Tetrahedron Letters No. 45, pp 4327 - 4330.
0040-4039/78/1101-4327$02.00/0

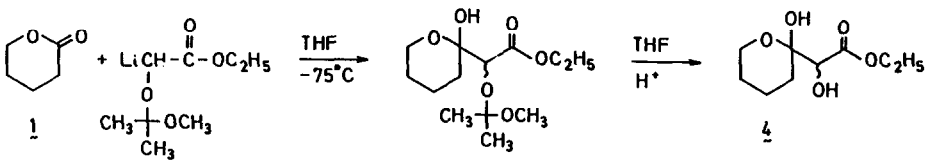
SYNTHESIS OF ETHYL 1,3,6-TRIOXASPIRO[4.5]DECANE-4-CARBOXYLATE DERIVATIVES FROM δ-LACTONES [PREPARATION OF 2-METHOXY-2-GLYCOLAMIDE-TETRAHYDRO-2H-PYRAN; ELABORATION OF PEDERAMIDE SIDE-CHAIN]

Angelina J. Duggan, Michael A. Adams and Jerrold Meinwald

Department of Chemistry, Cornell University, Ithaca, New York 14853

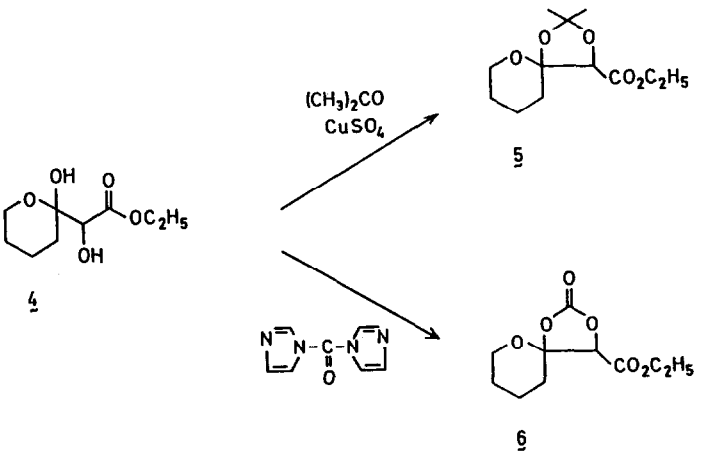
In a preceding communication we reported the preparation of hemiketals by the addition of lithium ester enolates to the carbonyl groups of δ-lactones and γ-lactones.[1,2] Herein, we describe the utility of these derivatives in the synthesis of 1,3,6-trioxaspiro[4.5]decanes which can be transformed into substituted glycolamides, synthons for molecules related to pederamide.[3]

We have observed that lithium ethyl O-(2-methoxy-2-propyl)glycolate (2)[4] reacts with δ-valerolactone at -75°C in THF to generate hemiketal 3 in 71% yield.[1] Since the alcohol protecting group derived from isopropenyl methyl ether is extremely labile,[5] the hemiketal 3 is converted in 90% yield to the α-hydroxy hemiketal 4[6] within minutes at ambient temperature in THF-dilute acid.



