepared by the same procedure, but yields never exceeded 50%. For the preparation of the cyclohexylidene ketals **2b** and **3b**, the procedure was applied as described by Tanaka and Yamashita[18] and in a patent.[19] Benzylidene acetals **2c** and **3c** were obtained in good yields by the method described by Chu *et al.*[20]

5,6-O-Isopropylidene ketals of **2** *and* **3**. Owing to their synthetic versatility and stability the isopropylidene ketals were of special interest and therefore subjected to a closer investigation. As literature methods for preparation of **3a** gave the compound in low yields only, alternative synthetic methods were investigated. A more successful approach towards **3a** was reported by Abushanab *et al.*[21] An essentially quantitative yield was obtained in a $CuSO_4$ promoted reaction. However, large quantities of the copper salt were required, so the method has little practical value for large-scale preparations. Subsequent to our studies, a convenient high-yield procedure was reported[22] which was based on the reaction between D-isoascorbic acid and 2,2-dimethoxypropane in acetone.

We were, however, looking for still simpler and less expensive methods. We found a practical alternative for synthesis of **3a** involving the reaction of D-isoascorbic acid in refluxing acetone in the presence of an acidic ion-exchange resin (Amberlite IR-120). The desired product was obtained in an essentially quantitative yield after 2–3 h. The catalyst was removed by filtration, and evaporation of the solvent yielded the crude product which could be used in the subsequent reactions without further purification.

Compound **2a** was prepared in quantitative yield by the same procedure.

Ruthenium-catalyzed oxidation of **2** *and* **3**. The desired glyceric acid derivatives, **1**, were next obtained by oxidative degradation of **2** and **3**. To accomplish this a Ru-catalyzed procedure in water was used without addition of organic co-solvents. As stoichiometric oxidant, sodium metaperiodate, sodium bromate or sodium hypochlorite (household bleach) was used. Sodium hypochlorite was preferred owing to its very low price.



2 or 3 (a-c) **1 (a-c)**

Scheme 1.

In order to reduce acid- or base-catalyzed epimerization of the glyceric acid products, the pH was kept close to neutral during the reaction. At lower pH the preferred oxidation agent (NaClO) is less stable than at higher pH. As a compromise we found pH = 8.0 to be satisfactory. At this pH, the active Ru-species in the catalyzed oxidation was mainly perruthenate, RuO_4^-, and we believe to some extent, also ruthenium tetraoxide, RuO_4. At higher pH the ruthenate anion, RuO_4^{2-}, predominates.[2,3] We found that the desired transformation actually took place in a wide pH-range, between pH = 4 and 12. In general the reproducibility was very satisfactory between pH = 7 and 9. During the Ru-catalyzed reaction the reaction mixture became increasingly acidic. Continuous control and adjustment of pH was therefore necessary.

The conversion of **2** and **3** into **1** took place readily at room temperature. However, as the oxidation was exothermic, it was more convenient to allow the temperature to reach 50–60 °C. The temperature was controlled by varying the addition rate of the oxidizing agent and eventually by external cooling. The oxidant, preferably sodium hypochlorite, was used in only a slight excess, approx. 11 oxidation equivalents. The Ru-catalyst also functioned as an indicator to monitor the progress of the reaction. Thus, as soon as the reducing organic material was consumed, the reaction mixture switched from dark-brown to a light greenish-yellow color characteristic for perruthenate in the presence of some RuO_4. At this point the pH also stopped changing. The Ru-catalyst was then isolated as RuO_4 by extraction of the reaction mixture with small portions of CCl_4. This process could be expedited if the pH at this point was adjusted to 5. Addition of a few equivalents of methanol to the CCl_4 solution reduced RuO_4 to a dark precipitate of low-valent Ru-species which was isolated by filtration. This precipitate could be used again as a catalyst without any further purification. Other workers have reported similar approaches, *e.g.*, Emmons *et al.*[9] In their work a number of Ru catalysts were used, also 5% Ru/C, which we cannot recommend, however, as initially only the carbon support is oxidized to carbon dioxide. Nevertheless, virtually any Ru-compound can be used as catalyst. Thus, besides using recycled Ru-catalyst, we found metallic Ru to work very well. It is recommended that the catalyst be activated

with oxidant prior to addition of the organic substrates. Sodium ruthenate and perruthenate needed no initiation period.

The organic products were isolated as their sodium salts after concentration of the aqueous solutions and crystallization. The products were routinely isolated in high yields. The results are shown in Table 1. The optical purities of the isopropylidene compounds (*R*)-**1a** and (*S*)-**1a** were 98 and 99% respectively, based on their optical rotations. Literature values were available only for these compounds. The optical rotation was not measured for the benzylidene derivative, as NMR spectroscopy indicated this to be an approx. 1:1 mixture of diastereomers. Contrary to what has been pointed out by others,[24] the use of hypochlorite in this system did not result in formation of detectable amounts of chlorinated products.

