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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2971–2973

A concise asymmetric synthesis of (+)-muscarine from (*S*)-γ-hydroxymethyl-γ-butyrolactone

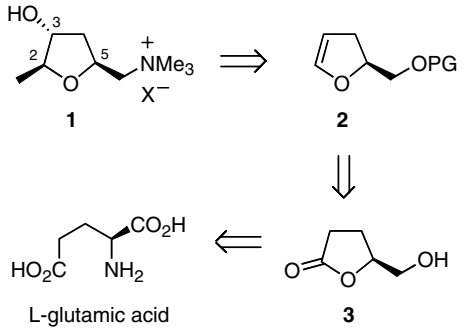
John Boukouvalas* and Ioan-Iosif Radu

Département de Chimie, Université Laval, Quebec City, Que., Canada G1K 7P4

Received 31 December 2006; revised 23 February 2007; accepted 1 March 2007
Available online 4 March 2007

Abstract—A highly stereoselective synthesis of (+)-muscarine iodide has been achieved in eight steps and 20% overall yield from commercially available (*S*)-γ-hydroxymethyl-γ-butyrolactone.

Few natural products have enjoyed the prominence of the alkaloid (+)-muscarine (**1**, X = OH or halogen, Scheme 1) in terms of history, biological activity, and impact to modern pharmacology and drug design.[1,2] Interest in the muscarinic field has been invigorated in recent years with the discovery that potent muscarinic agonists, such as **1**, could alleviate the short memory loss exhibited by Alzheimer's disease (AD) patients.[3] Although muscarine is not therapeutically useful due to adverse side-effects[2a] and its inability to cross the blood-brain barrier,[3] it is widely used as a biochemical tool for studying signal transduction pathways in cultured cells as well as in living systems.[4] The combination of growing demand and limited availability, along with a simple but stereochemically challenging structure have made **1** a classic target for synthesis.[5] Commendable efforts over the years have led to approximately 30 syntheses from carbohydrate and noncarbohydrate starting materials.[6,7] However, the majority of these syntheses suffer from excessive length or lack of selectivity.



Scheme 1. Retrosynthetic analysis of muscarine.

In continuation of our interest in the expedient construction of substituted tetrahydrofurans,[8,9] we now report a comparatively short, highly stereoselective synthesis of **1** from (*S*)-γ-hydroxymethyl-γ-butyrolactone (**3**). The latter is commercially available or inexpensively prepared in two steps from naturally abundant L-glutamic acid.[10] Notwithstanding the structural homology between **1** and **3**, there is currently only one, non-stereoselective 15-step synthesis of muscarine that makes use of a derivative of **3** as an early intermediate.[6a] Our approach differs from this, and the retrosynthetic analysis is shown in Scheme 1. Dihydrofuran **2** was viewed as a key intermediate whose alkylation and subsequent anti-Markovnikov hydration would install the contiguous methyl and hydroxyl substituents along with the correct stereochemistry at C2 and C3. In contemplating high diastereoface selectivity, the use of a bulky protecting group (PG), such as trityl or the more robust *tert*-butyldiphenylsilyl, was deemed essential.[10,11]

The synthesis began with the two-step conversion of **3** to lactol **5** according to established precedent[12] (Scheme 2). Exposure of **5** with mesyl chloride and triethylamine in dichloromethane, followed by heating, accomplished β-elimination to furnish dihydrofuran **6**[13] in 77% yield after purification by silica gel chromatography.[14] Attachment of the methyl substituent at C2 was realized with complete regioselectivity by taking advantage of

Keywords: 2,3-Dihydrofurans; Hydroboration; Lactones; Lithiation; (+)-Muscarine; Stereoselectivity.
* Corresponding author. Tel.: +1 418 656 5473; fax: +1 418 656 7916; e-mail: john.boukouvalas@chm.ulaval.ca

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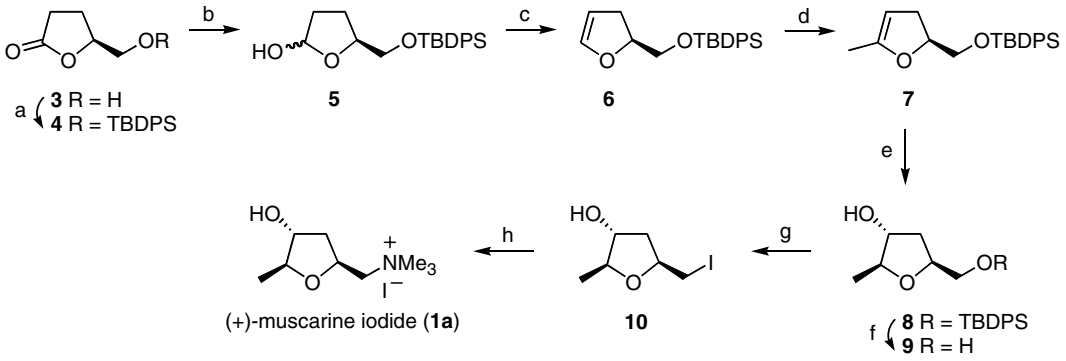
doi:10.1016/j.tetlet.2007.03.014



