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Stereocontrol of 5-*endo*-trig cyclisations by hydroxyl groups: a formal short synthesis of (+)-muscarine

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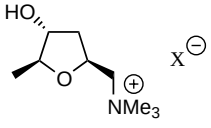
Abstract—5-*endo*-Trig iodocyclisation of the (*Z*)-ene-diol derivative **10** gives almost exclusively the hydroxy-tetrahydrofuran **11**, a precursor of (+)-muscarine **1** in four simple steps.

(+)-Muscarine **1** has enjoyed considerable prominence in the chemical and biological literature for many years, initially by reason of its ability to act as an acetylcholine agonist; more recently, the characterisation of many subtypes of muscarinic receptors has further enhanced this interest.[1] Hence, there is continuing demand for the synthetic provision of this highly active compound that occurs in the spectacular Fly Agaric mushroom *Amanita muscara*.[2] It should be added that the structure has also provided a testbed for a great diversity of novel synthetic strategies.[3]



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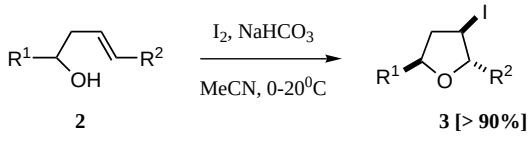
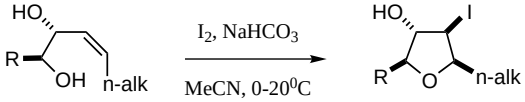
We have recently discovered that 2,5-*trans*-tetrahydrofurans **3** can be obtained highly stereoselectively by overall 5-*endo*-trig cyclisations of (*E*)-homoallylic alcohols **2** upon exposure to molecular iodine.[4] The 2,5-*cis* relationship of the α-substituents in muscarine **1** appeared to demand that the application of such electrophile-driven methodology to its synthesis would necessitate a similar cyclisation but of a suitably substituted (*Z*)-homoallylic alcohol, e.g. **4**. Unfortunately, our model studies[4] revealed that such reactions were quite inefficient while still exhibiting high stereocontrol in favour of the all-*cis*-isomers (Scheme 1).[5] However, further studies showed that incorporation of an additional hydroxy group which would eventually be positioned at one of the β-sites in a product iodotetrahydrofuran greatly enhanced the viability of such cyclisations of (*Z*)-homoallylic alcohols.[5] In particular, iodocyclisation of the model *anti*-(*Z*)-3-alkene-1,2-diol (**6**; *R*-alkyl, aryl) led almost exclusively (>10:1) to the tetrahydrofurans **7**, having the precise stereochemistry required for an efficient approach to muscarine **1** (Scheme 2). As ever, extensions of model studies to actual targets necessitate the inclusion of additional, potentially interfering functionality along with a correct pattern of protection. An optimum route to muscarine **1** using this latter methodology appeared to demand use of a masked hydroxymethyl group in place of the *n*-alkyl substituents in model **6**. At the outset, we had no information concerning the efficacy of such 5-*endo* cyclisations involving additions to allylic alcohol functions (cf. structure **10**). We did, however,



Scheme 1.



Scheme 2.

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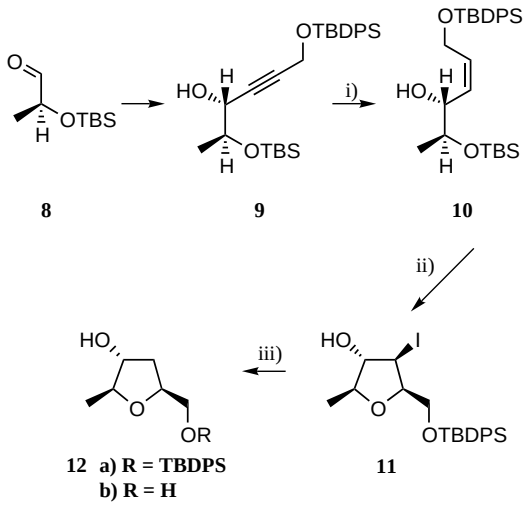
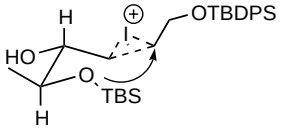