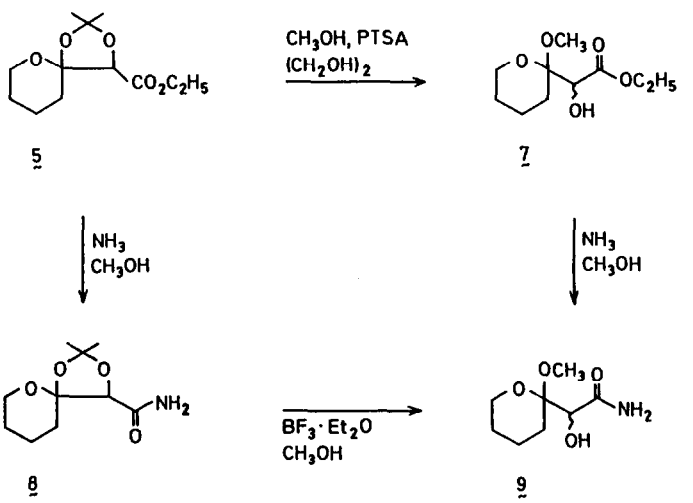
1 2 3 4

The stability of the cyclic hemiketal 4 allows this compound to react as a 1,2-diol, which serves as a convenient precursor for spirocyclic derivatives. Thus, the acetonide, ethyl 2,2-dimethyl-1,3,6-trioxaspiro[4.5]decane-4-carboxylate (5)[7] and the carbonate, ethyl 2-oxa-1,3,6-trioxaspiro[4.5]decane-4-carboxylate (6)[8] can be generated by the reaction of 4 with $CuSO_4$-acetone (or P_2O_5-acetone) and with 1,1-carbonyldiimidazole-benzene[9] in 86% and 90% yield respectively. These spirocyclic derivatives represent complementary intermediates for the preparation of substituted glycolamides with the side-chain characteristics of pederamide.

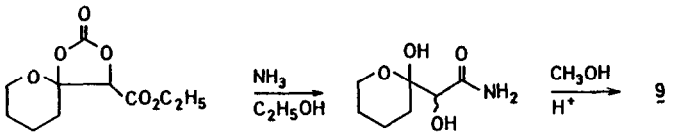


The acetonide ester 5, which is stable to basic conditions, can be deprotected in acidic methanol, with concomitant exchange of its angular hydroxy group for a methoxyl group, to generate the α-hydroxy ester 7 in 39% yield.[10] It was shown by Matsumoto et al. that compounds of this type can be converted to the substituted glycolamide 9, i.e. the pederamide model.[11]

A more efficient synthesis of the pederamide side-chain utilizing this chemistry was realized by converting the acetonide ester 5 to the acetonide amide 8[12] in 87% yield with ammonia-methanol. This intermediate can be deprotected and the angular methoxy group exchanged quantitatively with $BF_3 \cdot Et_2O$-methanol to generate 2-methoxy-tetrahydro-2H-pyran-2-glycolamide (9).[13] The glycolamides 8 and 9 served as models in our synthesis of pederolactone[3a] and pederamide[3b].



Alternatively, the carbonate 6, which is stable to acid, can be deprotected with ammonia-ethanol at room temperature to generate 2-hydroxy-tetrahydro-2H-pyran-2-glycolamide (10)[14] in 28% yield. This intermediate is converted to 9 in good yield with acidic methanol.



6 10

Acknowledgements: We are grateful to the American Cancer Society for generous support of this research via an Alberta Davis Memorial Grant for Cancer Research and the National Institutes of Health for support in the form of a Postdoctoral Fellowship (A.J.D.) and Graduate Traineeship (M.A.A.). We also thank Hoffmann-LaRoche, Inc. for generous samples of isopropenyl methyl ether.

NOTES AND REFERENCES

1. See: Reaction of Enolate Anions With Lactones, A.J. Duggan, M.A. Adams, P.J. Brynes and J. Meinwald; this journal, preceding communication.

2. The chemistry described in this publication and the preceding communication was first presented at the Tenth IUPAC Symposium on the Chemistry of Natural Products, August 1976 in Dunedin, New Zealand [see J. Meinwald, Pure and Applied Chemistry, 49, 1275 (1977)].

3. For the application of this chemistry to substituted lactones see (a) J. Meinwald, M.A. Adams and A.J. Duggan, Heterocycles, 7, 989 (1977); (b) M.A. Adams, Ph.D. dissertation, Cornell University, 1978.

4. Freshly distilled ethyl glycolate (116 g, 1.12 mol) was treated with neat isopropenyl methyl ether (93.6 g, 1.3 mol) at 0°C in the presence of a catalytic quantity of conc HCL (0.2 mL). The crude product was washed with $NaHCO_3$, dried with K_2CO_3, and distilled (bp 58-60°C, 2.5 torr.) to afford 170.7 g (87%) of the protected ester. Ethyl O-(2-methoxy-2-propyl)-glycolate (2): IR ($CHCl_3$) 1745 cm^{-1}; NMR ($CDCl_3$) δ 1.3 (3H, t, J = 7 Hz), 1.4 (6H, s), 3.25 (3H, s), 4.08 (2H, s), 4.23 (2H, q, J = 7 Hz); CIMS m/e (rel intensity): 145 (100, $M^+ - OCH_3$).

