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Diastereoselectivity in the Synthesis of 3(2H)-Furanones. Total Synthesis of (+)-Muscarine

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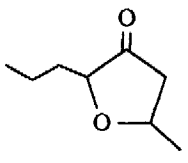
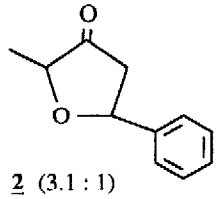
Summary: The carbenoid cyclization reaction to form disubstituted 2,5-3(2H)-furanones exhibited a stereoselection favoring the *cis* isomers. This phenomenon was exploited in an enantioselective synthesis of (+)-muscarine.

In the previous paper we reported a new approach towards the synthesis of 3(2H)-furanones using a Rh(II) catalyzed carbenoid C-H insertion cyclization of α-alkoxy diazoketones.[1] During the course of this work, it was observed that for unsymmetrically 2,5-disubstituted furanones, a stereoselection favoring the formation of the *cis* isomers was prevalent. The degree of diastereoselection varied in the four examples studied but consistently supported this trend. The assignments of stereochemistry were made by inspection of the ^{1}H NMR spectra of the *cis/trans* isomer pairs, as well as through nuclear Overhauser enhancement (NOE) measurements.[2]



1 (6.8 : 1)



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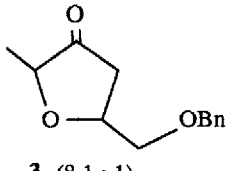
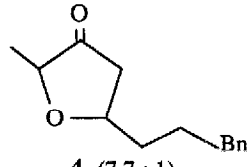


3 (8.1 : 1)

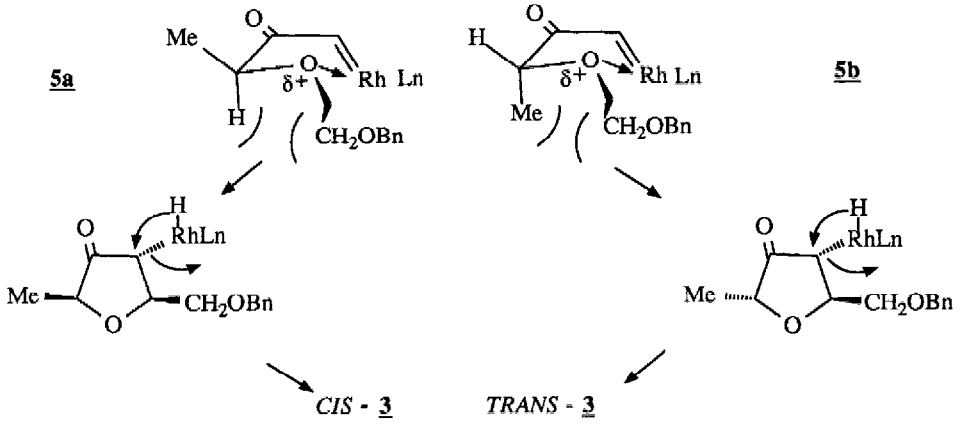


4 (7.7 : 1)

* numbers in parentheses refer to the *cis/trans* ratios

A rationale for the best case, furanone **3**, realizing a 8:1 *cis/trans* preference, was proposed according to the following scheme. The ether oxygen orients the conformation of the C-H insertion process by coordinating to the rhodium metal. This places the C2 α-hydrogen in either a pseudo-axial, **5a**, or pseudo-equatorial, **5b**, position. The insertion proceeds via a β-hydride transfer to the metal (a mechanism assisted by the adjacent

ether oxygen) leading to corresponding rhodium hydride species which reductively eliminate to the *cis* and *trans* furanones 3.[3] The steric compression is expected to be greater for intermediate **5b** which would lead to the minor *trans* isomer of **3**.[4] Originally, the lone pair of the benzyl ether was thought to participate in coordination to the metal, thereby orienting the bulky benzyl group in space. Examples **1**, **2**, and **4** lack this additional capacitiy for complexation. Moreover furanone **4**, isosteric with **3**, was produced with a similar diastereoselection. We concluded that the stereochemical bias is due to the steric requirements in the transition state.[5]



Initially example **3** was chosen with the goal of synthesizing the natural product, muscarine, a metabolite of the mushroom *Amanita muscaria*.[6] Muscarine binds with high affinity to the acetylcholine receptor and is routinely used to study cholinergic pharmacology. Muscarine, isolated from natural sources is frequently contaminated with allomuscarine (epimeric at C2 and C3) and its purification is tedious and impractical. Thus a short and efficient synthesis of (+)-muscarine has utilitarian value. With furanone **3** in hand, all that remained to complete the synthesis in a formal sense was the removal of the benzyl group by catalytic hydrogenation, and reduction of the ketone since the resulting diol **9**, has been converted to muscarine.[5h] This route relied on the stereo-random reduction of the ketone at C3.

