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Two-Step Stereoselective Conversion of 5-Monosubstituted 1,3-Dioxolan-4-ones into Selectively Protected 2,3-Erythro-1,2,3-Triols. A Route to Polyhydroxylated Molecules

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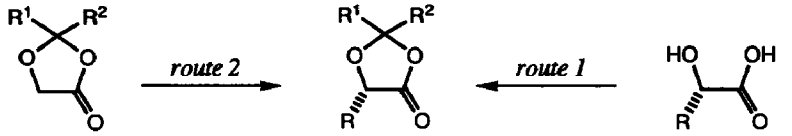
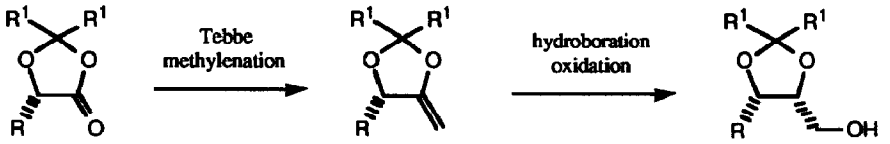
Key words : 1,3-dioxolan-4-one derivatives, Tebbe methylenation, polyols.

Abstract : 5-Monosubstituted 1,3-dioxolan-4-one **1** are stereoselectively converted into selectively protected 2,3-*erythro*-1,2,3-triols **3** via Tebbe methylenation, followed by hydroboration-oxidation.

5-Monosubstituted 1,3-dioxolan-4-ones are well established organic compounds which have mainly been prepared[1] from α-hydroxy acids (route 1). In sharp contrast, the 5-monosubstitution of dioxolanones derived from glycolic acid[2] (route 2) has hardly been explored[3] and has been recently developed by us[4].



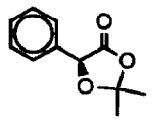
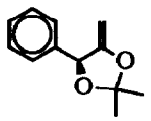
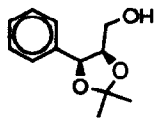
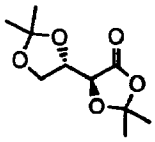
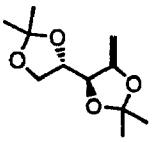
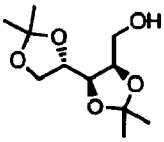
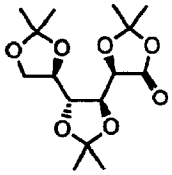
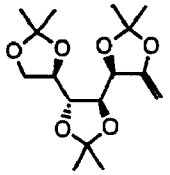
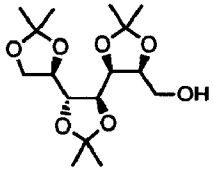
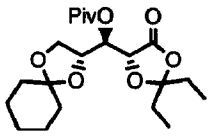
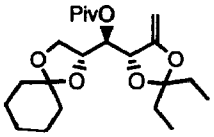
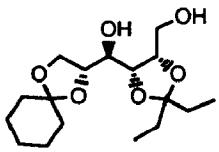
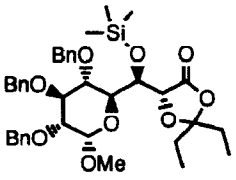
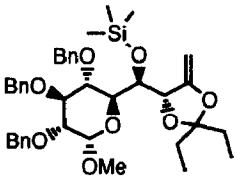
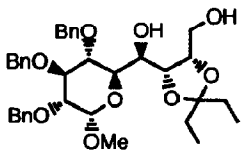
The purpose of this letter is to report on the following two-step stereoselective transformation[5] of dioxolanones **1**:



1 **2** **3**

Tebbe methylenation[6] of **1** is a high-yielding process (see Table 1) for the synthesis of 4-methylene-1,3-dioxolanes **2**[7]. The hydroboration[8,9] of **2** with BH_3.THF or BH_3.Me_2S proceeds regiospecifically by virtue of the highly polar nature of the substrate. A salient and welcome feature of this scenario is the high level of diastereoselection[10] - expected on the basis of steric grounds - attached to this hydroboration when performed with simple BH_3 reagents (see Table 1)[11]. Another intrinsic characteristic is that the resulting 2,3-*erythro*-1,2,3-triol is selectively protected on position 2 and 3, making target **3** directly available for further transformations.

