Tetrahedron Letters No. 30, pp 2679 - 2682. 0040-4039/78/0722-2679$02.00/0

SYNTHESIS OF MUSCARINE ANALOGUES: APPROACHES TO FUNCTIONALIZED TETRAHYDROFURANS

Z. Lysenko, F. Ricciardi, J. E. Semple, P. C. Wang and M. M. Joullie*

Department of Chemistry, University of Pennsylvania
Philadelphia, Pennsylvania 19104

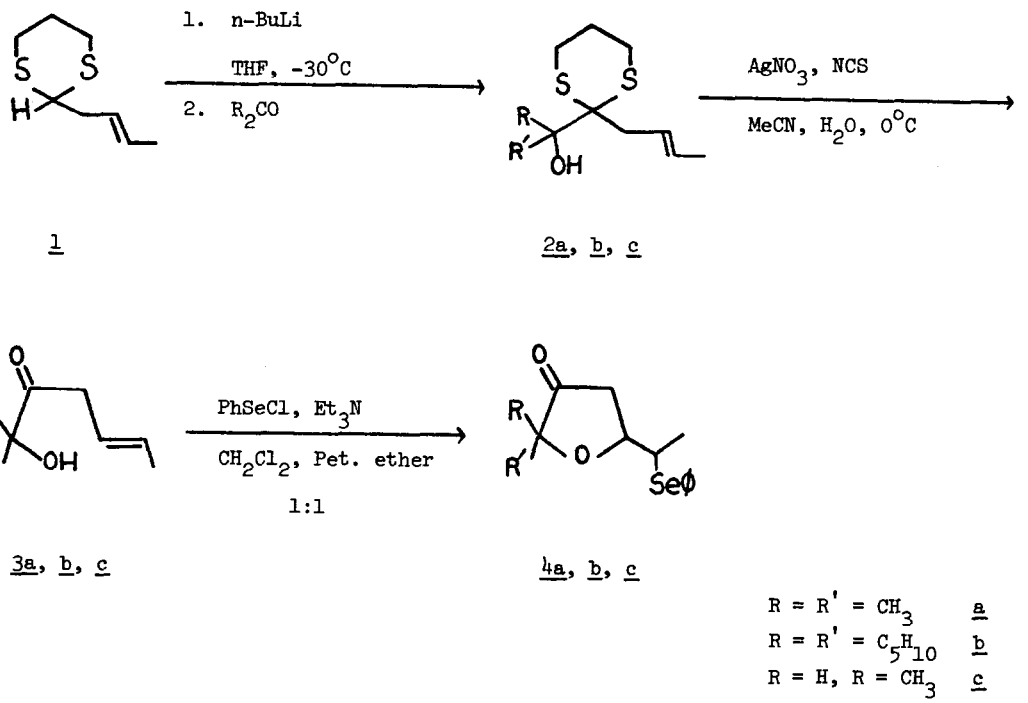
(Received in USA 28 December 1977; received in UK for publication 29 May 1978)

Functionalized tetrahydrofuran units are present in many naturally occurring products such as the Muscarines,[1] Ascofuranone,[2] and Dactyloxene B.[3] Our interest in Muscarine analogues, not only for their potential biological activity but also for their close relationship to other natural products currently being investigated in our laboratory (e. g. Ascofuranone), led us tc develop novel synthetic schemes for functionalized tetrahydrofurans.

We now wish to report one such scheme which can be used to prepare several Muscarine analogues (Scheme 1). Thus, treatment of 1 with 1.1 eq. of n-butyllithium at -30°C in anhydrous tetrahydrofuran followed by addition of the appropriate carbonyl compound affords the corresponding alcohols[4] 2a (bp 120-125°C/0.06 mm Hg), 2b (bp 150-155°C/0.05 mm Hg), and 2c (bp 90-100°C/0.01 mm Hg). Removal of the 1,3-dithiane functionality using the methodology developed by Corey[5] gave α-hydroxyketones (3a-c) which, due to their tendency to isomerize to α,β-unsaturated ketones, were then cyclized *in situ* with phenylselenenyl chloride[6,7] in methylene chloride and petroleum ether (bp 30-60°C) (1:1) at -78° to afford 4a, 4b, and 4c in 80% yield respectively, as pale yellow oils after silica gel chromatography, 4a: MS Calcd for $C_{14}H_{18}O_2Se$, 298.0471. Found, 298.0469; IR (neat) 1750 cm^{-1}; ^{1}HNMR ($CDCl_3$, 220MHz)δ 1.20 (s, 3H), 1.24 (s, 3H), 1.45 (d, 3H), 2.30-2.70 (m, 2H), 3.30-3.35 (m, 1H), 4.10-4.30 (m, 1H), 7.15-7.30 (m, 3H), 7.50-7.70 (m, 2H); 4b: MS Calcd for $C_{17}H_{22}O_2Se$, 338.0876. Found, 338.0879; IR (neat) 1750 cm^{-1}; ^{1}HNMR ($CDCl_3$, 220MHz)δ 1.50-1.70 (m, 13H), 2.35-2.70 (m, 2H), 3.35-3.55 (m, 1H), 4.10-4.30 (m, 1H), 7.15-7.30 (m, 3H), 7.50-7.70 (m, 2H); 4c: MS Calcd for $C_{13}H_{16}O_2Se$, 284.0314. Found, 284.0310; IR (neat) 1750 cm^{-1}; ^{1}HNMR ($CDCl_3$, 220MHz)δ 1.20 (d, 3H), 1.50 (d, 3H), 2.25-2.70 (m, 2H), 3.30-3.50 (m, 1H), 4.00-4.40 (m, 2H), 7.15-7.30 (m, 3H), 7.50-7.70 (m, 2H).