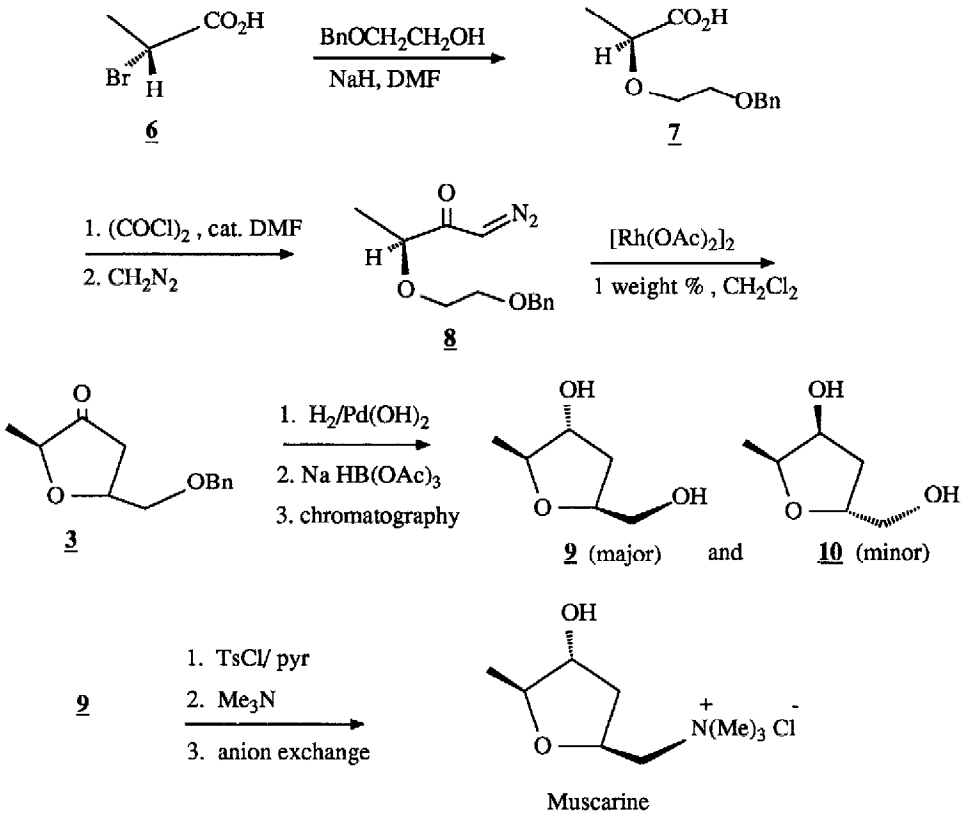
The preparation of optically pure muscarine using our approach required setting the stereochemistry at the C2 chiral center in the S configuration. This was achieved using R-2-bromopropionic acid, derived from D-alanine[7] and displacing the bromide with the sodium alkoxide of 2-benzyloxyethanol. The reaction proceeded with complete inversion of configuration to produce the acid **7**.[8] Diazotization via standard methodology afforded **8** in 64% overall yield from bromopropionic acid. Cyclization catalyzed by $[Rh(OAc)_2]_2$ afforded a modest 47% yield of **3** (8:1 *cis/trans*). After hydrogenolysis of the benzyl, the isomers were separated by preparative gas chromatography (10% OV 351) for purposes of characterization. For larger scale preparations the diastereomers were carried through to the next step.

We decided to address the stereospecific reduction of the ketone at C3, employing the recently described reducing agent $NaHB(OAc)_3$.[9] This agent requires the presence of an alcohol function proximal to the ketone to effect a intermediate complex which delivers the hydride *syn* to the pendant alcohol. The reaction was carried out using the procedure of Saksena and Mangiaracina with the added modification of adding 4A molecular sieves to the reaction mixture. The reduction produced diols **9** and **10** (derived from the minor *trans* isomer of **3**)

as the sole products in 71 % yield, indicating that the reduction is stereospecific. A simple chromatographic separation at this stage afforded pure **9**, $[\alpha]_D$= -16.9° (c =1.14, EtOAc).

