HETEROCYCLES, Vol. 55, No. 7, 2001, pp. 1323 - 1328, Received, 26th March, 2001

CONVENIENT NEW SYNTHESES OF *R*-(+)-5-BENZYLOXYMETHYL-5*H*-FURAN-2-ONE- A BUILDING BLOCK *EN ROUTE* TO L-NUCLEOSIDES

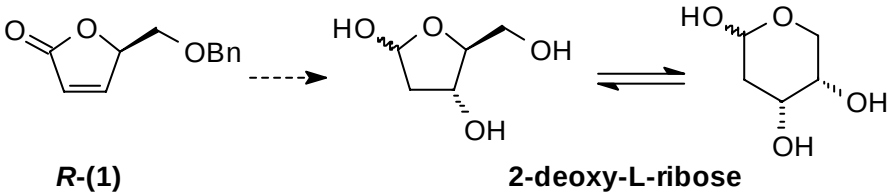
Fabio Fazio, Davis Maliakal, and Manfred P. Schneider*

FB 9-Bergische Universität-GH-Wuppertal, D-42097 Wuppertal, Germany

Abstract - *R*-(+)-5-Benzyloxymethyl-5*H*-furan-2-one (*R*-(**1**)) was obtained from commercially available *R*-(-)-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 $PhSeCH_2CO_2H$ or $PhSCH_2CO_2H$; b) oxidation to the corresponding 1-oxides and c) concomitant or thermally induced *syn*-elimination. *R*-(**1**) was obtained with ≥97% ee and ≥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 ≥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 α,β-butenolides can be obtained starting from epoxides involving nucleophilic ring opening reactions of the oxirane system employing either phenylselanylacetic acid ($PhSeCH_2CO_2H$)[3] or phenylsulfanyl acetic acid ($PhSCH_2CO_2H$)[4], both of which are easily prepared in one step reactions.[5]

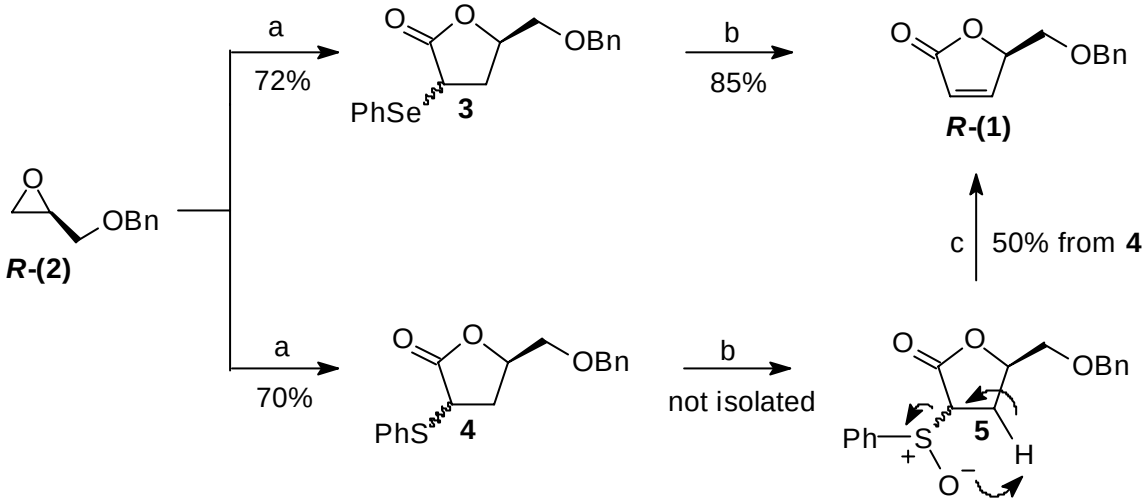
Figure 1



***R*-(1)** **2-deoxy-L-ribose**

Using commercially available[6] *R*-(-)-2-benzyloxymethyl oxirane (*R*-(**2**)) (≥98% ee), we were indeed able to obtain *R*-(**1**) in two steps with an overall yield of 61% when $PhSeCH_2CO_2H$ was used, and in three steps with an overall yield of 35% when $PhSCH_2CO_2H$ was used. (Scheme 1).

