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TOTAL SYNTHESIS OF THE MUSCARINES

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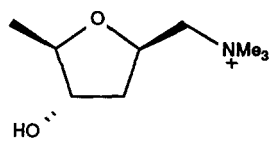
Summary The total syntheses of racemic muscarine and *allo*-muscarine have been achieved using as a key step the stereospecific photochemical ring expansion of a cyclobutanone

Muscarine (**1**) and *allo*-muscarine (**2**), components of the red fly agaric mushroom *Amanita muscaria*, were the subjects of intense scrutiny even before their structures were known [2] The action of muscarine on smooth muscle so resembles that of acetylcholine that direct action on cholinergic receptors in the autonomic nervous system has come to be called muscarinic More recently, muscarine's involvement with "second messengers" such as inositol phospholipid metabolites has been demonstrated [3] The availability of muscarine stereoisomers and analogues has permitted a fairly detailed mapping of the cholinergic receptor [4] These important biological considerations have generated considerable interest in muscarine among synthetic chemists,[5] and indeed organic synthesis has been an important contributor to this area



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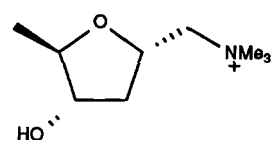

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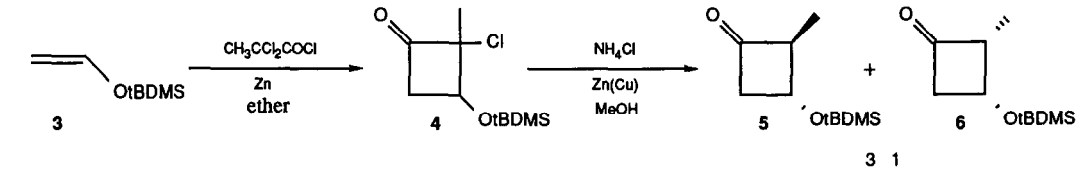
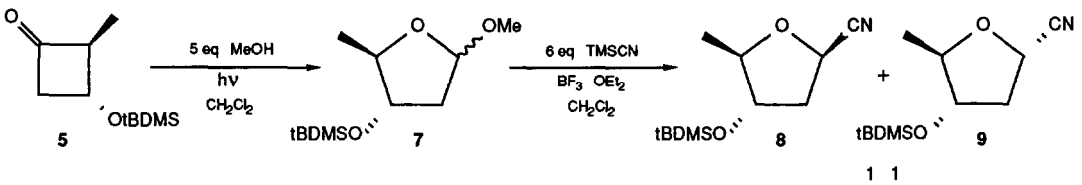
We have undertaken the synthesis of the muscarines using the photochemical generation of oxacarbenes from cycloalkanones [6] Recent studies[7] have revealed this reaction as a useful entrée into tetrahydrofuran structures For applications in natural products synthesis, stereoselectivity in the ring expansion is a primary requirement The reaction has been postulated to have a radical mechanism,[8] which generates concern that stereochemistry might be lost, but concerted mechanisms have also been proposed [9] One example of the ring expansion of an α-chiral cyclobutanone proceeds with retention of configuration [10] In a related 3-furanone, however, complete loss of stereochemistry is observed [11] The application of the photochemical ring expansion to the stereoselective generation of the muscarine skeleton was therefore of interest

The synthetic plan called for the construction of a cyclobutanone with *trans* stereochemistry of the α-methyl and β-alkoxyl groups. The cycloaddition of several ketenes with enol ethers has been reported to form 3-

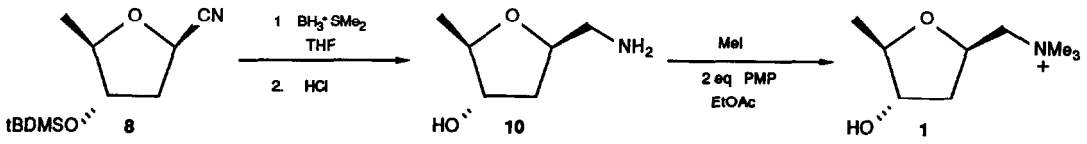
alkoxycyclobutanones in good yield [12] Cycloaddition of silyl enol ether 3[13] with methylchloroketene, generated by the zinc dechlorination of 2,2-dichloropropionyl chloride,[14] gives the chlorocyclobutanone in 80% yield as a 4 1 mixture of isomers [16] Although it is reported[12] that activated zinc must be used in the generation of the ketene, we found that this is unnecessary Reductive removal of the halogen may be accomplished in 82% yield using zinc-copper couple in methanol saturated with ammonium chloride Only a trace of β-elimination product is observed The cyclobutanones 5[16] and 6[16], obtained as a 3 1 *trans cis* mixture (assigned on the basis of literature data[12b]), are easily separated by flash chromatography (5 95 ether/hexanes) They are extremely prone to loss of the siloxy group, yielding α-methylcyclobutenone In contrast to the situation in the dehalogenation step, conducting the subsequent photochemical step at slightly above ambient temperature results in enone only However, irradiation of **5** at -78° in methylene chloride containing 5 equiv MeOH (conditions previously developed[7b]) completely suppresses enone formation and provides in 55% yield a 2 1 mixture of acetals **7** [16] The low temperature reaction conditions have been previously shown to increase yields[7a] by suppressing decarbonylation and β-cleavage processes However, in this instance 10% of the cyclopropane (decarbonylation product) and 23% of the *trans* silyl enol ether (β-cleavage product) are obtained Notably, there is no trace of any isomeric ring expansion product having the *cis* stereochemistry of the methyl and siloxy groups





