SYNTHESIS OF A THIOMUSCARONE ANALOG

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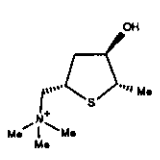
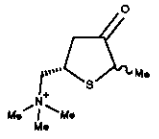
Abstract - A novel synthesis of the thiomuscarone analog, 1-thia-2,8-dimethyl-3-oxo-8-azaspiro[4.5]decane (**4**) has been achieved. Other thiolan-3-ones which are highly substituted in the 5-position should be available by this method which provides an alternative to the classical Michael reaction-Dieckmann sequence.

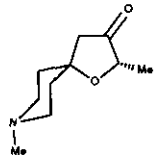
Eugster et al. have long ago synthesized racemic thiomuscarine (**1**) and thiomuscarone (**2**).[1] Thiomuscarone epimerized with extreme facility, existed as a diastereomeric mixture, and was considerably more potent than thiomuscarine which had only marginal muscarinic activity.[2]



Thiomuscarine 1



Thiomuscarone 2



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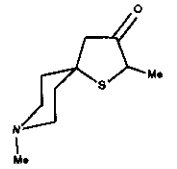

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Recently, an enantiomerically pure compound, (EPC), synthesis of muscarone analog (**3**) has been reported from our laboratories,[3] and it was expected that its thiomuscarone analog (**4**) would also be of interest. Synthetic studies directed toward (**4**) are reported herein.

The first approach (**Figure 1**) pursued was the classical Michael addition-Dieckmann sequence which was employed in Eugster's synthesis of thiomuscarine. Compound (**5**), readily available by Wadsworth-Emmons olefination of 4-N-carboethoxypiperidone, could not be converted by us via either one or two step Michael reaction-Dieckmann sequences[4] with thiolactic acid methyl ester to the thiophenone (**7**). It was, however, possible to achieve the desired reaction, albeit in low yield, using an acid catalyzed variant of this sequence. When carboxylic acid (**6**), which was prepared quantitatively by hydrolysis of (**5**) with pyridine-NaOH,[5] was heated in thiolactic acid with $Fe(OAc)_2$, a 7% yield of (**8**) was achieved.

This synthesis was not satisfactory and led us to explore novel synthetic routes (**Scheme 1**) to the oxothiolane system of (**8**) using the key intermediate, enone (**9**),[6] from the synthesis of muscarone analog (**3**). Sulfur functionality was introduced by Mitsunobu reaction of silyl ether hydrolysis product (**10**) with thioacetic acid[7] to give thioacetate (**11**). Attempts to hydrolyze (NH_3, NH_2NH_2) or directly cyclize (**11**) under acidic conditions afforded complex product mixtures. The stable thiol (**14**) was readily prepared by hydrazinolysis of thioacetate (**13**) which was prepared from enone

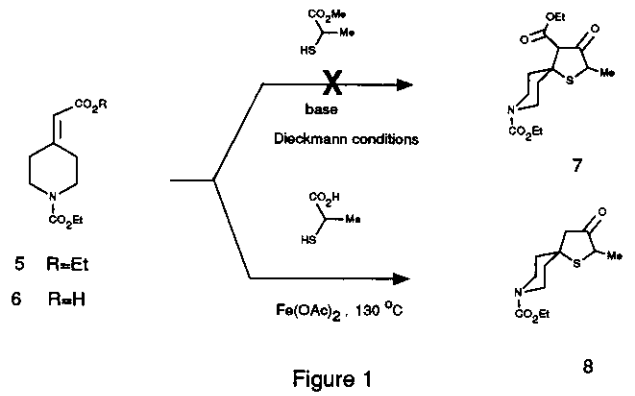
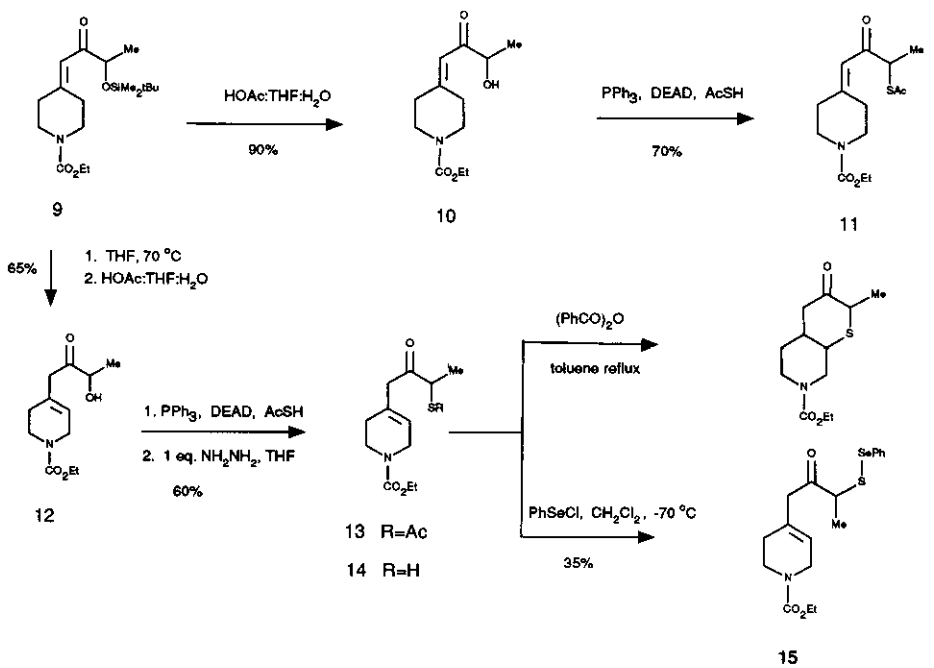


