PRACTICAL CHIRAL ROUTE TO MUSCARINE AND ITS THREE DIASTEREOMERS

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A practical route to all possible stereoisomers of the muscarine alkaloids in optically pure forms has been developed starting from a readily accessible chiral starting material.

KEY WORDS chiral synthesis; muscarine; *epi*-muscarine; *allo*-muscarine; *epiallo*-muscarine

The interesting physiological activity on the parasympathetic nervous system of (+)-(2*S*,3*R*,5*S*)-muscarine (**1**), isolated from *Amanita muscaria*, has generated much interest over the years.[1] This has greatly stimulated chiral construction of muscarine (**1**) itself as well as three other naturally occurring diastereoisomers, (+)-(2*S*,3*S*,5*S*)-*epi*-muscarine (**2**), (+)-(2*S*,3*R*,5*R*)-*allo*-muscarine (**3**), and (−)-

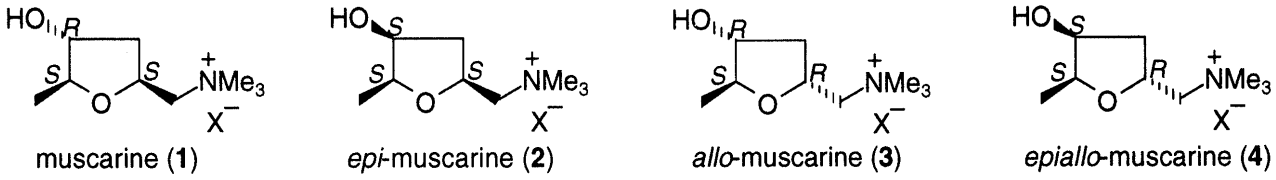

Chart 1

(2*S*,3*S*,5*R*)-*epiallo*-muscarine (**4**). Although a number of chiral syntheses have been performed,[1] there has been no flexible method enabling us to produce all four diastereomers based on the same methodology. We report here a convenient method for the practical preparation of muscarine (**1**) and its three diastereomers in optically pure forms by employing *cis*-dihydroxylation reaction on the olefin

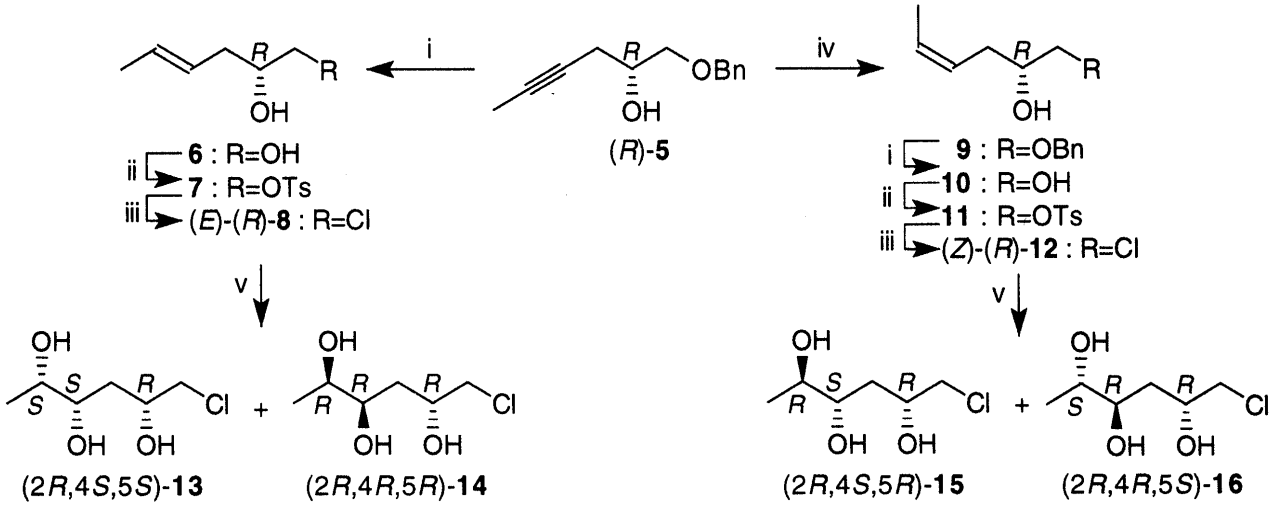

Chart 2. *Reagents and conditions*: i) Na, liq. NH_3 (84% for **6**; 75% for **10**). ii) *p*-TsCl, pyridine (90% for **7**; 85% for **11**). iii) LiCl, DMF (80% for **8**; 96% for **12**). iv) H_2, Lindlar cat., AcOEt (91%), v) see Table 1.