The condensation of **7** with trimethylsilyl cyanide was examined under a variety of conditions A potential pitfall in the planned Lewis acid-catalyzed condensation is formation of acyclic alkoxy nitriles *via* a ring-opened oxonium ion Consistent with previous reports,[15] this ring-opening is observed to the extent of 25% when the Lewis acid is stannic chloride Boron trifluoride etherate proved a better choice On a 0 1 mmol scale, the mixture of nitriles **8** and **9** is formed to the exclusion of ring-opened products and in 90% yield On scale up, these compounds are still obtained in 80% yield, but 10% of acyclic material is also found It did not prove possible to increase the formation of **8** (muscarine stereochemistry) at the expense of **9** (*allo*-muscarine stereochemistry) by a change of reaction conditions The equilibrium ratio of **8 9** (*tert*-BuOK, *tert*-BuOH, THF) is 45 55 Kinetic protonation (LDA, AcOH) leads to a similar ratio of isomers For practical purposes, the mixture is of little consequence, since the epimeric nitriles are easily separated by flash chromatography (5 95 EtOAc/hexanes) The anomeric identity of the nitriles **8** and **9** was determined by ^{1}H NMR[16] in accord with previous investigations [5f,17]

The elaboration of the nitrile in either series to the natural products was accomplished by the same 2-step sequence Treatment of **8** with borane-methyl sulfide complex[18] followed by acid hydrolysis gives the deprotected primary amine in 99% yield Quaternization of **10** with excess methyl iodide and 1,2,2,6,6-pentamethylpiperidine (PMP)[19] followed by ion-exchange to the chloride gives muscarine in 71% yield The compound obtained is identical by both ^{1}H NMR and bioassay with material obtained from Sigma Similarly, *allo*-muscarine is obtained in 67% overall yield from **9**



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16. ^{1}H NMR ($CDCl_3$)· **4** (major)· δ 4 51 (dd, J=6,8, 1H), 3 32 (dd, J=8,18, 1H), 3 01 (dd, J=6,18, 1H), 1 57 (s, 3H), 0 90 (s, 9H), 0 12 (s, 3H), 0 10 (s, 3H) **5** δ 4 09 (ddd, J=5 5,6 0,6.7, 1H), 3 21 (m, 1H), 3.12 (ddd, J=1.4,6 7,17 3, 2H), 3 04 (ddd, J=3 6,6 0,17 3, 1H), 1 15 (d, J=7, 3H), 0.90 (s, 9H), 0 09 (s, 3H), 0 08 (s, 3H) **6**· δ 4 59 (dt, J=3,7, 1H), 3 29 (m, 2H), 2 80 (dd, J=3,19, 1H), 1 10 (d, J=7, 3H), 0.89 (s, 9H), 0 07 (s, 3H), 0 06 (s, 3H) **7** (major) δ 4 99 (dd, J=2,5, 1H), 4 09 (dt, J=5,7, 1H), 3 86 (dq, J=5,6, 1H), 3 33 (s, 3H), 2 13 (ddd, J=2,7,13, 1H), 1 98 (ddd, J=5,7,13, 1H), 1.26 (d, J= 6, 3H), 0 87 (s, 9H), 0 05 (s, 3H), 0 04 (s, 3H) (minor) δ 4 90 (dd, J=3,6, 1H), 3 81 (dq, J=6,7, 1H), 3.71 (dt, J=7,9, 1H), 3 36 (s, 3H), 2.44 (ddd, J=6,8,14, 1H), 1 74 (ddd, J=3,7,14, 1H), 1 23 (d, J=6, 3H), 0 87 (s, 9H), 0.04 (s, 3H), 0 03 (s, 3H) **8**. δ 4 72 (t, J=7, 1H), 4 07 (dt, J=4,6, 1H), 3.90 (dq, J=3,7, 1H), 2 38 (ddd, J=6,8,13, 1H), 2 20 (ddd, J=4,7,13, 1H), 1.24 (d, J=7, 3H), 0 87 (s, 9H), 0 06 (s, 6H) **9** δ 4 77 (dd, J=3,9, 1H), 4 05 (dq, J=4,6, 1H), 3 93 (dt, J=4,6, 1H), 2 45 (ddd, J=6,9,13, 1H), 2 15 (dt, J=4,13, 1H), 1 19 (d, J=6, 3H), 0 90 (s, 9H), 0 07 (s, 6H) **10** δ 4 13 (m, 1H), 3 98 (dt, J=4,6, 1H), 3 86 (dq, J=4,6, 1H), 2 88 (dd, J=4,13, 1H), 2 70 (dd, J=6,13, 1H), 1 93 (ddd, J=6,9,13, 1H), 1 85 (ddd, J=3,6,13, 1H), 1 24 (d, J=6, 3H)

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