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Practical synthesis of optically pure 3,4-epoxy-5-methyldihydro-2(3*H*)-furanones from D-xylose by regio- and stereo-selective functionalization*

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ABSTRACT

The known 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose was converted into its 3-*p*-nitrobenzoate (**13a**) and 3-methanesulfonate (**13b**). (−)-(3*S*,4*S*,5*R*)-3,4-Epoxy-5-methyldihydro-2(3*H*)-furanone [(−)-**8**] was synthesized from **13a** in 5 steps by conversion of **13a** into its methyl glycoside, 3-*O*-mesylation, glucosidic cleavage with CF_3CO_2H, epoxide formation with sodium methoxide and PCC-oxidation. (+)-(3*R*,4*R*,5*R*)-3,4-Epoxy-5-methyldihydro-2(3*H*)-furanone [(+)-**9**] was prepared from **13b** in 3 steps by deacetonation with CF_3CO_2H, epoxide formation with sodium methoxide, and PCC oxidation. These epoxides may be useful intermediates for the total synthesis of natural products of the α-alkyl-β-hydroxy-γ-methylbutyrolactone type (**1**).

INTRODUCTION

The aim of this research was to develop the "chiral-pool" methodology[1,2] for preparative, stereoselective synthesis of epoxides (−)-**8** and (+)-**9**, starting from carbohydrates. In the past few years, compounds **2**–**7** have been isolated from various biological sources[3–5].

We envisaged the synthesis of these compounds *via* a chiral synthon approach as a potential general method for the synthesis of compounds of type **1**. We considered that the most convenient method was to set out from such epoxide synthons as (−)-**8** and (+)-**9**.

These epoxides would permit introduction of the required stereochemistry at C-2 and C-3, by regio- and stereo-controlled epoxide ring-opening. Ortuno and coworkers[6] described the synthesis of (+)-**9** and (−)-**9** and their reaction with cuprates. Compound (−)-**9** reacted with cuprates stereo- and regio-selectively to yield (−)-blastomycinone (**6**).

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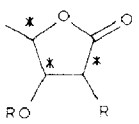

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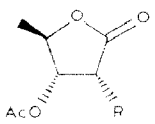

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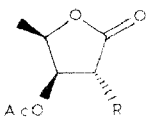
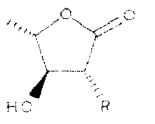
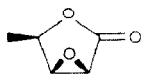
3 R = $-(CH_2)_{15}CH_3$



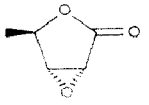
4 R = $-(CH_2)_{13}CH_3$
5 R = $-(CH_2)_{15}CH_3$



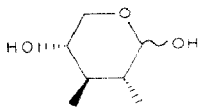
6 R = $-(CH_2)_{13}CH_3$
7 R = $-(CH_2)_{10}CH{=}CH_2$



(−)-8



(+)-9

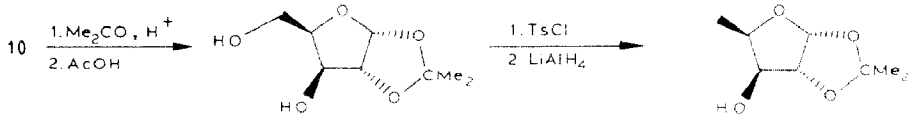


10

D-Xylose (**10**) is a cheap, optically pure starting material for the synthesis of (−)-**8** and (+)-**9**. The corresponding enantiomers should be obtainable from L-arabinose. Other authors have attempted to synthesize this class of natural products by different approaches[6,7], starting from D-ribonolactone, (*S*)-lactic acid, glutamic acid, or D-threaric acid. The route described herein offers some advantages, because of its generality, facility, and stereospecificity.

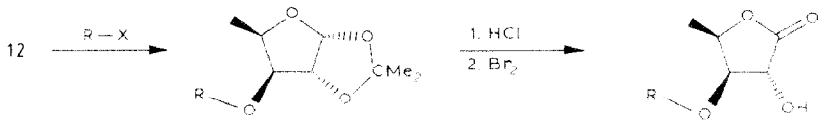
RESULTS AND DISCUSSION

1,2-*O*-Isopropylidene-α-D-xylofuranose (**11**), prepared according to a literature procedure[8] from D-xylose (**10**), was tosylated with *p*-toluenesulfonyl chloride in triethylamine (81% total, 68% monotosylated, 13% ditosylated[9]).