Scheme 2. Reagents and conditions: (a) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C → rt, 3 h (86%); (b) DIBAL, CH_2Cl_2, −78 °C, 2 h (95%); (c) MsCl, Et_3N, CH_2Cl_2, −20 → 40 °C, 2.5 h (77%); (d) *t*-BuLi (2 equiv), THF, −78 → 0 °C, 45 min, then TMEDA (2 equiv) or HMPA (1 equiv), 10 min, then MeI (10 equiv), rt, 12 h (85%); (e) $ThxBH_2$ (2 equiv), THF, 0 °C, 16 h, then aq 3 N NaOH/aq 30% H_2O_2, rt, 6 h (59%); (f) TBAF, THF, 0 °C → rt, 2 h (93%); (g) Ph_3P (1.5 equiv), I_2 (1.4 equiv), imidazole (3 equiv), PhMe, 70 °C, 3 h (74%); (h) Me_3N, EtOH, reflux, 3 h (92%).

the propensity of dihydrofurans to undergo kinetic deprotonation at the vinylic center α to the oxygen atom.[15] Thus, sequential treatment of **6** with *t*-BuLi and a 10-fold excess of methyl iodide in the presence of either TMEDA or HMPA afforded **7** in 85% yield.[16]

With the carbon skeleton in place, attention focused on the hydration of the vinyl ether moiety by means of hydroboration–oxidation.[17] Of the various reagents tried, including BH_3·DMS, dicyclohexylborane, 9-BBN, disiamylborane, and thexylborane ($ThxBH_2$), the last two proved the most effective giving **8**[6e] as the only detectable isomer in yields of 55% and 59%, respectively. Subsequent removal of the silyl protecting group provided diol **9** which was cleanly transformed to the relay iodide **10**[18a] on heating with iodine and triphenylphoshine in the presence of imidazole.[19] Finally, heating **10** in a sealed tube with trimethylamine in ethanol[6b] delivered (+)-muscarine iodide (**1a**) whose spectral and physical properties[18b] were in excellent agreement with those reported in the literature.[6a,7e]

In summary, a highly selective asymmetric synthesis of (+)-muscarine has been achieved in eight steps and 20% overall yield from (*S*)-γ-hydroxymethyl-γ-butyrolactone. This straightforward synthetic route builds the 3-oxygenated *cis*-2,5-disubstituted THF unit with complete regio- and stereoselectivity and should be readily adaptable to the preparation of other natural and unnatural products of biomedical importance.[20]

Acknowledgments

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC), Merck Frosst Canada and Eisai Research Institute (Andover, MA, USA) for financial support. We also thank FQRNT (Québec) for a postgraduate scholarship to I.-I.R.

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16. *Data for* **7**: $[\alpha]_D^{20}$ +33.7 (*c* 2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.76–7.70 (m, 4H), 7.48–7.33 (m, 6H), 4.75–4.65 (m, 1H), 4.50 (m, 1H), 3.80 (dd, $J = 10.5$, 5.5, 1H), 3.73 (dd, $J = 10.5$, 4.9, 1H), 2.75–2.63 (m, 1H), 2.56–2.47 (m, 1H), 1.80 (s, 3H), 1.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 135.5, 133.6, 129.5, 127.5, 93.8, 81.3, 66.1, 32.3, 26.7, 19.2, 13.4; Anal. Calcd for $C_{22}H_{28}O_2Si$: C, 74.95; H, 8.00. Found: C, 75.03; H, 8.22.
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18. (a) Iodide **10**: $[\alpha]_D^{20}$ −32.8 (*c* 1.8, $CHCl_3$), lit.[7e] (ee 96%) $[\alpha]_D^{20}$ −30.7 (*c* 0.874, $CHCl_3$); (b) (+)-Muscarine iodide (**1a**): $[\alpha]_D^{20}$ +6.33 (*c* 0.30, EtOH), lit.[7e] $[\alpha]_D^{20}$ +6.36 (*c* 0.346, EtOH).
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