The synthesis was completed by selective tosylation of the primary alcohol in 69% yield, heating the tosylate with trimethylamine in a sealed tube, and ion exchange with the Dowex-1-chloride resin to furnish (+)-muscarine chloride in 72% yield (from the tosylate).[10,11]

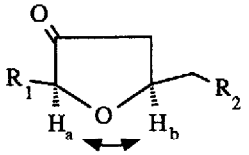
Synthesis of (+) - Muscarine



In conclusion, the selectivity observed in the cyclization of diazoketone **8** provided a short and practical route to (+)-muscarine, in nine steps from the starting bromoacid in a global yield of 7.3%, and further demonstrates the utility of the carbenoid C-H insertion approach to 3-(2H)-furanones.

References and Notes:

1. See preceeding paper.
2. Proton NMR spectra consistently indicated that the chemical shift of H_b was upfield in the *cis* substituted furanones compared with the *trans* substituted furanones. Stereochemical assignments were confirmed by NOE experiments.



NOEs 8 - 12%

3. A similar mechanism, invoking hydride transfer, was proposed by D. F. Taber and R. E. Ruckle Jr. J. Am. Chem. Soc. *108*, 7686, (1986).
4. Equilibration of the *cis/trans* cyclization mixture (8:1) of furanones **3**, using CD_3ONa/CD_3OD produced a thermodynamic 1:1 mixture of isomers.
5. As we offer no experimental data to support our mechanism, we remain open to alternative interpretations. In accordance with the referee's suggestion, it is of course possible that direct C-H insertion is taking place, and the stereoselectivity is due to the conformational preference of the folding ether. This preference could be governed by the overlap of the target C-H bond and the nonbonding electrons on the adjacent oxygen. Clearly further work is required to yield a better mechanistic understanding.
6. Previous syntheses of muscarine: a) F. Kogl, H. C. Cox, C. A. Salemink, *Experientia*, *13*, 137, (1957). b) E. Hardegger, F. Lohse, Helv. Chim. Acta, *40*, 2383, (1957) and *41*, 2401, (1958). c) H. C. Cox, E. Hardegger, F. Kogl, P. Liechti, F. Lohse, C. A. Salemink, Helv. Chim. Acta, *41*, 229, (1958). d) T. Matsumoto, A. Ichihara, N. Ito, Tetrahedron, *25*, 5889, (1969). e) J. Whiting, Y. K. Au-Young, B. Belleau, Can. J. Chem. *50*, 3322, (1972). f) G. Fronza, C. Fuganti, P. Graselli, Tetrahedron Lett., 3941, (1978). g) P. C. Wang, M. M. Joullié, Tetrahedron Lett., 1657, (1978). h) A. M. Mubarak, D.M. Brown, Tetrahedron Lett., 2453, (1980). i) W. C. Still, J. A. Schneider, J. Org. Chem., *45*, 3375, (1980). j) S. Pochet, T. Dinh-Hyunh, J. Org. Chem., *47*, 193, (1982). k) M. Chmielewski, P. Guzik, Heterocycles, *22*, 7, (1984). l) R. Amouroux, B. Gerin, M. Chastrette, Terahedron, *41*, 5321, (1985). m) J. Mulzer, A. Angermann, W. Munch, G. Schlichthorl, A. Hentzchel, Liebigs Ann. Chem., 7, (1987). n) A. Bandzouzi, Y. Chapleur, J. Chem. Soc., Perkin I, 661, (1987). o) M. C. Pirrung, C. V. DeAmicis, Tetrahedron Lett., *29*, 159, (1988).
7. M. Harfenist, D. C. Hoerr, R. Crouch, J. Org. Chem. *50*, 135671, (1985).
8. Optical purity (>97%) was determined using NMR shift reagent $Eu(hfc)_3$ from Aldrich on the methyl ester of **7**.
9. A. K. Saksena, P. Mangiaracina, Tetrahedron Lett., *24*, 273, (1983).
10. All products were characterized spectroscopically by NMR, IR, and MS.
11. The synthetic compound was compared with a commercial sample of 80% pure (+) - muscarine chloride obtained from Sigma Chemicals and demonstrated the same spectral properties. Data for (+) - muscarine(Cl): $[\alpha]_D$= +8.18° (c=2.97,EtOH) *Literature value (Merck Index) = +8.1° (c=3.5,EtOH).* ^1H NMR (MeOH-D_4): δ1.25 (3H, d, J=3.5Hz), 1.83-2.10 (2H, complex m), 3.25(9H,s), 3.54(2H,ddd, J^1=13.6Hz, J^2=9.6Hz, J^3=1.8Hz), 3.94-4.03 (2H, complex m), 4.63 (1H, q, J=6.0Hz); ^{13}C NMR (MeOH-D_4): δ18.8, 38.4, 53.6, 70.4, 71.9, 75.4, 84.3.

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