Experimental

General. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX-100 NMR spectrometer, or on a JEOL JNM-EX400 FT NMR SYSTEM, using $CDCl_3$, MeOH-d_4 or D_2O as solvents and tetramethylsilane (TMS) as the internal standard. IR spectra were obtained on a NICOLET 20-SXC FT-IR spectrometer. Mass spectra were recorded on an AEI MS-902 spectrometer at 70 eV (IP) and 200°C inlet temperature. Optical rotations were measured on a PERKIN-ELMER 241 polarimeter. GLC measurements were performed on a VARIAN 3700 chromatograph equipped with a BP-5 capillary column (25 m) or a BP-1 capillary column (25 m). All melting points are uncorrected.

5,6-O-Isopropylidene-L-ascorbic acid, **2a** *and 5,6-O-isopropylidene-D-isoascorbic acid,* **3a**. *General procedure.* To a solution containing 4.0 g, 0.023 mol of either L-ascorbic acid $\{[\alpha]_D^{25} = +23.4°$ ($c = 1.0$, H_2O), (lit.[25] $[\alpha]_D^{20} = +24°)\}$ or D-isoascorbic acid $\{[\alpha]_D^{25} = -16.8°$ ($c = 2.0$, $H_2O)\}$, in 40 ml of acetone was added 1.0 g of an acidic ion-exchange resin (Amberlite IR-120) as catalyst and the mixture was refluxed for 2–3 h. The catalyst was removed by filtration and the solvent evaporated off under reduced pressure to give the isopropylidene acetals **2a** and **3a** in essentially quantitative yields. The crude products were used directly in the subsequent step without further purification. Spectroscopic data of the products were recorded after recrystallization from acetone–hexane mixtures, and were in all details equivalent to those of authentic samples.

2a. M.p. 219–220°C (lit.[4] 214–218°C) $\{[\alpha]_D^{25} = -25.2°$ ($c = 1.0$, $H_2O)\}$.

3a. M.p. 187–189°C $\{[\alpha]_D^{25} = +26.5°$ ($c = 1.0$, $H_2O)\}$.

Table 1.

Compound	Yield, %	$[\alpha]_D^{25}$	ee (%)
(*R*)-**1a**	91	+22.9° (c=2.0, H_2O) (lit.[9c] +23.5°)	98
(*S*)-**1a**	87	+23.4° (c=2.0, H_2O) (lit.[9c] −23.4°)	99
(*R*)-**1b**	86	+25.6° (c=3.0, H_2O)	
(*S*)-**1b**	87	−24.6° (c=3.0, H_2O)	
(*S*)-**1c**	71		

5,6-O-Cyclohexylidene-L-ascorbic acid, **2b**, *and 5,6-O-cyclohexylidene-D-isoascorbic acid,* **3b**. *General procedure.* These materials were prepared according to the procedure reported by Tanaka *et al.*[18] The crude products obtained after evaporation of the solvent were used directly in the subsequent oxidation step without further purification. Spectroscopic data of the products were recorded after recrystallization from acetone–hexane mixtures, and were in all details equivalent to those of authentic samples.

2b Yield: 57%. M.p. 183–186°C $\{[\alpha]_D^{25} = +12.7°$ ($c = 1.0$, acetone)$\}$.

3b Yield: 85%. M.p. 176–178°C (lit. 177–178.5°C) $\{[\alpha]_D^{25} = +17.8°$ ($c = 1.0$, acetone), (lit. 18.0°)$\}$ corresponding to ee better than 98%.

5,6-O-Benzylidene-L-ascorbic acid, **2c**. This compound was prepared using the procedure reported by Chu *et al.*[20] and was obtained in 28% yield. NMR spectroscopy indicated an approx. 1:1 diastereomeric mixture. The spectroscopic properties were in agreement with those reported in the literature.

Ruthenium-catalyzed oxidation of acetals and ketals of ascorbic acid, **2a–c**, *and isoascorbic acid,* **3a–c**. *General procedure.* To a solution containing 10 mmol of compounds **2** or **3** in 25 ml of water were added 15 mg of RuO_2-hydrate, (approx. 1 mol%) and the pH was adjusted to 8.0 with NaOH (2 M). To the stirred solution were then slowly added ca. 85 ml, 0.11 mol, of a ca. 10% (ca. 1.3 M) solution of sodium hypochlorite. The temperature increased to 55–60°C and was kept there by regulating the addition rate and, when necessary, by means of an ice–water bath. During the reaction the pH was monitored and kept constant at 8.0 by addition of 2 M sodium hydroxide solution. An automatic pH-controller was used for the pH adjustment. Usually, the reactions ceased after 40 to 60 min, as indicated by the appearance of a clear green–yellow color. At the same time pH became constant. The reaction mixture was then cooled to room temperature, and the Ru-catalyst extracted with five 5 ml portions of CCl_4. The aqueous phase was concentrated under reduced pressure and then extracted with 50 ml of refluxing methanol. Inorganic salts were removed by filtration, and upon cooling the desired crystalline products precipitated.

