CONVENIENT NEW SYNTHESSES OF $R$-($\pm$)-5-BENZYLLOXYMETHYL-$5H$-FURAN-2-ONE- A BUILDING BLOCK EN ROUTE TO L-NUCLEOSIDES

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Abstract - $R$-($\pm$)-5-Benzylloxymethyl-$5H$-furan-2-one ($R$-(1)) was obtained from commercially available $R$-($\pm$)-2-benzyloxymethyl oxirane ($R$-(2)) in two and three steps, respectively. Key steps are a) the nucleophilic ring opening of the oxirane moiety with dianions derived from either PhSeCH$_2$CO$_2$H or PhSCH$_2$CO$_2$H; b) oxidation to the corresponding 1-oxides and c) concomitant or thermally induced $\text{syn}$-elimination. $R$-(1) was obtained with $\geq 97\%$ ee and $\geq 95\%$ ee, respectively.

We recently reported a novel synthesis of 2-deoxy-L-ribose and building blocks derived thereof using the enantiomerically pure title compound ($R$-(1)) as starting material (Figure 1).$^1$ Although $R$-(1) can be obtained with an enantiomeric excess $\geq 98\%$ ee starting from L-ascorbic acid (29% overall yield), this synthetic methodology requires six steps.$^{1,2}$ With non-natural, L-configurated nucleosides as ultimate synthetic targets we were prompted to explore alternative and more efficient routes towards $R$-(1). It has been reported that $\alpha,\beta$-butenolides can be obtained starting from epoxides involving nucleophilic ring opening reactions of the oxirane system employing either phenylselanylacetic acid (PhSeCH$_2$CO$_2$H)$^3$ or phenylsulfanyl acetic acid (PhSCH$_2$CO$_2$H)$^4$, both of which are easily prepared in one step reactions.$^5$

![Figure 1](attachment:image.png)

**Figure 1**

- $R$-(1) 
- 2-deoxy-L-ribose
Using commercially available\textsuperscript{6} \(R\)-(-)-2-benzyloxymethyl oxirane (\(R\)-(2)) (\(\geq 98\%\) ee), we were indeed able to obtain \(R\)-(1) in two steps with an overall yield of 61\% when PhSeCH\(_2\)CO\(_2\)H was used, and in three steps with an overall yield of 35\% when PhSCH\(_2\)CO\(_2\)H was used. (Scheme 1).

Thus, nucleophilic ring opening of \(R\)-(2) with the dilithium salt of PhSeCH\(_2\)CO\(_2\)H followed by heating with AcOH overnight led to 5-benzyloxymethyl-3-phenylselanyl-dihydrofuran-2-one (3) in 72\% yield as mixture of diastereoisomers. Oxidation of the phenylselanyl function with NaIO\(_4\) was accomplished with concomitant formal \textit{syn}-elimination of benzeneselenenic acid (PhSeOH) leading directly and in 85\% yield to \(R\)-(1).

Alternatively, ring opening of \(R\)-(2) with the dilithium salt of PhSCH\(_2\)CO\(_2\)H led to 5-benzyloxymethyl-3-phenylsulfanyl-dihydrofuran-2-one (4) in 70\% yield again as mixture of diastereoisomers. Oxidation with NaIO\(_4\) in this case produced a diastereoisomeric mixture of the corresponding sulfoxides (5), which after work up and without purification were refluxed in toluene for 30 min, leading to \(R\)-(1) in 50\% yield (two steps starting from 4).

For the determination of the optical purity \(R\)-(1) was converted into \(R\)-(6) (Scheme 2) for improved separation\textsuperscript{7} by HPLC on a chiral support: column LiChoCART 250-4 (\(S, S\))-Whelk-5\\textmu m eluent \(n\)-hexane/isopropanol (97/3 \(v/v\)), flow rate 1 mL/min, detector UV 254 nm. \(R\)-(1) showed an enantiomeric purity of \(\geq 97\%\) ee when the procedure with PhSeCH\(_2\)CO\(_2\)H was used and \(\geq 95\%\) ee in the case of PhSCH\(_2\)CO\(_2\)H (Figure 2).
In summary, the essential building block $R$-(1) for 2-deoxy-L-ribose and L-nucleosides derived thereof can now be obtained quickly and efficiently by using the dilithium salt of either PhSeCH$_2$CO$_2$H or PhSCH$_2$CO$_2$H for the required ring opening reactions. While the use of PhSeCH$_2$CO$_2$H allows the production of $R$-(1) in only two steps with an overall yield of 61%, the use of PhSCH$_2$CO$_2$H (three steps, 35% yield) may be of advantage from an ecological point of view avoiding the employment of toxic selenium compounds. Both reactions can be scaled up to 5g without any difficulties.
EXPERIMENTAL