Scheme 3. *Reagents and conditions*: (i) H_2, 5% Pd–$CaCO_3$, quinoline, MeOH, 20°C, 1 h; (ii) IBr (2 equiv.), MeCN, −10°C, 5 h; (iii) H_2, 5% Pd–C, Et_3N, MeOH, 20°C, 5 h, then NH_4F, MeOH, 20°C, 12 h.

know that *O*-protection was necessary, as unmasked allylic alcohols undergo partial oxidation to the corresponding enals when exposed to iodine. We elected to use a large silicon based group for this necessary protection in the hope that this would be compatible with the iodocyclisation conditions. Herein, we report a successful outcome to these ideas.

Beginning with methyl (*S*)-lactate, the *O*-silyl aldehyde **8** was prepared in two efficient steps by sequential *O*-silylation (TBSCl, imidazole, DMAP (cat.), THF, 12 h, 20°C, 97%) and Dibal-H reduction (Et_2O, −78°C to +20°C, 3 h, 97%). Non-chelation controlled and hence highly *anti*-selective addition of lithiated *O*-TBDPS propargyl alcohol (BuLi, 12-crown-4, −78°C, 4 h)[6] favoured formation of the yne-diol **9** (ca. 85:15), which was obtained as a single enantiomer in 60–65% yields following column chromatography (Scheme 3). Lindlar reduction (5% Pd–$CaCO_3$, quinoline, MeOH, H_2 (1 atm.), 20°C, 1 h, 90%) then provided the key *anti*-(*Z*) cyclisation precursor **10**.

Optimised conditions for the iodocyclisation featured the use of iodine monobromide in place of iodine in acetonitrile at −10°C for 5 h and direct reaction of the *O*-silyl derivative **10**, rather than the corresponding free alcohol, thereby obviating the need for an additional deprotection step. This gave the desired iodo-tetrahydrofuran **11** in ca. 70% isolated yield, as a single isomer after chromatography; again, structural assignment relied heavily upon comparative spectral data[5] along with independent NOE measurements. Removal of the iodine by hydrogenolysis[7] proceeded uneventfully to give the trisubstituted tetrahydrofuran **12a** (91%), which was finally deprotected (NH_4F, MeOH, 12 h, 20°C) to give the tetrahydrofuran-2-methanol **12b**. Removal of the iodine in this manner was distinctly preferable to the more commonly encountered radical-based methods using tin hydrides,[8] especially as the final purification was so much easier. The final product **12b** exhibited spectroscopic and analytical data identical to those previously reported.[9] In particular, there was good agreement between the observed optical rotation {$[\alpha]_D^{20}$ −5.8 (*c* 0.5, $CHCl_3$)} and the reported values {lit.[9] $[\alpha]_D^{20}$ −6.0 (*c* 0.5, $CHCl_3$)}. The diol **12b** has been converted efficiently into (+)-muscarine tosylate (**1**; X = OTs) by sequential selective tosylation of the primary alcohol and thermolysis with trimethylamine in methanol at 80°C.[9] Hence, the foregoing approach represents a nine-step synthesis of (+)-muscarine **1** starting from methyl (*S*)-lactate.



13

The origin of the excellent level of stereoselection observed in the key cyclisation step presumably lies in the transition state conformation **13** in which both substituents (HO and Me) are positioned equatorially. It remains unclear whether the additional hydroxyl group exerts any more subtle effects, as the excellent yield of the cyclised product **11** is in extreme contrast to those obtained from simple (*Z*)-homoallylic alcohols **4**.[4] Whatever the explanation conformation **13** should at least provide a model suitable for use in future synthetic planning.[10]

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10. Full analytical and spectroscopic data consistent with all the proposed structures have been obtained.