Since functionalized spirofurans[8] occur frequently in natural products, we chose 4b as a model for the synthesis of Muscarine analogues (Scheme 2). Thus, treatment of 4b with 1.2 eq. of sodium borohydride in methanol at room temperature quantitatively afforded a 4:1 mixture 5b trans [^{1}HNMR ($CDCl_3$, 220MHz)δ 1.25-1.85 (m, 14H), 2.40-2.60 (m, 1H), 2.94 (d, 1H), 3.45 -3.60 (m, 1H), 3.90-4.00 (m, 1H), 4.05-4.15 (m, 1H), 7.15-7.30 (m, 3H), 7.50-7.70 (m, 2H)] and 5b cis [^{1}HNMR ($CDCl_3$, 220MHz)δ 1.25-1.85 (m, 14H), 1.95-2.05 (m, 1H), 2.25 (broad s, 1H), 3.15-3.30 (m, 1H), 3.95-4.05 (m, 1H), 4.10-4.25 (m, 1H), 7.15-7.30 (m, 3H),

7.50-7.70 (m, 2H)], and are separated upon the usual workup via column chromatography using silica gel (Merck) and methylene chloride as solvent (5a: CH_2Cl_2, Rf=0.15,PMA; 5b: CH_2Cl_2, Rf=0.33, PMA; silica gel (Merck). Protection of the alcohol group by acetylation followed by oxidative dehydroselenation of the corresponding acetate with ozone in methylene chloride at -78°C afforded 6 in 78% yield[9] isolated as a colorless oil after silica gel chromatography; IR (neat) 1745, 1625 cm^{-1}; ^{1}HNMR ($CDCl_3$, 220MHz)δ 1.20-1.80 (m, 11H), 2.05 (s, 3H), 2.50-2.78 (m, 1H), 4.32-4.45 (m, 1H), 5.00-5.10 (m, 1H), 5.00-6.00 (m, 3H). Ozonolysis of 6 in methanol at -78°C followed by reductive decomposition with dimethyl sulfide[10] afforded aldehyde 7, which decomposed slowly on standing, IR (neat) 2700, 1745, 1725 cm^{-1}. Crude 7 was thus oxidized immediately with Jones reagent to the corresponding carboxylic acid which, in turn, was converted via its acid chloride to the corresponding dimethylamide, 8 in 46% overall yield; IR (neat) 1745, 1640 cm^{-1}; ^{1}HNMR ($CDCl_3$, 220MHz)δ 1.30-1.80 (m, 11H), 2.05 (s, 3H), 2.45-2.60 (m, 1H) 2.95 (s, 3H), 3.15 (s, 3H), 4.48-4.60 (m, 1H), 4.90-5.00 (m, 1H). Reduction of the amide with lithium aluminum hydride in refluxing tetrahydrofuran and methylation the resulting amine with excess methyl iodide at 0°C in 1:1 tetrahydrofuran/petroleum ether (bp 30-60°) afforded muscarine analogue 9 which was purified by recrystallization from 1:1 toluene-acetone to give white needles,