General Methods
Reagents were obtained from commercial suppliers and used without further purification. Compounds containing selenium are toxic by inhalation and if swallowed. All glassware and syringes were dried in an oven overnight, allowed to cool and stored under a positive pressure of argon before use. The solvents were dried before use as follows: THF distilled from potassium/benzophenone ketyl, DMF over CaO. NH₄NO₃ was dried overnight in a desiccator containing P₂O₅ (CAUTION: NH₄NO₃ is a potential explosive, handle with care, do NOT heat). Merck silica gel 60 (70-230 mesh) was used for column chromatography. TLC was run on SiO₂ 60F₂₅₄ (Merck), detection with UV and Vanillin/H₂SO₄ reagent. ¹H and ¹³C NMR spectra were measured at 400 MHz (Bruker). Chemical shifts are reported relative to CDCl₃ at 7.27 ppm. IR spectra were measured with a Perkin-Elmer Infrared Spectrophotometer 1420; the optically rotations with a Perkin-Elmer 241 (chloroform stabilized with 1% ethanol). MS spectra were measured with a Varian MAT 311 A (EI, 70 eV). The melting points are uncorrected.

General procedure for the syntheses of 3 and 4
To a stirred solution of diisopropylamine (2.0 mL, 14.36 mmol) in 15 mL of dry THF, at -78 °C under argon, butyllithium 1.6 M in hexane (9.0 mL, 14.36 mmol) was added dropwise and the mixture stirred for 15 min. Then 6.52 mmol (1 eq) of the corresponding acid (PhSeCH₂CO₂H or PhSCH₂CO₂H) in 5 mL of dry THF was added dropwise and after stirring for 1 h at -78 °C, R-(-)-2-benzyloxymethyl oxirane R-(2) (1 mL, 6.52 mmol) dissolved in 10 mL of dry THF was added. The mixture was stirred for 3 h at rt. Then at 0 °C 5 mL of AcOH were added and the resulting solution was refluxed under argon overnight. The mixture was diluted with 20 mL of Et₂O, washed with a saturated aqueous solution of NaHCO₃ (3x10 mL), brine and dried over anhydrous Na₂SO₄. The solvents were removed under reduced pressure and the crude product containing the mixture of diastereoisomers (3) or (4) filtered over silica gel using as eluent n-hexane/AcOEt (2/1 v/v) (Rf 0.3 and 0.4). 1.7 g (72%) of 3 were isolated when PhSeCH₂CO₂H was used or 1.4 g (70%) of 4 when PhSCH₂CO₂H was used (in both cases no effort was made to separate the diastereoisomers).

R-(-)-5-Benzyloxymethyl-5H-furan-2-one (R-(1)) from 3
3 (1.7 g, 4.70 mmol) was dissolved in 50 mL of H₂O/MeOH (1/1 v/v) and NaIO₄ (3.0 g, 14.10 mmol) was added at rt. After 1 h the reaction mixture was diluted with AcOEt (50 mL), washed successively with H₂O (20 mL), an aqueous solution of Na₂S₂O₃ (20 mL), brine and then dried over
Purification by chromatography on silica gel using as eluent Et₂O/n-hexane (2/1 v/v) afforded \((\text{R})-1\) in 85% yield (816 mg). Oil, \(R_f\): 0.28 Et₂O/n-hexane (2/1 v/v). \([\alpha]_{20}^D = +136^\circ\) (c 1.37, CHCl₃); ee ≥ 97%; ¹H NMR (CDCl₃) \(\delta\) 7.50 (dd, \(J=5.67\) Hz, \(J=1.39\) Hz, CO-CH=CH), 7.38-7.27 (m, 5H, Ph), 6.17 (dd, \(J=5.67\) Hz, \(J=1.96\) Hz, CO-CH=CH), 5.17 (m, CH=CH-CH=CH), 4.58 (s, PhCH₃), 3.74 (dd, \(J=10.35\) Hz, \(J=5.19\) Hz, PhCH₂OCH₃), 3.69 (dd, \(J=10.50\) Hz, \(J=5.05\) Hz, PhCH₂OCH₃). ¹³C NMR (CDCl₃) \(\delta\) 172.63 (C=O), 153.80 (CO-CH=CH), 137.27 (C₆H₄), 128.46 (C₆H₄), 127.93 (C₆H₄), 127.67 (C₆H₄), 122.55 (CO-CH=CH), 82.13 (CH=CH-CH=CH), 73.74 (PhCH₂), 69.47 (PhCH₂OCH₂). IR (film, cm⁻¹) 3070 (=C-H), 3045 (=C-Harom), 3015 (=C-Harom), 2890 (-CH₂-asym), 2845 (-CH₂-sym), 1750 (C=O), 1590 (C=C). MS m/z 204 (M⁺), 161, 151 (C₉H₁₀O₂⁺), 126, 108 (PhCH₂O⁺), 98 [(M+1) -PhCH₂O]⁺, 91 (tropylium ion), 82 (C₅H₅O⁺), 77 (Ph⁺), 62, 49, 44 (100%), 36.