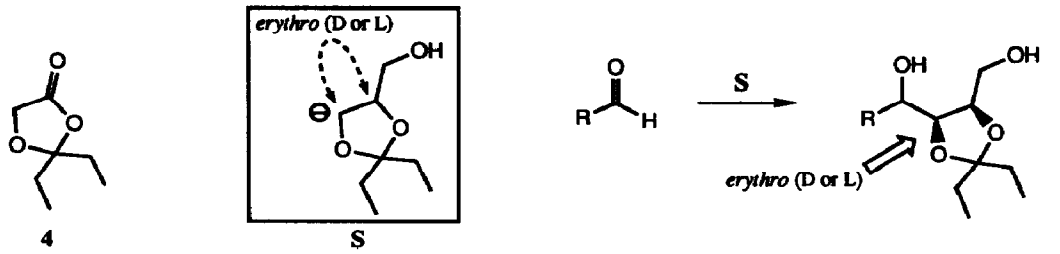
Table 1

entry	1[12]	2	yield (%) of 2	3 (major isomer)	method	yield (%) of 3[a]	ds[3b] (%)
a			96		A	57	83
b			95		A	71	>98
c			96		A	68	>98
d			69		B	79[b]	96
e			100[c]		B	86[e]	>98

Yield refers to chromatographically and spectroscopically homogeneous compounds. General experimental procedures, *methylenation* : to a solution of 1 (1 eq, 1 mmol) in anhydrous toluene (3 ml), THF (0.5 ml) and pyridin (0.5 ml), stirred at -78°C under argon atmosphere, Tebbe reagent was added (1.2-1.5 eq., *ca* 0.5 M in toluene, 2.4-3 ml) and the mixture was allowed to warm up at rt. After tlc control, the solution was cooled to -30°C, diluted with ether and sodium hydroxide 20% aqueous solution (3 ml) was added under argon atmosphere. After 10 min at rt the solution was filtered through a celite pad, eluted with ether, and then evaporated under reduced pressure. 2 was obtained as a colorless syrup after flash chromatography on silica gel, eluting with hexane / ethyl acetate. *Hydroboration-oxidation* : to a 0.5 M solution of 2 (1 mmol) in anhydrous THF, BH_3.THF (method A) or $BH_3.Me_2S$ (method B) (1M solution in THF, 1 mmol) was added at 0°C, under argon atmosphere. After 0.5h at rt, a sodium hydroxide 5% aqueous solution (0.5 ml) and an hydrogen peroxide 30% aqueous solution (0.5 ml) were added at 0°C. The mixture was stirred for 0.5h, then diluted with water. THF was evaporated and the product was extracted with dichloromethane. The organic layer was washed with brine, dried on anhydrous sodium sulfate, filtered, and evaporated. 3 was purified by flash chromatography on silica gel.

a. Isolated yield of *erythro*-3, ds > 98% (RMN 250 MHz); b. 9% of a 60 : 40 mixture of 5,6-*O*-cyclohexylidene-2,3-*O*-(3'-pentylidene)-3-*O*-pivaloyl-D-allitol and 5,6-*O*-cyclohexylidene-2,3-*O*-(3'-pentylidene)-3-*O*-pivaloyl-D-altritol was also isolated; c. Crude yield; d. This isolated yield calculated from 1e includes 38% of methyl-2,3,4-tri-*O*-benzyl-7,8-*O*-(3'-pentylidene)-β-L-*ribo*-D-*gluco*-1,5-pyrano-nonoside 3e and 48% of methyl-2,3,4-tri-*O*-benzyl-7,8-*O*-(3'-pentylidene)-6-*O*-trimethylsilyl-β-L-*ribo*-D-*gluco*-1,5-pyrano-nonoside. On storage the latter was spontaneously transformed into 3e.