Scheme 1



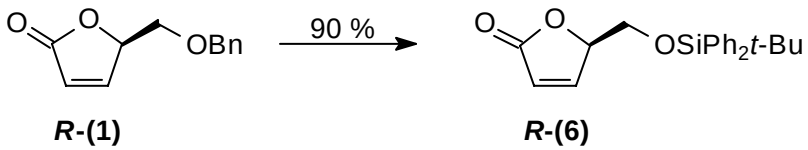
a) 1. $PhXCH_2CO_2H$ (X=Se or S), LDA, THF, -78 °C – rt, 3 h; 2. AcOH, reflux, overnight. b) $NaIO_4$, $MeOH/H_2O$, rt, 1 h from **3**, overnight from **4**. c) toluene, reflux, 30 min.

Thus, nucleophilic ring opening of *R*-(**2**) with the dilithium salt of $PhSeCH_2CO_2H$ 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 *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 $PhSCH_2CO_2H$ 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[7] by HPLC on a chiral support: column LiChoCART 250-4 (*S*,*S*)-Whelk-5µm eluent *n*-hexane/isopropanol (97/3 *v/v*), flow rate 1 mL/min, detector UV 254 nm. *R*-(**1**) showed an enantiomeric purity of ≥97% ee when the procedure with $PhSeCH_2CO_2H$ was used and ≥95% ee in the case of $PhSCH_2CO_2H$ (Figure 2).

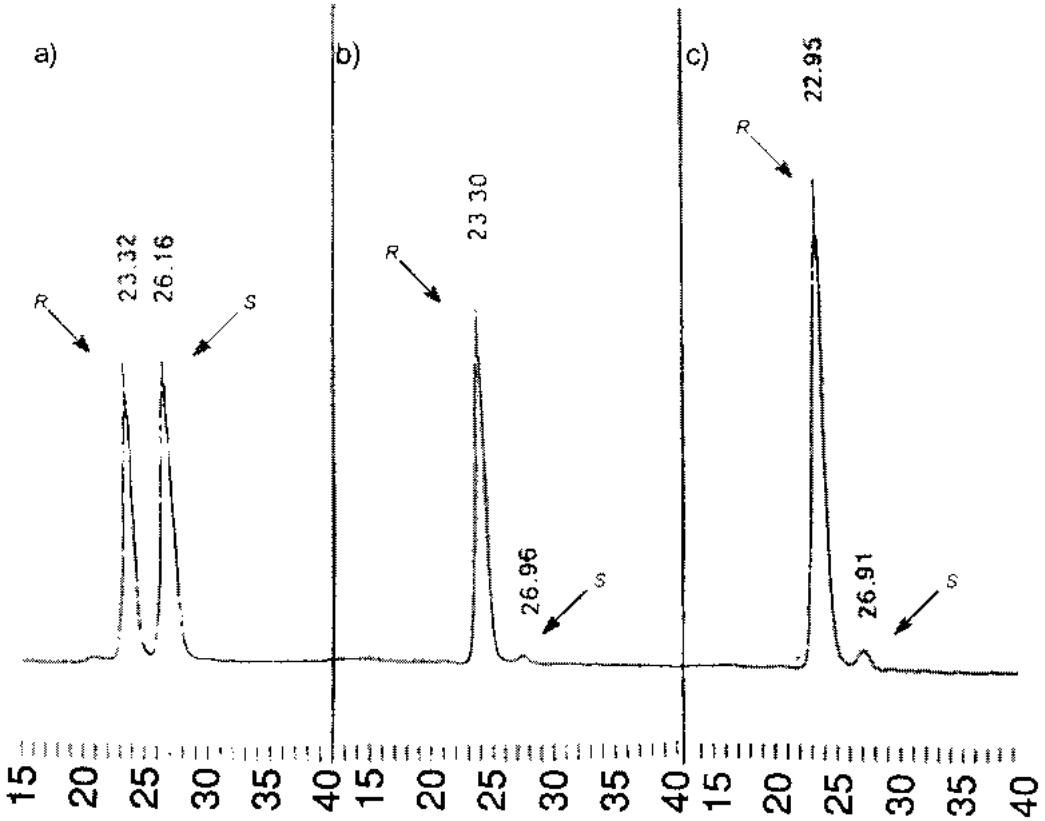
Scheme 2



***R*-(1)** **R-(6)**

1. Pd/C 10%, AcOEt, rt, 1 h; 2. *t*-$BuPh_2SiCl$, NH_4NO_3, DMF, rt, 24 h.

Figure 2



HPLC analysis. Column LiChoCART 250-4 (*S*,*S*)-Whelk-5µm eluent *n*-hexane/isopropanol (97/3 *v/v*), flow rate 1 mL/min, detector UV 254 nm. a) racemic mixture of **6**; b) *R*-(**6**) from $PhSeCH_2CO_2H$, ee ≥97%; c) *R*-(**6**) from $PhSCH_2CO_2H$, ee ≥95%.

