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Synthesis of (+)-muscarine from (*S*)-(−)-5-hydroxymethyl-2(5*H*)-furanone

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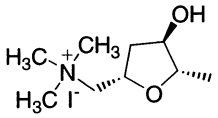
Abstract

(+)-Muscarine has been synthesized from (*S*)-(−)-5-hydroxy-2(5*H*)-furanone via rather a long pathway to provide easy access to a wide variety of its analogues. © 2000 Published by Elsevier Science Ltd.

Numerous synthetic methods of (+)-muscarine (**I**)[1] and its analogues[2] as muscarinic agonists for the development of therapeutics for Alzheimer's disease[3] have been reported. But the synthetic approaches for the analogues were very limited in their versatility, since they utilized quite specific methods such as stereospecific cyclization, chemoenzymatic resolution, etc. In order to study the substituent effect of muscarine analogues on binding to the muscarinic receptors, we needed a new synthetic strategy for producing a large number of muscarine derivatives. In this report, we describe a synthetic route to (+)-muscarine that opens the way to various modifications.[4] Commercially available (*S*)-(−)-5-hydroxymethyl-2(5*H*)-furanone,[5,6] which has been utilized as an important precursor in natural product synthesis and as a template in the synthesis of polypropiate-derived structural units, was used as the starting material.



(+)-Muscarine (I)

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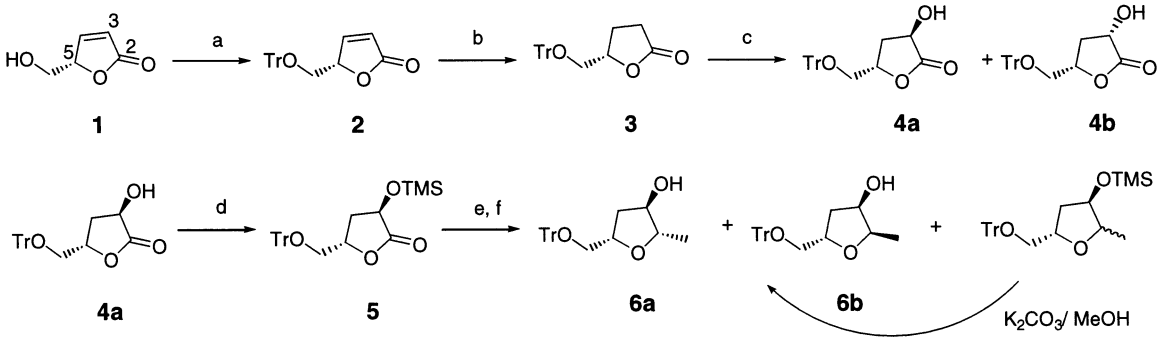
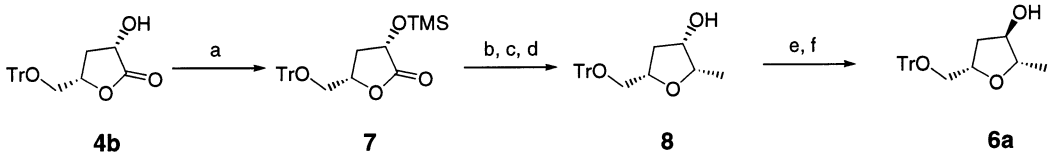
Treatment of (*S*)-(−)-5-hydroxy-2(5*H*)-furanone **1** with chlorotriphenylmethane in pyridine at 70°C for 16 h gave tritylated butenolide **2** in 83% yield (Scheme 1). The α,β-unsaturated lactone **2** was hydrogenated at 2 bar using H_2/Pd on $CaCO_3$ to give the lactone **3** in 96% yield. Saturated lactone **3** was reacted with 1.0 M LiHMDS at −78°C followed by the addition of freshly prepared *O*-electrophile, MoOPH[7] at −25°C to afford diastereomeric alcohols **4a** and **4b** in a ratio of 12:1.[8] The high stereoselectivity must have resulted from the bulkiness of the trityl group.[9]



Scheme 1. Conditions: (a) TrCl, pyridine, 70°C, 83%; (b) H_2/Pd on $CaCO_3$, THF, 2 bar, 96%; (c) LiHMDS, −78°C, MoOPH, −25°C for 30 min, 71% (**4a**/**4b** = 12:1); (d) TMSCl, pyridine, 0°C–rt, 86%; (e) 0.5 M Tebbe reagent, THF/toluene (1:3), pyridine, −40°C; (f) Raney Ni/H_2 (2 bar), THF, 78% (**6a**/**6b** = 44:56) (two steps)