*(S)-Sodium 2,2-dimethyl-1,3-dioxolane-4-carboxylate, (S)-***1a**. *By oxidation of 5,6-O-isopropylidene-L-ascorbic acid, (***2a***).* Yield: 87%. IR (KBr): 2988, 1604, 1415, 1377, 1313, 1116, 1073, 961 cm^{-1}. ^1H NMR (100 MHz, D_2O): δ 1.46 (s, 3 H), 1.52 (s, 3 H), 3.75 (dd, J = 8.1 and 5.9 Hz, 1 H), 4.15 (dd, J = 6.4 and 8.1 Hz, 1 H), 4.52 (dd, J = 6.2 and 5.6, 1 H). ^{13}C NMR (25 MHz, D_2O): δ 25.5, 25.9, 68.1, 76.2, 111.6, 178.7. $[\alpha]_D^{25} = -23.4°$ (c = 2.0, H_2O), [lit.[9c] −23.7° (c = 2.0, H_2O)][9c] corresponding to an ee of better than 99%.

*(R)-Sodium 2,2-dimethyl-1,3-dioxolane-4-carboxylate, (R)-***1a**. *By oxidation of 5,6-O-isopropylidene-D-isoascorbic acid (***3a***).* Yield: 91%. The spectroscopic properties were identical with those of product (*S*)-**1a**. $[\alpha]_D^{25} = +22.9°$ (c = 2.0, H_2O), [lit.[9c] +23.5° (c = 2.0, H_2O)] corresponding to an ee of better than 98%.

*(S)-Sodium spiro[cyclohexane-1,2'-(1,3-dioxolane)]-4'-carboxylate (S)-***1b**. This product was prepared from the L-ascorbic acid ketal, **2b**. Yield: 87%. IR (KBr): 2937, 1616, 1449, 1419, 1372, 1145, 1099, 962, 939, 622 cm^{-1}. ^1H NMR (100 MHz, MeOH-d_4): δ 1.42–1.97 (m, 10 H), 3.75 (d, J = 7.9 Hz, 1 H), 4.07 (d, J = 7.9, 1 H), 4.54 (m, 1 H). ^{13}C NMR (25 MHz, MeOH-d_4): δ 25, 26, 28, 35, 36, 67, 74, 112, 171. $[\alpha]_D^{25} = -24.3°$ (c = 3.0, H_2O).

*(R)-Sodium spiro[cyclohexane-1,2'-(1,3-dioxolane)]-4'-carboxylate (R)-***1b**. This product was prepared from the D-isoascorbic acid ketal, **3b**. Yield: 86%. The spectroscopic properties were identical with those of the above product. $[\alpha]_D^{25} = +25.6°$ (c = 3.0, H_2O).

*(S)-Sodium 2-phenyl-1,3-dioxolane-4-carboxylate, (S)-***1c**. This product was prepared from the L-ascorbic acid ketal, **2c**. Yield: 71%. IR (KBr): 2933, 1598, 1454, 1337, 1298, 969, 935, 881, 847, 623 cm^{-1}. ^1H NMR (100 MHz, MeOH-d_4): δ 3.82 (dd, J = 8.1 and 6.1 Hz, 1 H), 4.08 (dd, J = 8.3 and 6.2 Hz, 1 H), 4.52 (m, 1 H), 5.67 (s, 1 H), 7.25 (m, 5 H). ^{13}C NMR (25 MHz, MeOH-d_4): δ 70, 74, 104, 129, 130, 172.

Acknowledgements. The authors are grateful to The Norwegian Research Council for financial support of this work.