11 12

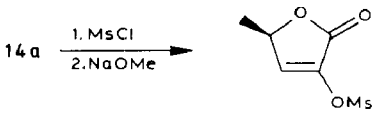
Deoxygenation at C-5 was achieved in 84% yield using lithium aliminium hydride, giving compound **12**. Starting from **12**, (−)-**8** could be synthesized by the general method of Pougny and Sinaÿ[10]. The synthesis was modified to avoid the use of large quantities of silver salts. After esterification of **12** with *p*-nitrobenzoyl chloride (90% yield), a one-pot procedure involving deprotection and subsequent bromine oxidation gave the 2-hydroxylactone **14a** in 55% yield.



13 14

a, R = *p*-$NO_2C_6H_4CO$ b, R = Ms a, R = *p*-$NO_2C_6H_4CO$ b, R = Ms

This reaction, which has been described for similar compounds[11], proved both useful and general. Deprotection and oxidation occurred only at C-1. Application of this method to compound **13b** led to **14b** in 65% yield. Subsequent mesylation of **14a** occurred smoothly in 85% yield. The epoxide formation by treatment with sodium methoxide failed; we obtained only the β-eliminated product **15**, in 61% yield. Such β-elimination processes have been described for related lactones by other authors[7,12].



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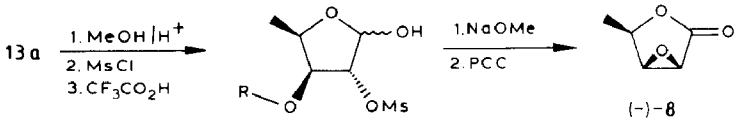
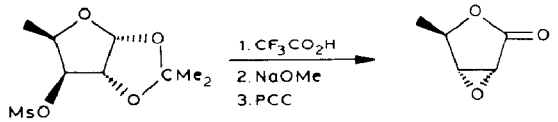
Synthesis of (−)-**8** was finally achieved as shown in the following scheme:



16

The methyl glycoside, obtained from **13a** in 82% yield, was mesylated followed by treatment with trifluoroacetic acid to give compound **16** in good (56%) overall yield. Treatment of **16** with 6 equivs. of sodium methoxide gave the desired epoxide in excellent (88%) yield, which underwent oxidation by using PCC (pyridinium chlorochromate). The best conditions for this reaction required freshly prepared PCC–acetate buffer, and the presence of molecular sieves. Under these conditions, (−)-**8** was obtained in 60% yield. Preparation of the stereoisomeric lactone (+)-**9** succeeded by a similar route.



13b

The 1,2-position underwent deprotection by treatment with 97% trifluoroacetic acid, and the formation of the epoxide was achieved in 60% yield. Oxidation under similar conditions as already described gave the epoxylactone (+)-**9** in 60% yield.

EXPERIMENTAL

1,2-O-Isopropylidene-5-deoxy-α-D-xylofuranose (**12**). — To 0.450 g (11.9 mmol) of $LiAlH_4$ in 35 ml diethyl ether was added 2.104 g (6.109 mmol) of 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose[9] during 5 min. After 3 h of gentle reflux, 1 mL of ice-cooled water was added dropwise very carefully during 15 min. After

evolution of hydrogen stopped, 15 mL of 10% H_2SO_4 was added. Separation and extraction with three 35 mL portions of diethyl ether, washing with 30 mL of brine, and drying (Na_2SO_4) gave 0.896 g (84.1%) of **12** as a colorless oil, which crystallized spontaneous in white needles, m.p. 66–67 °, $[\alpha]_D^{20} = -20.7°$ (*c* 1.9, $CHCl_3$). ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 1.308 (d, 3 H, *J* 6.8 Hz, 1.316 (s, 3 H), 1.502 (s, 3 H), 1.65 (s, 1 H), 3.997 (s, 1 H), 4.322 (qd, 1 H, J_q 2.4, J_q 6.5 Hz), 4.527 (d, 1 H *J* 3.7 Hz), and 5.892 (d, 1 H, *J* 3.7 Hz); ν_{max}^{KBr} 3400, 2980–2880 cm^{-1}.

Anal. Calc. for $C_9H_{14}O_4$ (174.20): C, 55.16; H, 8.10. Found: C, 54.94; H, 8.00.