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 $PhSeCH_2CO_2H$ or $PhSCH_2CO_2H$ for the required ring opening reactions. While the use of $PhSeCH_2CO_2H$ allows the production of *R*-(**1**) in only two steps with an overall yield of 61%, the use of $PhSCH_2CO_2H$ (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. NH_4NO_3 was dried overnight in a desiccator containing P_2O_5 (**CAUTION**: NH_4NO_3 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 SiO_2 $60F_{254}$ (Merck), detection with UV and Vanillin/H_2SO_4 reagent. ^1H and ^{13}C NMR spectra were measured at 400 MHz (Bruker). Chemical shifts are reported relative to $CDCl_3$ 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 ($PhSeCH_2CO_2H$ or $PhSCH_2CO_2H$) 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 Et_2O, washed with a saturated aqueous solution of $NaHCO_3$ (3x10 mL), brine and dried over anhydrous Na_2SO_4. 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*) (R_f 0.3 and 0.4). 1.7 g (72%) of **3** were isolated when $PhSeCH_2CO_2H$ was used or 1.4 g (70%) of **4** when $PhSCH_2CO_2H$ was used (in both cases no effort was made to separate the diastereoisomers).

R-(+)-5-Benzyloxymethyl-5*H*-furan-2-one (*R*-(1)) *from 3*

3 (1.7 g, 4.70 mmol) was dissolved in 50 mL of H_2O/MeOH (1/1 *v/v*) and $NaIO_4$ (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 H_2O (20 mL), an aqueous solution of $Na_2S_2O_3$ (20 mL), brine and then dried over

anhydrous Na_2SO_4. Purification by chromatography on silica gel using as eluent Et_2O/*n*-hexane (2/1 *v/v*) afforded (*R*)-**1** in 85% yield (816 mg). Oil, R_f: 0.28 Et_2O/*n*-hexane (2/1 *v/v*). $[\alpha]_D^{20}$ = +136° (*c* 1.37, $CHCl_3$); ee ≥97%; ^{1}H NMR ($CDCl_3$) δ 7.50 (dd, *J*=5.67 Hz, *J*=1.39 Hz, CO-CH=C<u>H</u>), 7.38-7.27 (m, 5H, Ph), 6.17 (dd, *J*=5.67 Hz, *J*=1.96 Hz, CO-C<u>H</u>=CH), 5.17 (m, CH=CH-C<u>H</u>), 4.58 (s, PhC<u>H</u>$_2$), 3.74 (dd, *J*=10.35 Hz, *J*=5.19 Hz, $PhCH_2OC\underline{H}_a$), 3.69 (dd, *J*=10.50 Hz, *J*=5.05 Hz, $PhCH_2OC\underline{H}_b$). ^{13}C NMR ($CDCl_3$) δ 172.63 (C=O), 153.80 (CO-CH=<u>C</u>H), 137.27 ($C_{ar.}$), 128.46 ($C_{ar.}$), 127.93 ($C_{ar.}$), 127.67 ($C_{ar.}$), 122.55 (CO-<u>C</u>H=CH), 82.13 (CH=CH-<u>C</u>H), 73.74 (Ph<u>C</u>H$_2$), 69.47 ($PhCH_2O\underline{C}H_2$). IR (film, cm^{-1}) 3070 (=C-H), 3045 (=C-H_{arom}), 3015 (=C-H_{arom}), 2890 (-CH_2-$_{asym}$), 2845 (-CH_2-$_{sym}$), 1750 (C=O), 1590 (C=C). MS *m/z* 204 (M^+), 161, 151 ($C_9H_{10}O_2^+$), 126, 108 ($PhCH_2O^+$), 98 [(M+1) -$PhCH_2O$]$^+$, 91 (tropyllium ion), 82 ($C_5H_5O^+$), 77 (Ph^+), 62, 49, 44 (100%), 36.

R*-(+)-5-Benzyloxymethyl-5*H*-furan-2-one (*R*-(1)) *from 4

4 (1.4 g, 4.56 mmol) was dissolved in 50 mL of H_2O/MeOH (1/1 *v/v*) and $NaIO_4$ (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 H_2O (20 mL), an aqueous solution of $Na_2S_2O_3$ (20 mL), brine and then dried over anhydrous Na_2SO_4. The sovents 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 Et_2O/*n*-hexane (2/1 *v/v*) afforded *R*-(**1**) in 50% yield (465 mg). ee ≥95%, $[\alpha]_D^{20}$ = +134° (*c* 1.28, $CHCl_3$). All the spectroscopic data were identical to those of *R*-(**1**) synthesized from **3**.