References

1. Glochowski, C., Bischoff, T. E., Garst, M. E., Kaplan, L. J., Dietrich, S. W., Aswad, A. S., Gaffney, M. A., Aoki, K. R., Garcia, C. and Wheeler, L. A. *J. Med. Chem. 34* (1991) 392.
2. (a) Lok, C. M., Ward, J. P. and van Dorp, D. A. *Chem. Phys. Lipids 16* (1976) 115; (b) Bhatia, S. K., Hajdu, J. *J. Org. Chem. 53* (1988) 5034; (c) Hirth, H., Walther, W. *Helv. Chim. Acta. 68* (1985) 1863.
3. (a) Bouzoubaa, M., Leclerc, G., Rakhit, S. and Andermann, G. *J. Med. Chem. 28* (1985) 896; (b) Hamada, Y., Kawai, A., Matsui, T., Hara, O. and Shioiri, T. *Tetrahedron 46* (1990) 4823.
4. Jung, M. E. and Shaw, T. J. *J. Am. Chem. Soc. 102* (1980) 6304.
5. (a) Wei, C. C., Bernardo, S. D., Tengi, J. P., Borgese, J. and Weigele, M. *J. Org. Chem. 50* (1985) 3462; (b) Hubschwerlen, C. *Synthesis* (1986) 962.
6. Tanaka, A. and Yamashita, K. *Agric. Biol. Chem. 44* (1980) 199.
7. Burger, A., Hetru, C. and Luu, B. *Synthesis* (1989) 93.
8. Walkup, R. D. and Cunningham, R. T. *Tetrahedron Lett. 28* (1987) 4019.
9. (a) Emons, C. H. H., Kuster, B. M. F., Vekemans, J. A. J. M. and Sheldon, R. A. *Tetrahedron Asym. 2* (1991) 359; (b) Schäfer, H. Y. and Schneider, R. *Tetrahedron 47* (1991) 715; (c) Ruholl, H. and Schäfer, H. J. *Synthesis* (1988) 54.
10. (a) Eliel, E. and Banks, H. D. *J. Am. Chem. Soc. 94* (1972) 171; (b) *EP 0 413 401 A3*; Schwarz, K. H., Kleiner, K., Ludwig, R., Schrotter, E. and Schick, H. *Liebigs Ann. Chem.* (1991) 503; (c) Reichstein, T., Pedolin, A. and Grussner, A. *Helv. Chim. Acta 18* (1935) 598; (d) Dumont, R. and Pfandler, H. *Helv. Chim. Acta. 66* (1983) 814; (e) Iwadara, K. *Bull. Chem. Soc. Jpn. 14* (1939) 131.
11. Jurczak, J., Pikul, S. and Bauer, T. *Tetrahedron 42* (1986) 447.
12. (a) Bergelson, L. D., Ed. *Lipid Biochemical Prep.*, Elsevier, 1980; (b) Kanda, P. and Wells, M. A. *J. Lipid Res. 22* (1981) 879.
13. (a) Lok, C. M., Ward, D. A. and van Dorp, D. A. *Chem. Phys. Lipids 16* (1976) 115; (b) Mai, K. H. X. and Patil, G. *PCT/US85/00213* (1985).
14. Potie, M., der Eyken, Y. V., Vandewalle, M., Dewanckele, J. M. and Röper, H. *Tetrahedron Lett. 30* (1989) 5319.
15. (a) Sharpless, K.B., Tuddenham, D. and Walker, F. J. *J. Org. Chem. 47* (1982) 1373; (b) Behrens, C. H. and Sharpless, K. B. *Aldrichimica Acta 16* (1983) 67; (c) Pfenninger, A. *Synthesis* (1986) 89.
16. Lohray, B. B., Kalantar, T. H., Kim, B. M., Park, C. Y., Shibata, T., Wai, J. S. M. and Sharpless, K. B. *Tetrahedron Lett. 30* (1989) 2041.
17. Jackson, K. and Jones, J. *Can. J. Chem. 47* (1969) 2498.
18. Tanaka, A. and Yamashita, K. *Synthesis* (1987) 570.
19. Voeffray, R. *Eur. Pat. Appl. EP 325967.*
20. Chu, T. M. and Slaunwhite, W. R. Jr. *Steroids 12* (1968) 309.
21. Abushanab, E., Vemishetti, P., Leiby, R. W., Singh, H. K., Mikkilineni, A. B., Wu, D. C.-J., Saibaba, R. and Panzica, R. P. *J. Org. Chem. 53* (1988) 2598.
22. Le Merrer, Y., Graver-Pelletier, C., Dumas, J. and Depezay, J. C. *Tetrahedron Lett. 31* (1990) 1003.
23. (a) Lee, D. G., Congson, L. N., Spitzer, U. A. and Olson, M. E. *Can. J. Chem. 62* (1984) 1835; (b) Boeleijk, A. E. M. and Reedijk, J. *J. Mol. Cat. 89* (1994) 63.
24. Brænden, J. E. *Dicyclopentadiene Derivatives*, Ph.D. Thesis, NTH 1991, Trondheim, Norway.
25. Haworth, W. N., Hirst, E. L. and Zilwa, S. S. *J. Chem. Soc.* (1934) 1155.

Received September 5, 1994.