5-Deoxy-1,2-O-isopropylidene-3-O-p-nitrobenzoyl-α-D-xylofuranose (**13a**). — A mixture of compound **12** (1.085 g, 6.22 mmol) and 1.387 g (7.47 mmol) of *p*-nitrobenzoyl chloride were refluxed for 45 min in 30 mL of dry pyridine. After addition of EtOAc (60 mL) and water (20 mL) the mixture was acidified with conc. HCl (30 mL) at 0 °. Separation and extraction with two 60 mL portions of EtOAc, and drying (Na_2SO_4) gave 2.386 g of a residue, which was recrystallized from EtOH (12 mL) to give 1.811 g (90.0%) of **13a** as light-yellow crystals, m.p. 111.5–112 °, $[\alpha]_D^{20} = -30.0°$ (*c* 2.20, $CHCl_3$). ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 1.329 (d, 3 H, *J* 6.5 Hz), 1.342 (s, 3 H), 1.562 (s, 3 H), 4.567 (qd, 1 H, J_q 2.8, J_q 6.5 Hz), 4.686 (d, 1 H, *J* 3.9 Hz), 5.976 (d, 1 H, *J* 2.8 Hz), 5.998 (d, 1 H, *J* 3.9 Hz), 8.223 (dt, 2 H, J_d 9.0, J_t 2.0 Hz), and 8.313 (dt, 2 H, J_d 9.0, J_t 2.0 Hz), $\nu_{max}^{CHCl_3}$ 3020, 2405, 1729, 1605, and 1530 cm^{-1}.

Anal. Calc. for $C_{16}H_{17}NO_7$ (323.31): C, 55.72; H, 5.30; N, 4.33. Found: C, 55.67; H, 5.31; N, 4.58.

1,2-O-Isopropylidene-3-O-mesyl-5-deoxy-α-D-xylofuranose (**13b**). — A mixture of **12** (0.371 g, 2.13 mmol) and MsCl (0.293 g, 2.56 mmol) were stirred for 2.5 h at room temperature in 6 mL of dry pyridine. After addition of EtOAc (40 mL) the organic phase was washed with three 35 mL portions of $KHSO_4$ to remove the pyridine. Drying over Na_2SO_4, and evaporation gave 0.527 g (98.0%) of **13b** as a colorless oil, $[\alpha]_D$ = −10.2° (*c* 2.10, $CHCl_3$). ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 1.32 (s, 3 H), 1.350 (d, 3 H, *J* 6.3 Hz), 1.508 (s, 3 H), 3.087 (s, 3 H), 4.456 (qd, 1 H, J_q 2.4, J_q 6.3 Hz), 4.769 (d, 1 H, *J* 3.9 Hz), 4.892 (d 1 H, *J* 2.4 Hz), and 5.932 (d, 1 H, *J* 3.9 Hz), $\nu_{max}^{CHCl_3}$ 3020, and 2395 cm^{-1}.

Anal. Calc. form $C_{11}H_{20}O_6S$ (252.3): C, 42.85; H, 6.39. Found: C, 43.06; H, 6.29.

1-α-3R,4S,5R)-3-Hydroxy-4-p-nitrobenzoyloxy-5-methyldihydro-2(3H)-furanone (**14a**). — Compound **13a** (0.195 g, 0.60 mmol), 1,4-dioxane (3.0 mL), water (0.3 mL) and conc. HCl (0.3 mL) were stirred for 3 h at 75 °. After neutralization with solid $NaHCO_3$, Br$_2$ (0.120 g, 0.75 mmol) was added and the mixture was stirred for 4 h at room temperature. After addition of water (1.0 mL) and 20% aq. $Na_2S_2O_3$ (1.0 mL), the aqueous phase was extracted 3 times with EtOAc (10 mL), washed with 20% aq. $Na_2S_2O_3$ (3.0 mL) and dried (Na_2SO_4) to give 0.202 g of a residue. Chromatography on silica gel (25 g) with 1:1 EtOAc–hexane gave 0.093 g (55.0%) of crystalline **14a**: m.p. 206–206.5 °, $[\alpha]_D^{25}$ + 115.3° (*c* 1.0, $CHCl_3$). ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 1.422 (d, 3 H, *J* 6.3 Hz), 3.074 (d, 1 H, *J* 2.9 Hz), 4.713 (dd, 1 H, *J* 2.9, 6.3 Hz), 5.121 (t, 1 H, *J* 6.4 Hz), 5.562 (t, 1 H, *J* 6.4 Hz), 8.247 (t, 2 H, *J* 9.3 Hz), and 8.344 (d, 2 H, *J* 9.3 Hz); ν_{max}^{KBr} 3330, 1750, 1720, and 1510 cm^{-1}.

