PRACTICAL CHIRAL ROUTE TO MUSCARINE AND ITS THREE DIASTEREOMERS

Yukio OHSHIBA, Takehiko YOSHIMITSU, and Kunio OGASAWARA*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan

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 (+)-(2S,3R,5S)-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, (+)-(2S,3S,5S)-*epi*-muscarine (**2**), (+)-(2S,3R,5R)-*allo*-muscarine (**3**), and (−)-

muscarine (**1**)   *epi*-muscarine (**2**)   *allo*-muscarine (**3**)   *epiallo*-muscarine (**4**)
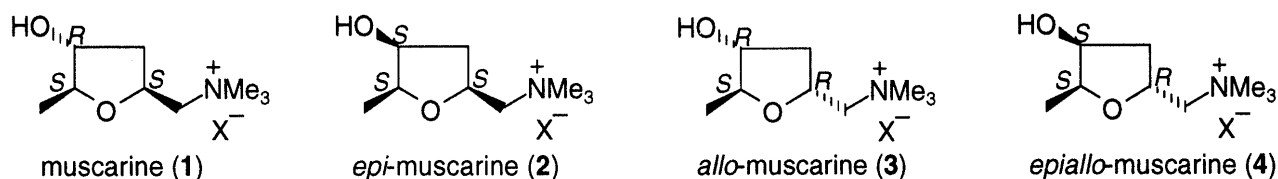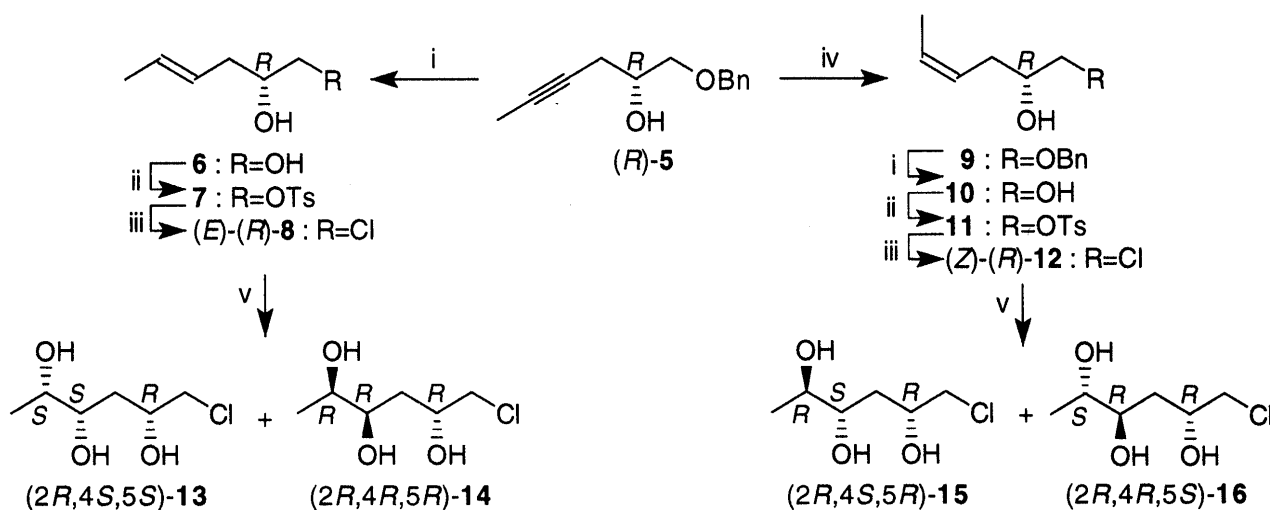
Chart 1

(2S,3S,5R)-*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

(2R,4S,5S)-**13**   (2R,4R,5R)-**14**   (2R,4S,5R)-**15**   (2R,4R,5S)-**16**

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.
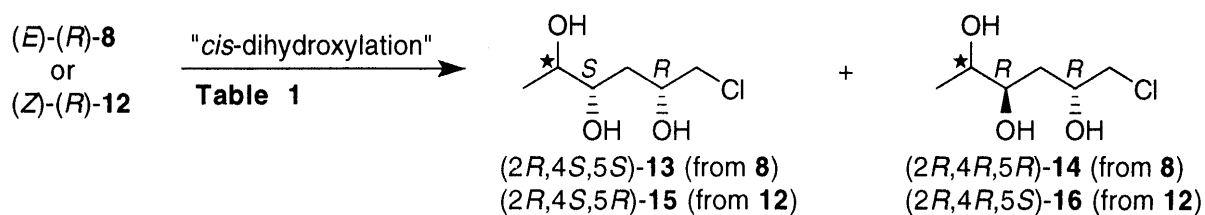
(E)-(R)-8
or
(Z)-(R)-12