Entries d and e (Table 1) materialize a short synthetic pathway to polyhydroxylated molecules or higher sugars. We may consider the dioxolanone **4** as a masked surrogate of the synthon **S** :



4 **S**

Table 2. Selected physical data for compounds 3.

3	$[\alpha]_D$	^{1}H-NMR	
3a	+80[§] c 2.73 CH_2Cl_2	250 MHz C_6D_6	1.28, 1.50 (2s, 6H, CH_3), 2.90 (s, 1H, OH), 3.00 (dd, 1H, H_{3b}), 3.20 (dd, 1H, $J_{3a,3b}$ 10.9 Hz, H_{3a}), 4.20 (ddd, 1H, $J_{2,3b}$ 4.2, $J_{2,3a}$ 7.8 Hz, H_2), 4.58 (d, 1H, $J_{1,2}$ 6.9 Hz, H_1).
3b	-16[+] c 0.1 $CHCl_3$	400 MHz C_6D_6	3.76 (m, 2H, H_{1a}, H_{1b}), 3.82 (dd, 1H, H_3), 3.91 (2dd, 2H, $J_{5a,5b}$ 15.2, $J_{4,5b}$ 1.1 Hz, H_{5a}, H_{5b}), 4.07 (dd, 1H, $J_{2,1a}$ 5.4, $J_{2,3}$ 6.5 Hz, H_2), 4.10 (ddd, 1H, $J_{4,5a}$ 7.9, $J_{4,5b}$ 1.1, $J_{3,4}$ 4.0 Hz, H_4).
3c	+17 c 0.7 $CHCl_3$	250 MHz C_6D_6	1.21, 1.23, 1.27, 1.34, 1.53, 1.59 (6s, 18H, CH_3), 2.64 (s, 1H, OH), 3.79-4.0 (m, 6H), 4.04 (dt, 1H), 4.19 (t, 1H), 4.40 (dd, 1H).
3d	+34 c 1.43 $CHCl_3$	400 MHz $CDCl_3$	3.80 (ddd, 1H, $J_{OH,1a}$ 8, $J_{1a,1b}$ 11.5, $J_{1a,2}$ 5 Hz, H_{1a}), 3.88 (ddd, 1H, $J_{OH,1b}$ 4.5, $J_{1b,2}$ 8 Hz, H_{1b}), 3.93 (dd, 1H, $J_{2,3}$ 6, $J_{3,4}$ 10 Hz, H_3), 3.97 (t, 1H, $J_{5,6b}$, $J_{6a,6b}$ 8 Hz, H_{6b}), 4.04 (dd, 1H, $J_{5,6a}$ 6.5 Hz, H_{6a}), 4.12 (dd, 1H, $J_{4,5}$ 3 Hz, H_4), 4.38 (ddd, 1H, H_2), 4.39 (ddd, 1H, H_5).
3e	+18 c 1.3 $CHCl_3$	400 MHz $CDCl_3$	3.39 (s, 3H, CH_3O), 3.50 (dd, 1H, $J_{1,2}$ 3.5, $J_{2,3}$ 9.7 Hz, H_2), 3.63 (dd, 1H, $J_{3,4}$ 9, $J_{4,5}$ 10 Hz, H_4), 3.70 (d, 2H, $J_{8,9}$ 6Hz, 2H_9), 3.87 (d, 1H, $J_{6,7}$ 10, $J_{5,6}$ 0 Hz, H_6), 3.91 (d, 1H, H_5), 4.04 (t, 1H, H_3), 4.21 (dd, 1H, $J_{7,8}$ 6 Hz, H_7), 4.31 (q, 1H, H_8), 4.59 (d, 1H, H_1).

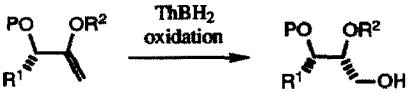
[§] L-*threo*-**3a** (ds 95%) : $[\alpha]_D$ +24 (c 0.36, CH_2Cl_2), lit[15] $[\alpha]_D$ +19 (c 2.9, CH_2Cl_2). [+] lit[16] (D-isomer) $[\alpha]_D$ +24 (c 1.8, $CHCl_3$).