Anal. Calc. for $C_{12}H_{11}NO_7$ (381.23): C, 51.25; H, 3.94; N, 4.98. Found: C, 50.89; H, 4.06; N, 4.88.

(+)-(3R,4S,5R)-3-Hydroxy-4-mesyloxy-5-methyldihydro-2(3H)-furanone (**14b**). — Compound **13b** (0.250 g, 0.99 mmol) was treated as described for compound **14a**. Chromatography on silica gel (25 g) with 1:1 EtOAc – toluene afforded 0.137 g (65.7%) of crystalline **14b**, m.p. 198°, $[\alpha]_D^{27}$ + 58.9° (*c* 1.715, $CHCl_3$); ^{1}H-n.m.r. (400 MHz, CD_3COCD_3): δ 1.438 (d, 3 H, *J* 6.8 Hz), 3.290 (s, 3 H), 4.667 (t, 1 H, *J* 5.9 Hz), 4.947 (qd, 1 H, J_d 2.4, J_q 6.8 Hz), 5.210 (t, 1 H, *J* 5.9 Hz), and 5.806 (d, 1 H, *J* 5.9 Hz); ν_{max}^{KBr} 3600-3200, 1770, and 1340 cm^{-1}.

Anal. Calc. for $C_6H_{10}O_6S$ (210.22): C, 34.28; H, 4.80. Found: C, 34.24; H, 4.62.

(5R)-3-Mesyloxy-5-methyl-2(5H)-furanone (**15**). — To a solution of 0.630 g (2.24 mmol) of **14a** and ethyldiisopropyl-amine (0.347 g, 2.69 mmol) in dry CH_2Cl_2 (10 mL) was added MsCl (0.359 g, 3.14 mmol) at 0° and the mixture was stirred for 1.5 h at room temperature. Evaporation and subsequent chromatography on silica gel (25 g) with 1:1 EtOAc – hexane gave 0.484 g (85.0%, after recovery of 0.184 g of educt **14a** as the second fraction) of crystalline (+)-(3*R*,4*S*,5*R*)-3-mesyloxy-5-methyl-4-*p*-nitrobenzoyloxy-dihydro-2(3*H*)-furanone; $[\alpha]_D^{24}$ +113.2° (*c* 2.35, $CHCl_3$); ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 1.440 (d, 3 H, *J* 6.8 Hz), 3.326 (s, 3 H), 5.188 (qd, 1 H, $J_d = J_q = 6.8$ Hz), 5.566 (d, 1 H, *J* 6.8 Hz), 5.751 (dd, 1 H, *J* 6.8 Hz), 8.251 (dt, 2 H, J_d 8.8, J_t 2.0 Hz), and 8.348 (dt, 2 H, J_d 8.8, J_t 2.0 Hz); $\nu_{max}^{CHCl_3}$ 1800, 1735, 1530, and 1265 cm^{-1}.

To 0.160 g of (+)-(3*R*,4*S*,5*R*)-3-mesyloxy-5-methyl-4-*p*-nitrobenzoyloxy-dihydro-2(3*H*)-furanone in MeOH (1.6 mL) and THF (1.6 mL) was added M methanolic NaOMe (0.44 mL, 0.44 mmol). After 1 h, addition of 0.30 g Amberlite IR-120 (H^+) brought the pH to 4, whereupon filtration and evaporation afforded 0.186 g of a residue, which was chromatographed on silica gel (25 g) with 1:1 EtOAc – hexane to yield 0.053 g (61.8%) of **15** as an oil that crystallized from 1:1 EtOAc – hexane; m.p. 76–76.5°, ^{1}H-n.m.r. (400 MHz $CDCl_3$): δ 1.536 (d, 3 H, *J* 6.8 Hz), 3.383 (s, 3 H), 5.174 (qd, 1 H, J_d, 1.9, J_q 6.8 Hz), and 7.169 (d, 1 H, *J* 1.9 Hz); $\nu_{max}^{CHCl_3}$ 2950–3120, 1770, and 1650 cm^{-1}.

Anal. Calc. for $C_6H_8O_5S$ (192.20): C, 37.56; H, 4.20. Found: C, 37.33; H, 4.14.