***R*-(+)-5-(*tert*-Butyldiphenylsilanyloxymethyl)-5*H*-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 H_2 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 NH_4NO_3 (94 mg, 1.17 mmol) and *tert*-butyldiphenylsilyl chloride (130 μL, 0.51 mmol) were added. After 24 h water (10 mL) was added and the mixture was extracted with Et_2O (2x10 mL). The organic layer was dried over anhydrous Na_2SO_4 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*). $[\alpha]_D^{20}$ = +76° (*c* 1.30,

$CHCl_3$) from **3**. $[\alpha]_D^{20}$ = +75° (*c* 1.42, $CHCl_3$) from **4**. ^{1}H NMR ($CDCl_3$) δ 7.62-7.36 (complex, 2Ph + CO-CH=C<u>H</u>), 6.15 (dd, *J*=5.77 Hz, *J*=1.76 Hz, CO-C<u>H</u>=CH), 5.04 (m, CH=CH-C<u>H</u>), 3.93 (dd, *J*=10.68 Hz, *J*=4.57 Hz, $PhCH_2OC\underline{H}_a$), 3.88 (dd, *J*=11.18 Hz, *J*=5.08 Hz, $PhCH_2OC\underline{H}_b$), 1.02 [s, $C(C\underline{H}_3)_3$]. ^{13}C NMR ($CDCl_3$) δ 172.82 (C=O), 153.94 (CO-CH=<u>C</u>H), 135.58 ($C_{ar.}$), 132.79 ($C_{ar.}$), 130.00 ($C_{ar.}$), 127.86 ($C_{ar.}$), 122.71 (CO-<u>C</u>H=CH), 83.19 (CH=CH-<u>C</u>H), 63.43 ($PhCH_2O\underline{C}H_2$), 26.70 [$C(\underline{C}H_3)_3$], 19.21 [$\underline{C}(CH_3)_3$]. IR (KBr, cm^{-1}) 3090 (=C-H), 3050 (=C-H_{arom}), 2880 (-CH_2-), 1740 (C=O), 1595 (C=C). MS *m/z* 295 (M^+ - *t*-Bu), 199 (100%, Ph_2SiO^+), 181, 135, 77 (Ph^+), 55.

ACKNOWLEDGMENT

We are grateful to DAISO CO., LTD. for a generous gift of *R*-(-)-2-benzyloxymethyl oxirane *R*-(**2**).

REFERENCES

1. F. Fazio and M. P. Schneider, *Tetrahedron: Asymmetry*, 2000, **11**, 1869.
2. C. Hubschwerlen, *Synthesis*, 1986, 962; B. Häfele and V. Jäger, *Liebigs Ann. Chem.* 1987, 85.
3. S. Hanessian, S. Sahoo, P. Saumya, and M. Botta, *Tetrahedron Lett.*, 1987, **28**, 1147; S. Hanessian, P. J. Hodges, P. J. Murray, and S .P. Sahoo, *J. Chem. Soc., Chem. Commun.*, 1986, 754; M. Figueredo, J. Font, and A. Virgili, *Tetrahedron*, 1987, **43**, 1881; K. Tomioka, F. Sato, and K. Koga, *Heterocycles*, 1982, **17**, 311; S. Hanessian, N. G. Cooke, B. De Hoff, and Y. Sakito, *J. Am. Chem. Soc.*, 1990, **112**, 5276.
4. S. Hanessian, P. J. Murray, and S. P. Sahoo, *Tetrahedron Lett.*, 1985, **26**, 5623; S. Hanessian and P. J. Murray, *Can J. Chem.*, 1986, **64**, 2231; J. Nokami, T. Ono, Y. Kajitani, and S. Wakabayashi, *Chem. Lett.*, 1984, 707; K. Akiba, Y. Takasu, and M. Wada, *Tetrahedron Lett.*, 1985, **26**, 2463.
5. H. J. Reich, F. Chow, and S. K. Shah, *J. Am. Chem. Soc.*, 1979, **101**, 6638; D. G. Lee and T. Chen, *J. Org. Chem.*, 1991, **56**, 5346.
6. DAISO CO., LTD. 1-10-8, Edobori, Nishi-ku, Osaka, Japan 550.
7. See our method for the determination of the optical purity of *R*-(**1**) in ref. 1.