References and Notes

1. Selected references : Farines, M.; Soulier, J. *Bull. Soc. Chim. Fr.* **1970**, 332-340; Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313-1324; Hoye, T. R.; Peterson, B. H.; Miller, J. D. *J. Org. Chem.* **1987**, *52*, 1351-1353; Ortholand, J. -Y.; Greiner, A. *Bull. Soc. Chim. Fr.* **1993**, *130*, 133-142.

2. For enolate substitution at C-5 : Pearson, W. H.; Cheng, M. -C. *J. Org. Chem.* **1986**, *51*, 3746-3748; Pearson, W. H.; Cheng, M. -C. *J. Org. Chem.* **1987**, *52*, 3176-3178; Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **1989**, *54*, 4235-4237; for a very recent radical substitution at C-5 : Beckwith, A. L. J.; Chai, C. L. L. *Tetrahedron* **1993**, *49*, 7871-7882. For somewhat related works, but introducing a double bond at C-5 : Ramage, R.; Griffiths, G. J.; Shutt, F. E.; Sweeney, J. N. A. *J. Chem. Soc., Perkin Trans. I* **1984**, 1531-1537; Ramage, R.; Rose, G. W.; MacLeod, A. M. *Tetrahedron Lett.* **1988**, *29*, 4877-4880; Simchen, G.; Siegl, G. *Liebigs Ann. Chem.* **1992**, 607-613.

3. The introduction at C-5 of a second substituent from 5-monosubstituted dioxolanones derived from *route 1* is in contrast relatively well studied; see a) Frater, G.; Müller, U.; Günther, W. *Tetrahedron Lett.* **1981**, *22*, 4221-4224. b) Seebach, D.; Naef, R. *Helv. Chim. Acta*, **1981**, *64*, 2704-2708. c) Heathcock, C. H.; Pirrung, M. C.; Young, S. D.; Hagen, J. P.; Jarvi, E. T.; Badertscher, U.; Märki, H. -P.; Montgomery, S. H. *J. Am. Chem. Soc.* **1984**, *106*, 8161-8174. d) Greiner, A.; Ortholand, J. -Y. *Tetrahedron Lett.* **1992**, *33*, 1897-1900.
4. Untersteller, E.; Thèse de Doctorat de l'Université Paris VI, December 1993.
5. This sequence has already been used on methyl and benzyl esters of fatty acids : Peterson, P. E.; Stepanian, M. *J. Org. Chem.* **1988**, *53*, 1903.
6. Tebbe, F. N.; Parshall, G. W.; Reddy, G. S.; *J. Am. Chem. Soc.* **1978**, *100*, 3611-3613; convenient preparation : Chou, T. S.; Huang, S. B.; Hsu, W. H. *J. Chin. Chem. Soc.* **1982**, *30*, 277-279; for a recent review, see : Pine, S. H. *Org. React.* **1993**, *43*, 1-91
7. For one example of such a process, see : Boeckman, R. K.; Yoon, S. K.; Heckendorn, D. K. *J. Am. Chem. Soc.* **1991**, *113*, 9682-9684.
8. Representative examples of the hydroboration of vinyl ethers : McGarvey, G. J.; Bajwa, J. S. *Tetrahedron Lett.* **1985**, *26*, 6297-6300 and references therein.
9. It is interesting to formally compare this procedure with the one reported by G. J. McGarvey[8] where selectively protected 2,3-*erythro*-1,2,3-triols have only been selectively obtained with $ThBH_2$ (thexylborane) and very peculiar hydroxyl protecting groups P and R^2. The degree of selectivity achieved using BH_3 as the hydroborating reagent was indeed limited and in favor of the opposite *threo* product :