5-Deoxy-2-O-mesyl-3-O-p-nitrobenzoyloxy-α,β-D-xylofuranose (**16**). – A solution of **13a** (1.500 g, 4.63 mmol) in MeOH (20 mL) was boiled under reflux for 14 h with Amberlite IR-120 B(H^+) ion-exchange resin (0.5 g). Filtration and concentration of the filtrate yielded 1.130 g (3.80 mmol, 82.1%) of the oily methyl glycoside; ^{1}H-n.m.r. (400 MHz, $CDCl_3$) of the main (55%) product (*β* anomer, tentative assignment): δ 1.388 (d, 3 H, *J* 6.4 Hz), 2.651 (d, 1 H, *J* 3.9 Hz, 3.461 (s, 3 H), 4.308 (ddd, 1 H, *J* 7.3, 4.9, 1.8 Hz), 4.653 (dq, 1 H, J_d 5.1, J_q 6.4 Hz), 4.887 (d, 1 H, *J* 1.4 Hz), 5.352 (dd, 1 H, *J* 3.4, 4.9 Hz), 8.223 (d, 2 H, *J* 8.8 Hz), and 8.313 (d, 2 H, *J* 8.8 Hz); minor (45%) product, α anomer: δ 1.252 (d, 3 H, *J* 6.9 Hz), 3.011 (d, 1 H, *J* 3.9 Hz), 3.534 (s, 3 H), 4.383 (ddd, 1 H, *J* 3.9, 3.4, 1.4 Hz), 4.558 (dq, 1 H, J_d 5.1, J_q 6.9 Hz), 5.044 (d, 1 H, *J* 4.9), 5.195 (dd, 1 H, *J* 1.8, 5.1 Hz), 8.235 (d, 2 H, *J* 8.8 Hz), and 8.313 (d, 2 H, *J* 8.8 Hz); $\nu_{max}^{CHCl_3}$ 3420, 2920, 1720, and 1525 cm^{-1}.

Anal. Calc. for $C_{13}H_{15}NO_7$ (297.27): C, 52.53; H, 5.09; N, 4.71. Found: C, 52.10; H, 5.12; N, 4.47.

The 1.130 g of product was mesylated as described for compound **13b**. Chromatography on silica gel (80 g) with 1:1 EtOAc – hexane afforded 1.152 g (75.0%) of methyl

5-deoxy-2-*O*-mesyl-3-*O*-*p*-nitrobenzoyloxy-α,β-D-xylofuranoside as a colorless oil; ^{1}H-n.m.r. (400 MHz, $CDCl_3$) of the main product (β anomer, tentative assignment): δ 1.371 (d, 3 H, *J* 6.8 Hz), 3.183 (s, 3 H), 3.471 (s, 3 H), 4.670 (dp, 1 H, J_d 6.8 Hz), 5.077 (s, 1 H), 5.123 (d, 1 H, *J* 4.3 Hz), 5.456 (dd, 1 H, *J* 5.4, 1.9 Hz), 8.232 (d, 2 H, *J* 8.8 Hz), and 8.321 (d, 2 H, *J* 8.8 Hz); minor product (α anomer): δ 1.241 (d, 3 H, *J* 6.8 Hz), 3.124 (s, 3 H), 3.497 (s, 3 H), 4.619 (dq, 1 H, $J_q = J_d$ 6.8 Hz), 5.072 (s, 1 H), 5.160 (t, 1 H, *J* 4.4 Hz), 5.665 (dd, 1 H, *J* 5.4, 6.9 Hz), 8.244 (d, 2 H, *J* 8.8 Hz), and 8.316 (d, 2 H, *J* 8.8 Hz); $\nu_{max}^{CHCl_3}$ 2850–3050, 1730, and 1525 cm^{-1}.

Anal. Calc. for $C_{14}H_{17}NO_9S$ (375.36): C, 44.80; H, 4.57; N, 3.73. Found: C, 45.07; H, 4.67; N, 3.65.