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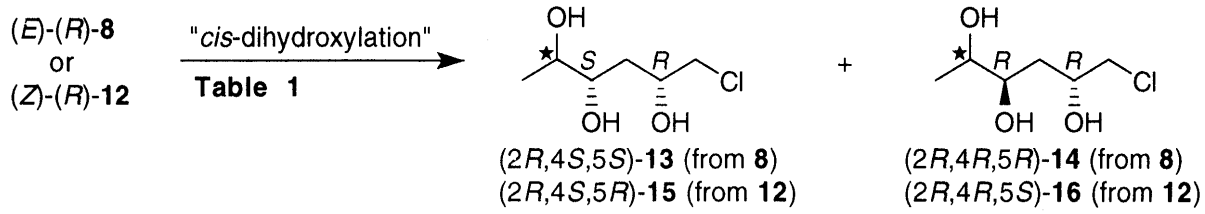
substrates bearing chiral secondary hydroxyl functionality. The present procedure necessitates diastereomeric separation; however, all diastereomers of the muscarine alkaloids may be obtained in both enantiomeric forms in optically pure form by employing the same methodology.



(2*R*,4*S*,5*S*)-**13** (from **8**)
(2*R*,4*S*,5*R*)-**15** (from **12**)

(2*R*,4*R*,5*R*)-**14** (from **8**)
(2*R*,4*R*,5*S*)-**16** (from **12**)

Chart 3

Table 1. *cis*-Dihydroxylation of (*E*)-(*R*)-**8** and (*Z*)-(*R*)-**12**

			Product (%)					Product (%)	
Entry	Substrate	Oxidant	**13**	**14**	Entry	Substrate	Oxidant	**15**	**16**
1	**8**	OsO_4[a]	25[c]	38[c]	4	**12**	OsO_4	38	60
2	**8**	AD-mix-α[b]	54	36	5	**12**	AD-mix-α	26	65
3	**8**	AD-mix-β[b]	6[c]	67[c]	6	**12**	AD-mix-β	33	62

a) OsO_4 (1 mol%), $K_3Fe(CN)_6$ (3 eq), and K_2CO_3 (3 eq) in 50% aqueous *tert*-BuOH (10 ml/mmol of substrate).
b) AD-mix reagent (1.4 g/mmol of substrate) was used in 50% aqueous *tert*-BuOH (10 ml/mmol of substrate).
c) Yield was that of the corresponding tetrahydrofuran (**18** from **13**; **19** from **14**) after the base-catalyzed cyclization.

The synthesis started with isomeric olefins *E*-**8** and *Z*-**12**, which were prepared from the common acetylenic alcohol[2] **5** originating from chiral *O*-benzylglycidol. Thus, (*R*)-1-benzyloxy-4-hexyne-2-ol [(*R*)-**5**], obtained in 66% yield from (*S*)-*O*-benzylglycidol in two steps,[2] was transformed into either the *E*-olefinic chlorohydrin (*E*)-(*R*)-**8** by sequential Birch reduction, mono-tosylation, and substitution or the *Z*-olefinic chlorohydrin (*Z*)-(*R*)-**12** by sequential *cis*-hydrogenation, Birch reduction, mono-tosylation, and substitution, both in satisfactory overall yields. When they were subjected to three dihydroxylation conditions, both afforded the corresponding two diastereomers in good total yields, though in not high diastereoselectivity (**Table 1**). Noteworthy was the stereochemical difference between AD-mix-α[4] and AD-mix-β[4] in the reaction with (*E*)-(*R*)-**8** where diastereoselection was exhibited only by the latter oxidant giving (2*R*,4*R*,5*R*)-**14** as the major product, as expected by the empirical rule.[4] On the contrary, the former oxidant did not exhibited high diastereoselection, though the expected (2*R*,4*S*,5*S*)-**13** was the major product. These may be taken in the former combination to be the "mismatched pairing[5]" and the latter to be the "matched pairing[5]." As expected,[4] the (*Z*)-olefin (*Z*)-(*R*)-**12** did not exhibit high diastereoselection; it furnished the mixture of (2*R*,4*S*,5*R*)-**15** and (2*R*,4*R*,5*S*)-**16** in about 1:2 ratio in an excellent total yield under all dihydroxylation conditions (Entries 4~6). The observed overwhelmed β-face selectivity (except in Entry 2) was presumed to be mostly due to the steric effect of the hydroxyl group present in **8** and **12**.