5. C.B. Reese, R. Saffhill, J.E. Sulston, Tetrahedron, 26, 1023 (1970).

6. Ethyl 2-hydroxy-tetrahydro-2H-pyran-2-glycolate (4): IR ($CHCl_3$): 3560, 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (3H, t, J = 7 Hz), 1.78 (6H, m), 3.8 (5H, m), 4.32 (2H, q, J = 7 Hz); CIMS m/e (rel intensity): 203 (2, $M^+ - 1$), 188 (15), 187 (100), 170 (11), 169 (93), 133 (11), 101 (52), 91 (16).

7. Ethyl 2,2-dimethyl-1,3,6-trioxaspiro[4.5]decane-4-carboxylate (5): IR ($CHCl_3$): 1770,

1740 cm^{-1}; NMR ($CDCl_3$): δ 1.29 (3H, t, J = 7 Hz), 1.44 (3H, s), 1.58 (3H, s), 1.77 (6H, m), 3.72 (2H, m), 4.2 (2H, m), 4.25 (1H, s); CIMS m/e (rel intensity): 188 (13), 187 (100), 169 (63).

Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.02; H, 8.20. Found: C, 58.74; H, 8.04.

8. Ethyl 2-oxa-1,3,6,trioxaspiro[4.5]decane-4-carboxylate (6): IR ($CHCl_3$): 1825, 1770 cm^{-1} NMR ($CDCl_3$): δ 1.31 (3H, t, J = 7 Hz), 1.8 (6H, m), 3.92 (2H, m), 4.32 (2H, q, J = 7 Hz), 4.74 (1H, s); CIMS m/e (rel intensity): 231 (11), 187 (14), 170 (11), 169 (100), 111 (11).
Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.03. Found: C, 51.95; H, 6.28.

9. J.P. Kutney and A.H. Ratcliff, Synth. Commun., 5, 47 (1975).

10. The reaction proceeds efficiently by treating 5 in acidic (p-toluenesulfonic acid) methanol at reflux temperature with 8 equivalents of ethylene glycol to trap the acetone as the diox lane. Ethyl 2-methoxy-tetrahydro-2H-pyran-2-glycolate (7): IR ($CHCl_3$) 3520, 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (3H, t, J = 7 Hz), 1.6 (6H, m), 3.0 (1H, s), 3.38 (3H, s), 3.7 (1H, s), 3.81 (1H, d, J = 2 Hz), 4.3 (2H, q, J = 7 Hz); CIMS m/e (rel intensity) 187 (100), 173 (30), 169 (59), 155 (21), 119 (15), 115 (44), 101 (11), 91 (27).
Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.05; H, 8.26. Found: C, 55.26; H, 8.25.

11. K. Tsuzuki, T. Watanabe, M. Yanagiya, and T. Matsumoto, Tetrahedron Letters, 4745 (1976).

12. An 85:15 mixture of isomers was obtained. The major isomer, mp 144-146°C, could be made to crystallize from hexane-diethyl ether. 2,2-Dimethyl-1,3,6-trioxaspiro[4.5]decane-4-carboxamide (8) major isomer: IR ($CHCl_3$) 3510, 3390, 1695, 1537 cm^{-1}; NMR ($CDCl_3$) δ 1.44 (3H, s), 1.60 (3H, s), 1.78 (6H, m), 3.75 (2H, m), 4.1 (1H, s), 6.2 (2H, m); CIMS m/e (rel intensity): 214 (0.14), 158 (100), 149 (9).
Anal. Calcd for $C_{10}H_{17}O_4N$: C, 55.81; H, 7.91; N, 6.51. Found: C, 55.76; H, 8.06; N, 6.39.

13. The exchange is not selective. The pure major isomer 8 generated a mixture of the threo and erythro isomers of 9. 2-Methoxy-tetrahydro-2H-pyran-2-glycolamide (9): IR ($CHCl_3$) 3500, 3460, 1685, 1575 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (6H, m), 3.35 (3H, s), 3.7 (2H, m), 3.83 (1H, s), 4.1 (1H, m), 6.65 (2H, s); CIMS m/e (rel intensity): 188 (1), 187 (10), 159 (100), 141 (36), 116 (31).

14. 2-Hydroxy-tetrahydro-2H-pyran-2-glycolamide (10): IR ($CHCl_3$) 3510, 1690 cm^{-1}. Yield not maximized.

(Received in USA 15 August 1978)