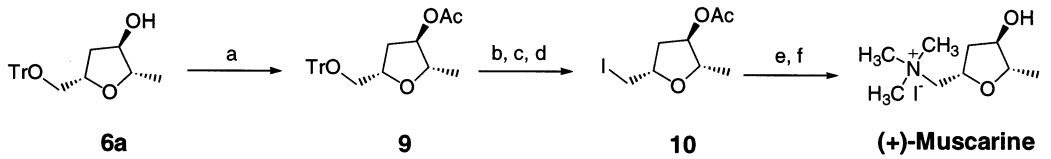
The alcohol **4a** with desired configuration was separated by flash column chromatography, and the free hydroxyl group was protected (TMSCl/pyridine, 86%) to give **5**. The carbonyl group of the lactone **5** was transformed to methyl group via *exo*-methylene formation with 0.5 M Tebbe reagent[10] solution in toluene followed by catalytic hydrogenation. Catalytic hydrogenation using Pd on $CaCO_3$ followed by desilylation gave **6a** and **6b** in a ratio of 1:11. Presumably the *syn*-addition of H_2 from less-hindered α-face resulted in the predominant formation of undesired diastereomer **6b** with (2*R*,3*R*,5*S*)-configuration as a precursor of (−)-*epiallo*-muscarine. Alternatively, Raney Ni mediated hydrogenation in EtOH gave a mixture of deprotected and protected diastereomers in an overall yield of 78% (two steps). After desilylation by K_2CO_3 in MeOH, we could obtain **6a** and **6b** in a ratio of 44:56. In situ generation of some deprotected alcohol during the reaction might have led to hydroxy-directed hydrogenation of double bond to increase the amount of **6a**.[11]

(3*S*,5*S*)-Lactone **4b** could efficiently be converted to **6a** (Scheme 2). Protection by TMSCl in pyridine produced lactone **7** in 85% yield. Treatment of **7** with Tebbe reagent followed by reduction with Pd on $CaCO_3$ under H_2 and deprotection of TMS group gave exclusively the expected (2*S*,3*S*,5*S*)-diastereomer **8** in 67% yield (three steps). Inversion of the alcohol at C-3 was achieved in 67% yield (two steps) using Mitsunobu condition[12] (DEAD, benzoic acid, PPh_3, 0°C, THF) and then hydrolysis to give **6a**.



Scheme 2. Conditions: (a) TMSCl, pyridine, 0°C–rt, 85%; (b) 0.5 M Tebbe reagent, THF/toluene (1:3), pyridine, −40°C; (c) H_2/Pd on $CaCO_3$, THF, 2 bar; (d) K_2CO_3 in MeOH, 67% (three steps); (e) DEAD, benzoic acid, PPh_3, 0°C, THF; (f) 20% aqueous K_2CO_3 solution in MeOH, 67% (two steps)

Thus obtained **6a** having appropriate configuration was reacted with acetic anhydride in the presence of sodium acetate at 60°C to yield the acetate **9**. $FeCl_3 \cdot 6H_2O$ was a highly efficient reagent for detritylation. To a solution of **9** in CH_2Cl_2 was added solid $FeCl_3 \cdot 6H_2O$, stirred at room temperature for 20 min, and purified.[13] Activation of the primary hydroxyl group with *p*-toluenesulfonyl chloride in pyridine at −20°C followed by iodination using NaI in 2-butanone at 80°C gave the iodide **10**[14] in 56% yield (three steps). Finally, deacetylation by 20% aqueous K_2CO_3 solution in MeOH followed by treatment with excess trimethylamine in EtOH gave (+)-muscarine iodide (Scheme 3). All the spectroscopic data of prepared (+)-muscarine were consistent with those reported in the literature.[15,16]



6a **9** **10** **(+)-Muscarine**

Scheme 3. Conditions: (a) Ac_2O, NaOAc, 60°C, 70%; (b) $FeCl_3 \cdot 6H_2O$, CH_2Cl_2; (c) TsCl, pyridine, −20°C; (d) NaI, 2-butanone, 80°C, 56% (three steps); (e) 20% aqueous K_2CO_3 solution in MeOH, 72%; (f) NMe_3 in EtOH, reflux, 92%

In summary, the synthesis of (+)-muscarine from (*S*)-(−)-5-hydroxy-2(5*H*)-furanone has been accomplished. Although the yield of each step was not so high, the whole process is meaningful in that it opened a novel pathway to the muscarine derivatives. Preparation of muscarine derivatives utilizing this strategy is now under progress.