Very fortunately, the product mixtures from both **8** and **12** were readily (or after a base-catalyzed cyclization) separable by column chromatography to give the corresponding tetrahydrofurans, **18**~**21**, *via* the transient epoxide intermediates **17** on exposure of the separated glycol, **13**~**16**, to aqueous base, respectively. Thus, (2*R*,4*S*,5*S*)-**13** was treated with potassium carbonate (5 eq) in 50% aqueous *tert*-

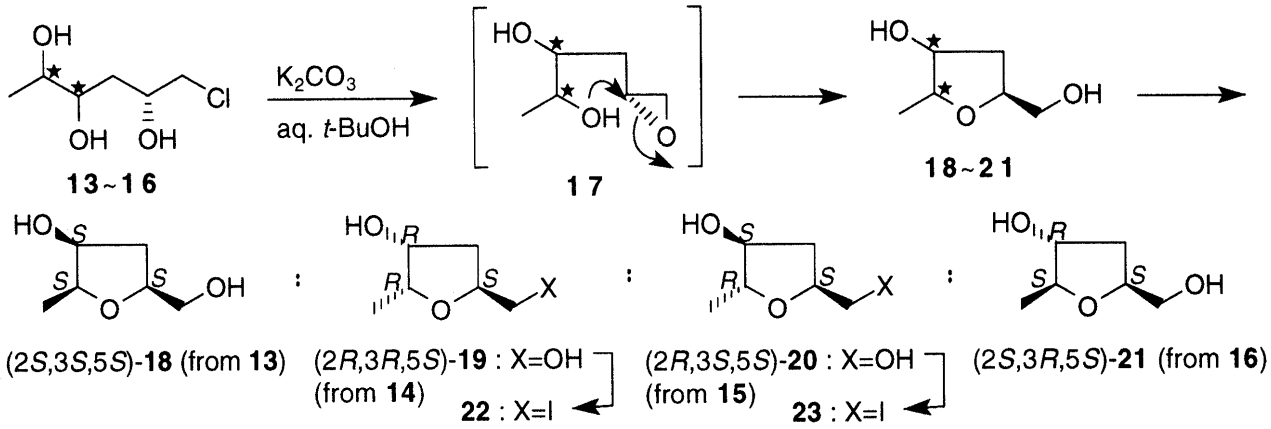


Chart 4

butanol at room temperature to afford the tetrahydrofuran (2*S*,3*S*,5*S*)-**18**, $[\alpha]_D^{31}$ +47.7° (*c*=0.90, $CHCl_3$) [lit.[6]: $[\alpha]_D^{25}$ +51.6° (*c* 0.50, $CHCl_3$)], in 65% yield. Quite similarly, (2*R*,4*R*,5*R*)-**14** gave (2*R*,3*R*,5*S*)-**19**, $[\alpha]_D^{30}$ –4.22° (*c*=0.96, $CHCl_3$), in 61% yield, which then was treated with iodine in the presence of triphenylphosphine and imidazole[7] to give the iodide **22**, $[\alpha]_D^{25}$ –42.2° (*c*=1.1, $CHCl_3$) [lit.[7]: –33.12° (*c*=0.88, $CHCl_3$): 81% ee], in 68% yield. (2*R*,4*S*,5*R*)-Triol (**15**) afforded the iodide **23**, $[\alpha]_D^{29}$ –14.7° (*c*=0.49, $CHCl_3$) [lit.[8]: $[\alpha]_D$ –10.64° (*c*=1.3, $CHCl_3$): 81% ee], in 47% overall yield *via* (2*R*,3*S*,5*S*)-alcohol **20**, $[\alpha]_D^{28}$ +45.0° (*c*=0.50, $CHCl_3$), while (2*R*,4*R*,5*S*)-triol (**16**) afforded (2*S*,3*R*,5*S*)-**21**, $[\alpha]_D^{27}$ –6.44° (*c*=0.42, $CHCl_3$) [lit.[2]: $[\alpha]_D^{22}$ –6.2° (*c*=0.5, $CHCl_3$)], in 69% yield.

Since natural (+)-*epi*-muscarine (**2**) from the (2*S*,3*S*,5*S*)-**18**[6] and natural (+)-muscarine (**1**) from the (2*S*,3*R*,5*S*)-**21**[2] have been obtained and since unnatural (–)-*epiallo*-muscarine (*ent*-**4**) from the (2*R*,3*R*,5*S*)-iodide[8] (**22**) and unnatural (+)-*allo*-muscarine (*ent*-**3**) from the (2*R*,3*S*,5*S*)-iodide[6] (**23**) have been obtained, the present procedure constitutes formal syntheses of all diastereomers of both the natural and the unnatural forms of the muscarine alkaloids using an appropriate chiral *O*-benzylglycidol.[3]

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