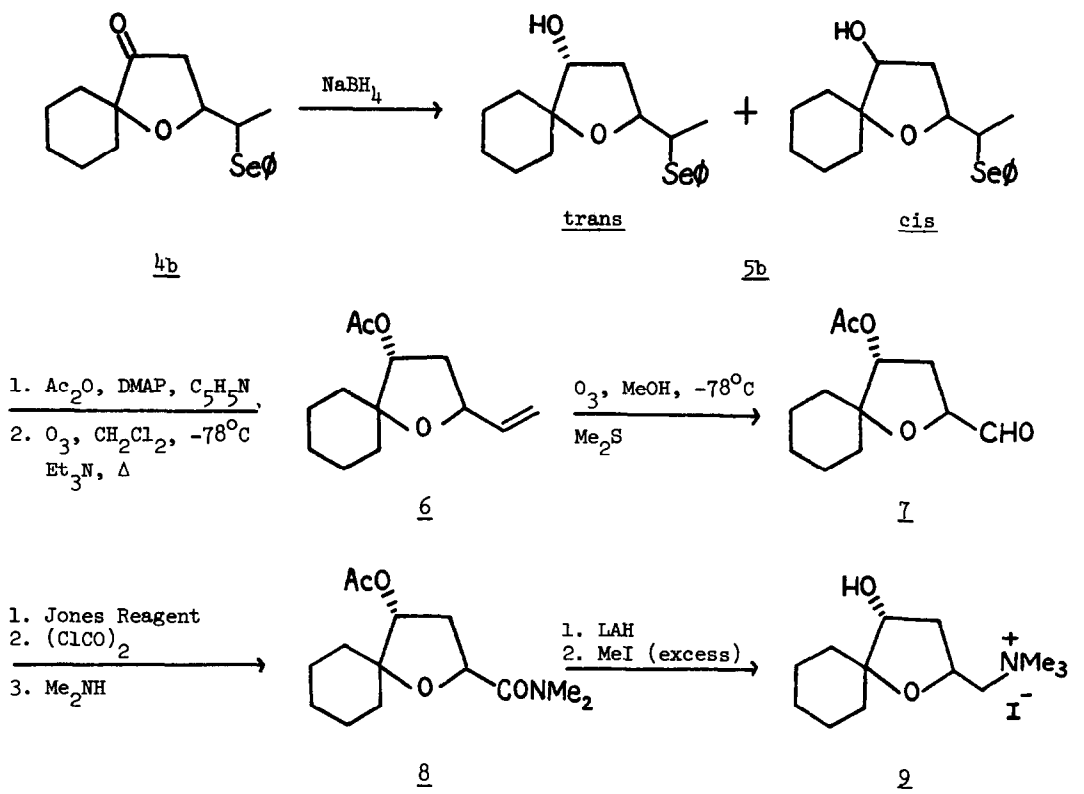


1 2a, b, c

3a, b, c 4a, b, c

R = R' = CH_3 a
R = R' = C_5H_{10} b
R = H, R = CH_3 c

Scheme 1



Scheme 2

mp 149-150°C: IR (KBr) 3350, 1040, 975, 915 cm^{-1}; ^{1}HNMR ^{11}(DMSO-d_6/Acetone-d_6, 220MHz)δ 1.15-1.85 (m, 1H, cyclohexyl C$\underline{H}_2$ and 3-C$\underline{H}$), 2.38-2.45 (m, 1H, 3-C$\underline{H}$), 3.15 (s, 9H, N(C$\underline{H}_3$)$_3$, 3.40-3.60 (m, 2H, C$\underline{H}_2$N), 3.85-3.95 (m, 1H, C$\underline{H}$OH), 4.50 (broad m, 1H, 2-C$\underline{H}$), 5.00 (d, 1H, O$\underline{H}$).

Anal. Calcd for $C_{13}H_{20}NO_2I$. 1.5 H_2O: C, 40.84, H, 7.25, N, 3.66
Found: C, 41.09, H, 7.11, N, 3.62.

Acknowledgement: We would like to thank Michael D. Miller for his assistance in some of the work presented here.

References:

1. (a) C. H. Eugster, Advances in Organic Chemistry, Methods and Results., Vol. II, p 427-456, Interscience Publishers, Inc., New York (1960).

(b) P. Wasser, Experientia, VII/7, 300 (1961)

2. T. Hosokawa, K. Suzuki, T. Okutomi, M. Sawada and K. Ando, Japan J. Pharmacol., 25, 35 (1975).

3. F. G. Schmitz and F. J. McDonald, Tetrahedron Letters, 2541 (1974).

4. E. J. Corey and D. Seebach, J. Org. Chem., 40, 231 (1975).

5. E. J. Corey and B. W. Erickson, J. Org. Chem., 36, 3553 (1971).

6. K. C. Nicolaou and Z. Lysenko, Tetrahedron Letters, 1257 (1977).

7. We have found that selenium-induced ring closures on α-hydroxyketoolefins have not been previously reported and can only be carried out under the conditions described. The utilization of reported methodology (cf. ref. 6) led to extensive decomposition and diminished yields.

8. D. J. Faulkner, Tetrahedron, 33, 1421 (1977).

9. For a review of selenium syn eliminations and related reactions, see: K. B. Sharpless, K. M. Gordon, R. F. Lauer, D. W. Patrick, S. P. Singer and M. W. Young, Chimica Scripta, (Sweden), (8A) 9, (1975) and references cited therein.

10. J. J. Pappas, W. P. Keaveny, E. Gancher and M. Berger, Tetrahedron Letters, 4273 (1966).

11. J. Whiting, Y. K. AuYoung and B. Belleau, Can. J. Chem., 50, 3322 (1972).