"cis-dihydroxylation"
Table 1

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

+

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

Chart 3

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

Entry	Substrate	Oxidant	Product (%) 13	Product (%) 14	Entry	Substrate	Oxidant	Product (%) 15	Product (%) 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 (2R,4R,5R)-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 (2R,4S,5S)-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 (2R,4S,5R)-15 and (2R,4R,5S)-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, (2R,4S,5S)-13 was treated with potassium carbonate (5 eq) in 50% aqueous *tert*-
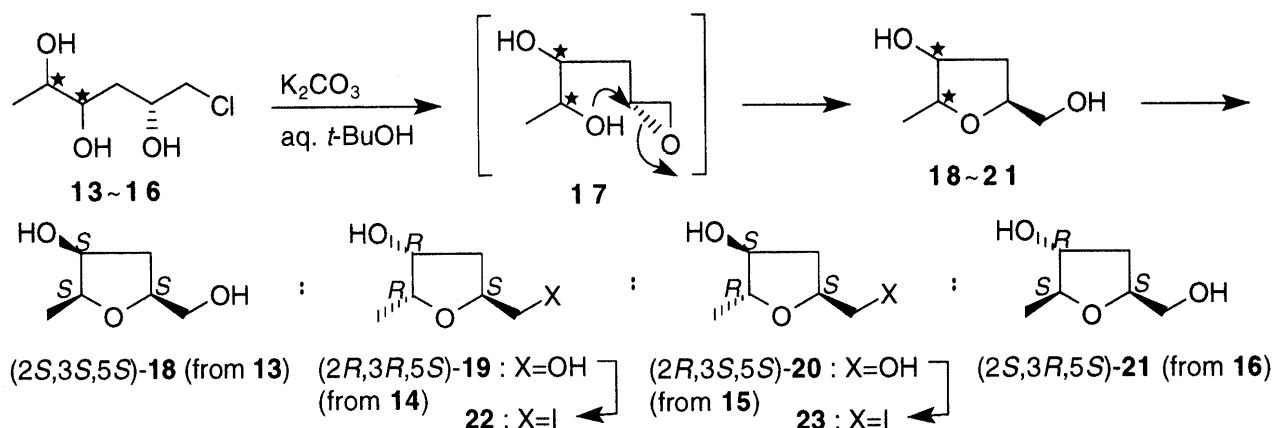
Chart 4

butanol at room temperature to afford the tetrahydrofuran (2S,3S,5S)-**18**, [α]$_D^{31}$ +47.7° (c=0.90, CHCl$_3$) [lit.[6]: [α]$_D^{25}$ +51.6° (c 0.50, CHCl$_3$)], in 65% yield. Quite similarly, (2R,4R,5R)-**14** gave (2R,3R,5S)-**19**, [α]$_D^{30}$ −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**, [α]$_D^{25}$ −42.2° (c=1.1, CHCl$_3$) [lit.[7]: −33.12° (c=0.88, CHCl$_3$): 81% ee], in 68% yield. (2R,4S,5R)-Triol (**15**) afforded the iodide **23**, [α]$_D^{29}$ −14.7° (c=0.49, CHCl$_3$) [lit.[8]: [α]$_D$ −10.64° (c=1.3, CHCl$_3$): 81% ee], in 47% overall yield via (2R,3S,5S)-alcohol **20**, [α]$_D^{28}$ +45.0° (c=0.50, CHCl$_3$), while (2R,4R,5S)-triol (**16**) afforded (2S,3R,5S)-**21**, [α]$_D^{27}$ −6.44° (c=0.42, CHCl$_3$) [lit.[2]: [α]$_D^{22}$ −6.2° (c=0.5, CHCl$_3$)], in 69% yield.

Since natural (+)-epi-muscarine (**2**) from the (2S,3S,5S)-**18**[6] and natural (+)-muscarine (**1**) from the (2S,3R,5S)-**21**[2] have been obtained and since unnatural (−)-epiallo-muscarine (ent-**4**) from the (2R,3R,5S)-iodide[8] (**22**) and unnatural (+)-allo-muscarine (ent-**3**) from the (2R,3S,5S)-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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