\(R\)-(+)\-5-Benzylxoyethyl-5H-furan-2-one \((R\)-(1)) from 4

4 (1.4 g, 4.56 mmol) was dissolved in 50 mL of H₂O/MeOH (1/1 v/v) and NaIO₄ (2.9 g, 13.68 mmol) was added at rt. After stirring overnight, the reaction mixture was diluted with AcOEt (50 mL), washed successively with H₂O (20 mL), an aqueous solution of Na₂S₂O₃ (20 mL), brine and then dried over anhydrous Na₂SO₄. The solvents were removed under vacuum, the crude product dissolved in toluene (10 mL) and refluxed for 30 min. Evaporation of toluene followed by column chromatography purification using as eluent Et₂O/n-hexane (2/1 v/v) afforded \(R\)-(1) in 50% yield (465 mg). ee ≥ 95%, \([\alpha]_{20}^D = +134^\circ\) (c 1.28, CHCl₃). All the spectroscopic data were identical to those of \(R\)-(1) synthesized from 3.

\(R\)-(+)\-5-(tert-Butyldiphenylsilanyloxyethylmethyl)-5H-furan-2-one \((R\)-(6))

To a solution of \(R\)-(1) (80 mg, 0.39 mmol) in 10 mL of AcOEt, 10 mg of 10% Pd/C were added and the suspension was degassed for 5 min under reduced pressure while stirring. Then, the flask was connected to a source of H₂ and stirred for 1 h at rt. The catalyst was removed by filtration and the solvent removed under vacuum. Quantitative deprotection was ascertained by NMR analysis. The crude product was dissolved in 2 mL of dry DMF and under argon at rt NH₄NO₃ (94 mg, 1.17 mmol) and tert-butyldiphenylsilanylsilyl chloride (130 µL, 0.51 mmol) were added. After 24 h water (10 mL) was added and the mixture was extracted with Et₂O (2x10 mL). The organic layer was dried over anhydrous Na₂SO₄ and the solvent evaporated under reduced pressure. The crude product was purified by chromatography on silica gel using as eluent n-hexane/AcOEt (4/1 v/v). Obtained were 124 mg (90%) white crystals, mp 79-80 °C. \(R_f\): 0.37 n-hexane/AcOEt (4/1 v/v). \([\alpha]_{20}^D = +76^\circ\) (c 1.30, CHCl₃).
CHCl₃) from 3. [α]²⁰°D = +75° (c 1.42, CHCl₃) from 4. ¹H NMR (CDCl₃) δ 7.62-7.36 (complex, 2Ph + CO-CH=CH), 6.15 (dd, J=5.77 Hz, J=1.76 Hz, CO-CH=CH), 5.04 (m, CH=CH-CH), 3.93 (dd, J=10.68 Hz, J=4.57 Hz, PhCH₂OCH₃), 3.88 (dd, J=11.18 Hz, J=5.08 Hz, PhCH₂OCH₃), 1.02 [s, C(CH₃)₃]. ¹³C NMR (CDCl₃) δ 172.82 (C=O), 153.94 (CO-CH=CH), 135.58 (Cₘ), 132.79 (Cₘ), 130.00 (Cₘ), 127.86 (Cₘ), 122.71 (CO-CH=CH), 83.19 (CH=CH-CH), 63.43 (PhCH₂OCH₂), 26.70 [C(CH₃)₃], 19.21 [C(CH₃)₃]. IR (KBr, cm⁻¹) 3090 (=C-H), 3050 (=C-H arom), 2880 (-CH₂-), 1740 (C=O), 1595 (C=C). MS m/z 295 (M⁺ - t-Bu), 199 (100%, Ph₂SiO⁺), 181, 135, 77 (Ph⁺), 55.

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REFERENCES

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7. See our method for the determination of the optical purity of R-(1) in ref. 1.