Figure 1

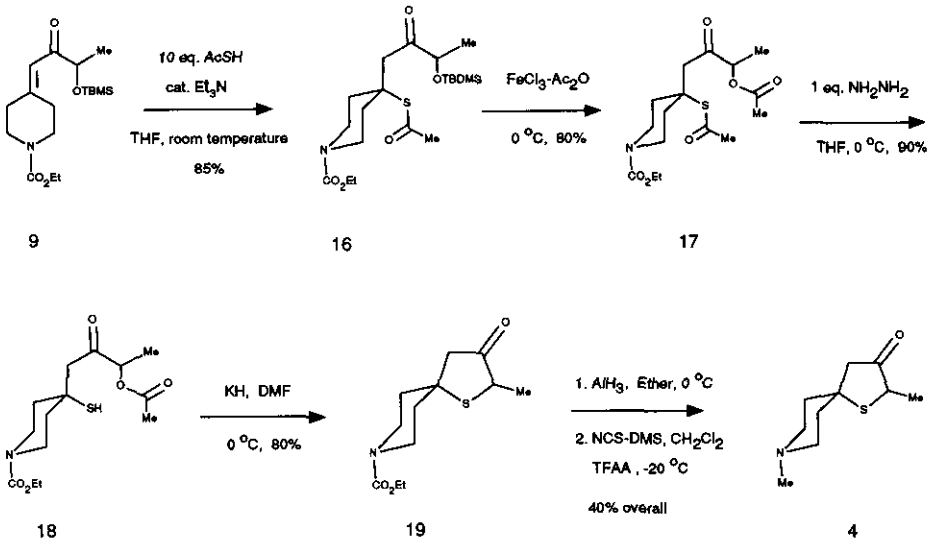
(12).[8] Attempts at acid-catalyzed intramolecular ring closure of (14) were unsuccessful, yielding complex product mixtures. Cyclization of (14) under radical conditions using benzoyl peroxide gave



Scheme 1

six-membered ring products whereas treatment with N-iodosuccinimide resulted in clean disulfide formation. Surprisingly, reaction of (14) with phenylselenyl chloride[9] in dichloromethane gave the stable thio-selenide (15) as the major product. The carbonyl function of (15) probably provides stability by electron donation to selenium.

Due to these difficulties in cyclization of the side chain sulfur function onto the preexisting ring, it was decided to reverse the sequence of bond connection. Thus, sulfur should be introduced first at the tertiary center of the piperidine ring and then the ring closure should occur at the side chain. This proved to be the better strategy and resulted in the synthesis depicted in **Scheme 2**. Stirring (**9**) overnight at room temperature in THF-thioacetic acid containing a catalytic amount of triethylamine



9 16 17 18 19 4

Scheme 2

afforded thioacetate (**16**). The silyl ether function of (**16**) was converted directly into the corresponding acetate (**17**) by the method of Ganem and Small[10], using $FeCl_3$ in acetic anhydride at 0 °C, and the thioacetyl function was cleaved selectively with hydrazine to give thiol (**18**). It is known that α-acetoxythiols can be converted to episulfides with base,[11]and, in fact, smooth episulfide[12] formation was observed upon reduction of the α-thioacetyl ketone (**13**) with sodium borohydride. This certainly occurs via acetyl transfer from sulfur to oxygen followed by thiolate displacement of acetate. These results provided the impetus for attempting the same reaction for the formation of the thiolan-3-one ring system. Indeed, when (**18**) was treated with potassium hydride in DMF at 0 °C, potassium acetate precipitated rapidly and concurrent clean formation of the ring closure product, thiolan-3-one (**19**), was observed. Conversion of (**19**) to thiomuscarone analog (**4**) was readily achieved by aluminum hydride reduction of the carbamate function to a 1:1 mixture of epimeric alcohols followed by Corey-Kim oxidation[13] of the mixture to (**4**) (mp HCl salt: 204-208 °C).

In conclusion a new five-step[14] sequence for the synthesis of the thiolan-3-one ring system has been devised which proceeds regiospecifically[4] and in moderate yield. Although the generality of the method has not been explored, it should provide a useful variant to the classical Michael addition-Dieckmann methodology.

REFERENCES AND NOTES

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6. Racemic (**9**) was used under the assumption that **4** would epimerize spontaneously by analogy with **2** and therefore not be isolable in optically pure form. The synthesis of **9** from 4-N-carboethoxypiperidone and a lactic acid derived phosphonate has been described.[3]
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14. Starting from a lactic acid derived phosphonate,[3] the overall yield of **19** is 45%.

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