Acknowledgements

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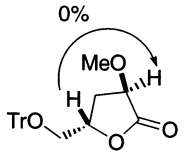
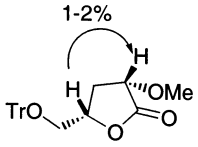
References

1. Popsavin, V.; Popsavin, M.; Radic, L.; Beric, O.; Cirin-Novta, V. *Tetrahedron Lett*. **1999**, *40*, 9305–9308 and references cited therein.
2. (a) Shapiro, G.; Buechler, D.; Hannet, S. *Tetrahedron Lett*. **1990**, *31*, 5733–5736. (b) Bravo, P.; Resnati, G.; Angeli, P.; Frigerio, M.; Viani, F.; Arnone, A.; Marucci, G.; Cantalamessa, F. *J. Med. Chem*. **1992**, *35*, 3102–3110. (c) Mentell, S. J.; Ford, P. S.; Watkin, D. J.; Fleet, G. W. J.; Brown, D. *Tetrahedron* **1993**, *49*, 3343–3358. (d) Vázquez-Tato, M. P.; Seijas, T. A.; Fleet, G. W. J.; Mathews, C. J.; Heminings, P. R.; Brown, D. *Tetrahedron* **1995**, *51*, 959–9740.
3. Quirion, R.; Aubert, I.; Lapchak, P. A.; Schaum, R. P.; Teolis, S.; Gauthier, S.; Araujo, D. M. In *Trends Pharmacol. Sci. (Supl. Subtypes Muscarinic Recept. IV)*; Levine, R. R.; Birdsall, N. J. M., Eds. Elsevier: Cambridge, 1989; Vol. 10, pp. 80–88.
4. Amici, M. D.; Micheli, C. D.; Molteni, G.; Pitrè, D.; Carrea, G.; Riva, S.; Spezia, S.; Zetta, L. *J. Org. Chem*. **1991**, *56*, 67–72.
5. Hanessian, S.; Murray, P. J. *Tetrahedron* **1987**, *43*, 5055–5072 and references cited therein.
6. (a) Mitome, H.; Miyaoka, H.; Nakano, M.; Yamada, Y. *Tetrahedron Lett*. **1995**, *36*, 8231–8234. (b) Tanaka, M.; Tomioka, K.; Koga, K. *Tetrahedron Lett*. **1985**, *41*, 3035–3038. (c) Boeckman Jr., R. K.; Heckendron, D. K.; Chinn, R. L. *Tetrahedron Lett*. **1987**, *28*, 3551–3554. (d) Ortuño, R. M.; Corbera, J.; Font, J. *Tetrahedron Lett*. **1986**, *27*, 1081–1084.

7. Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188–196.
8. Taschner, M. J.; Aminbhari, A. S. *Tetrahedron Lett.* **1989**, *30*, 1029–1032.
9. The stereochemistry of hydroxylated isomers (3*S*-α-OH or 3*R*-β-OH) was assigned by measuring NOE of *O*-methyl derivatives.



((3*R*)-β-OH)



((3*S*)-α-OH)

10. (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611–3615. (b) Pine, S. H.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212–1216.
11. (a) Stolow, R. D.; Sachdev, K. *J. Org. Chem.* **1971**, *36*, 960–966. (b) RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7128–7133.
12. Mitsunobu, O. *Synthesis* **1981**, 1–28.
13. Ding, X.; Wang, W.; Kong, F. *Carbohydr. Res.* **1997**, *303*, 445–448.
14. Compound **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (3H, d, $J=6.51$ Hz), 1.95 (1H, m), 2.09 (3H, s), 2.18 (1H, m), 3.24 (1H, dd, $J=10.1$ Hz, 6.3 Hz), 3.32 (1H, dd, $J=10.1$ Hz, 4.9 Hz), 4.10 (2H, m), 4.90 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 9.82, 20.6, 21.7, 39.1, 78.3, 80.4, 82.0, 170; $[\alpha]_D^{20}=-4.661$ ($c=0.515$, $CHCl_3$).
15. (+)-Muscarine iodide: ^{1}H NMR (300 MHz, D_2O) δ 1.22 (3H, d, $J=6.54$ Hz, $-CH_3$), 2.12 (1H, m, 2-H), 3.21 (9H, s, $-N(CH_3)_3$), 3.49 (1H, d, $J=5.4$ Hz), 3.61 (1H, d, $J=14.2$ Hz), 4.07 (1H, m, 4-H), 4.13 (1H, m, 3-H), 4.67 (1H, m, 1-H); ^{13}C NMR (75 MHz, D_2O) δ 19.5, 37.9, 54.4, 70.9, 72.3, 75.6, 84.4; HRMS (FAB, $[M-I]^+$) calcd for $C_9H_{20}NO_2$ 174.1494, found 174.1503 (lit.[15] anal. calcd for $C_9H_{20}INO_2$: C, 35.89; H, 6.69; N, 4.64. Found: C, 35.76; H, 6.40; N, 4.64); $[\alpha]_D^{20}=+6.4$ ($c=0.34$, EtOH) (lit.[15]; $[\alpha]_D^{20}=+6.36$ ($c=0.346$, EtOH)).
16. (a) Pochet, S.; Huynh-Dinh, T. *J. Org. Chem.* **1982**, *47*, 193–198. (b) Chan, T. H.; Li, C. J. *Can. J. Chem.* **1992**, *70*, 2726–2729.