10. A highly stereoselective *intramolecular* hydrosilylation of α-hydroxy enol ethers has been reported, giving the 2,3-*threo*-isomer : Tamao, K.; Nakagawa, Y.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 3712-3714.
11. For products **3a**, **3c**, **3d**, the stereochemistry of the major isomer was confirmed by hydrolysis (CF_3COOH / H_2O, 2/1, rt) to known polyols (1-*C*-phenyl-D-*erythro*-glycerol : Delton, M. H.; Yuen, G. U. *J. Org. Chem.* **1968**, *33*, 2473-2477; meso-*glycero*-*gulo*-heptitol : Wolfrom, M. L.; Wood, H. B. *J. Am. Chem. Soc.* **1951**, *73*, 2933-2934; Angyal, S. J.; Le Fur, R. *Carbohydr. Res.* **1984**, *126*, 15-26; 1,2,3,4,5,6-hexa-*O*-acetyl-allitol: Angyal, S. J.; Le Fur, R.; Gagnaire, D. *Carbohydr. Res.* **1972**, *23*, 121-134). The relative stereochemistry of the newly created 1,3-dioxolane heterocycle was also assigned by ^{1}H-NMR correlation (see Table 2): coupling constant between H_4 and H_5 (heterocycle numeration) is close to 6 Hz for all *erythro* products **3**, and close to 8 Hz for their *threo* isomer when detected (see also : Anet, F. A. L. *J. Am. Chem. Soc.* **1962**, *84*, 747-752).
12. Previously known compounds were prepared according to literature procedures, **1a** : Gerlach, U.; Hünig, S. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1283-1285. **1c** : Morgan, J. W. W.; Wolfrom, M. L. *J. Am. Chem. Soc.* **1956**, *78*, 2496-2497; the synthesis of this compound has recently been optimized by the use of anhydrous copper sulfate : Jarosz, S.; Zamojski, A. *16th International Carbohydrate Symposium*, Paris, France, July 5-10, **1992**, Poster A070, Abstracts p 105. **1b** : to a suspension of commercially available (Aldrich) potassium 3,4-*O*-isopropylidene-L-erythronate (1 g, 4.6 mmol) in anhydrous ether (2 ml) and 2,2-dimethoxypropane (0.86 ml, 4.6 mmol), boron trifluoride etherate (1 ml) was slowly added at 0°C. After 2h at rt, the solution was diluted with ether (10 ml) and neutralized with sodium carbonate (3 g). The product, obtained after filtration and evaporation, was purified by flash chromatography to a clear syrup (340 mg, 34%); $[\alpha]_D$ +7° (c 0.12, $CHCl_3$); ^{1}H-NMR (250 MHz, C_6D_6) : δ (ppm) 4.9 (ddd, 1H, $J_{2,3}$ 7.2, $J_{3,4a}$ 7.2, $J_{3,4b}$ 2.9 Hz, H_3), 3.70 (m, 3H, H_2, H_{4a}, H_{4b}), 1.30, 1.25, 1.08 (4s, 12H, $4CH_3$). Compounds **3d** and **3e** were obtained by aldol condensation of lithium enolate of 2,2-diethyl-1,3-dioxolan-4-one (**4**)[13] with the appropriate aldehyde[4]. The temporary protection of the secondary hydroxyl group by a pivaloate (**1d**) or a silyl ether (**1e**) was found essential both to achieve Tebbe methylenation and highly diastereoselective hydroboration.
13. The previously unreported dioxolanone **4** ($Eb_{22\ torr}$ 89°C) has easily been prepared (76% yield) from glycolic acid and diethylketone, according to Greiner[14].
14. Greiner, A.; Ortholand, J.-Y. *Tetrahedron Lett.* **1992**, *33*, 1897-1900.
15. Effenberger, F.; Hopf, M.; Ziegler, T.; Hudelmayer, J. *Chem. Ber.* **1991**, *124*, 1651-1659.
16. Alani-Shotorbani, G.; Buchanan, J. G.; Edgar, A. R.; Shahidi, P. K. *Carbohydr. Res.* **1985**, *136*, 37-52.

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