A solution of this α/β anomeric mixture of methyl glycosides (3.666 g, 9.77 mmol) in trifluoroacetic acid (15.0 mL), was stirred for 11 h at 75°, and then EtOAc (50 mL) and saturated aq. $NaHCO_3$ (110 mL) were added to bring the pH to 7. Extraction with EtOAc (100 mL) and drying over Na_2SO_4 gave 3.495 g of a residue. Chromatography on silica gel (150 g) with 1:1 EtOAc–hexane afforded 1.100 g (29.9%) of methyl 5-deoxy-2-*O*-mesyl-3-*O*-*p*-nitrobenzoyl-α,β-D-xylofuranoside and 1.857 g (75.1% after recovery of educt) product **16** as an oil; ^{1}H-n.m.r. (400 MHz, $CDCl_3$) of the main product (β-anomer, tentative assignment): δ 1.270 (d, 3 H, *J* 6.4 Hz), 1.629 (s, 1 H), 3.186 (s, 3 H), 4.757 (dq, 1 H, $J_q = J_d$ 6.4 Hz), 5.139 (dd, 1 H, 4.1 Hz), 5.530 (m, 1 H), 5.656 (m, 1 H), 8.241 (d, 2 H, *J* 8.8 Hz), 8.333 (d, 2 H, *J* 8.8 Hz); minor product, α-anomer: δ 1.413 (d, 3 H, *J* 6.4 Hz), 1.629 (s, 1 H), 3.200 (s, 3 H), 4.632 (dq, 1 H, J_d 1.2, J_q 6.4 Hz), 5.061 (dd, 1 H, *J* 1.4 Hz), 5.478 (dd, 1 H, *J* 4.8, 2.0 Hz), 5.656 (m, 1 H), 8.249 (d, 2 H, *J* 8.8 Hz), and 8.326 (d, 2 H, J 8.8 Hz).

(−)-(3S,4S,5R)-3,4-Epoxy-5-methyldihydro-2(3H)-furanone [(−)-**8**]. — To compound **16** (0.475 g, 1.314 mmol) in THF (8.0 mL), a M methanolic solution of NaOMe (8.0 mL, 8.0 mmol) was added at 0°. After 35 min at 0° the pH was adjusted to 6–7 with 2.0 mL of 20% HCl in MeOH. Successive filtration, concentration, and chromatography on silica gel (25 g) with 9:1 EtOAc–hexane gave 0.135 g (88.2%) of (*3S,4S,5R*)-*3,4-epoxy-5-methyltetrahydro-2-α/β*-furanol as an oil; ^{1}H-n.m.r. (400 MHz, $CDCl_3$) of the main product: δ 1.325 (d, 3 H, *J* 6.4 Hz), 3.26 (s, 1 H, OH), 3.637 (d, 1 H, *J* 2.6 Hz), 3.666 (d, 1 H, *J* 2.6 Hz), 4.280 (q, 1 H, *J* 6.4 Hz), and 5.418 (s, 1 H); $\nu_{max}^{CHCl_3}$ 3410, 2980, and 1045 cm^{-1}.

To 0.228 g (1.963 mmol) of this α/β-furanol in dry CH_2Cl_2 (20 mL) was added 4Å molecular sieves (0.110 g), NaOAc (0.340 g), and PCC (1.700 g, 7.852 mmol) at room temperature. After 2.5 h silica gel (~10 g) was added and stirring was continued for a further 10 min. Filtration through silica gel and washing ten times with EtOAc (5 mL) gave a clear solution that was evaporated to give 0.215 g of an oil. Chromatography on silica gel (25 g) with 1:1 EtOAc–hexane gave 0.135 g (60.2%) of (−)-**8** as a colorless oil; $[\alpha]_D^{27}$ −38.8° (*c* 12.25, $CHCl_3$); ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 1.485 (d, 3 H, *J* 6.4 Hz, 3.780 (d, 1 H, *J* 2.4 Hz), 4.045 (dd, 1 H, J_d 2.4, 1.5 Hz), and 4.634 (qd, 1 H, J_d 1.5, J_q 6.4 Hz); $\nu_{max}^{CHCl_3}$ 1785 cm^{-1}.

Anal. Calc. for $C_5H_6O_3$ (114.10): C, 52.63; H, 5.30. Found: C, 52.31; H, 5.12.

(+)-(3R,4R,5R)-3,4-Epoxy-5-methyldihydro-2(3H)-furanone [(+)-**9**]. —

Starting from compound **13b**, product (+)-**9** was obtained in the same manner as already described; $[\alpha]_D^{27}$ +26.0° (*c* 1.23, $CHCl_3$); ^{1}H-n.m.r. (270 MHz, $CDCl_3$): δ 1.425 (d, 3 H, *J* 6.6 Hz), 3.799 (dd, 1 H, *J* 2.5, 0.7 Hz), 3.959 (d, 1 H, *J* 2.5 Hz), and 4.700 (qd, 1 H, J_d 0.7, J_q 6.6 Hz); $\nu_{max}^{CHCl_3}$ 1780 cm^{-1}.

Anal. Calc. for $C_5H_6O_3$ (114.10): C, 52.63; H, 5.30. Found: C, 52.39; H, 5.10.

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