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A SIMPLE ROUTE TO THE 8-OXABICYCLO[3.2.1]OCTYL AND 9-OXABICYCLO[3.3.1]NONYL SYSTEMS. SYNTHESIS OF THE 8-OXA ANALOG OF COCAINE[1].

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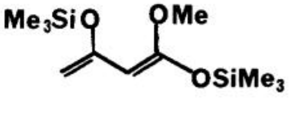
Summary: *In the presence of titanium tetrachloride, 1,3-bis(trimethylsiloxy)-1-methoxybuta-1,3-diene condenses with hexane-2,5-dione or 2,5-dimethoxytetrahydrofuran to give the 8-oxabicyclo[3.2.1]octyl compounds 3 and 6 respectively, and with 2,6-dimethoxytetrahydropyran to give the 9-oxabicyclo[3.3.1]nonyl derivative 8. Compound 6 is converted to a compound (9) which is the 8-oxa analog of cocaine.*

Recently we reported that 1,3-bis(trimethylsiloxy)-1-methoxybuta-1,3-diene (1) can serve as the equivalent of the dianion of methyl acetoacetate (2)^2. The reactivity of 1 differs from that of 2 in two important aspects: i) 1 reacts with electrophiles under neutral or acidic conditions whereas 2 is only formed under strongly basic conditions; ii) 2 reacts typically as 'hard' nucleophile in giving 1,2-adducts with conjugated carbonyl compounds whereas 1 reacts to give Michael adducts.



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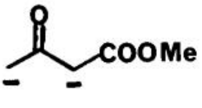

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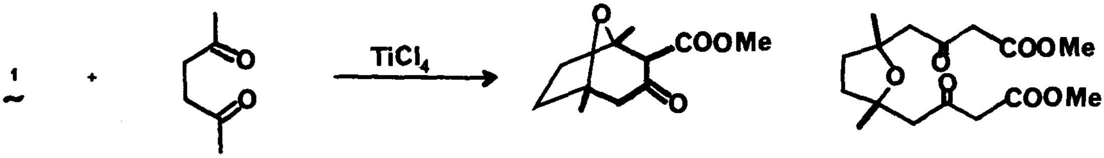
Furthermore, 1 can be considered as a three-carbon unit with two nucleophilic sites. It can therefore react with other fragments containing two electrophilic sites to give cyclic products. We have developed a novel regiocontrolled cycloaromatisation reaction based on this concept^3. We wish to report here the extension of this approach to the construction of seven- and eight-numbered rings. Essentially, it is based on the reaction of 1 with 1,4- and 1,5- dicarbonyl compounds or their equivalents.

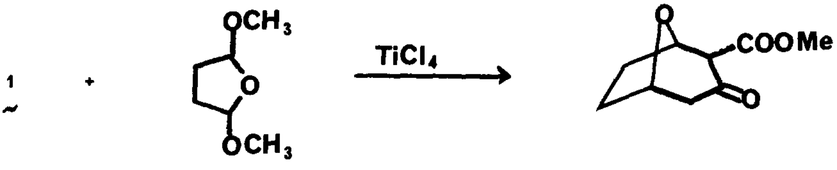
When 2,5-hexanedione was treated with titanium tetrachloride (1 equiv.)

and 1 in dry CH_2Cl_2 at -78° for 3 hr, two products, 3 and 4 were obtained. The bicyclic structure of 3 is evident from its chemical ionization mass spectrum (MH^+, m/e = 213) and pmr spectrum, in which the CH_3C-O- to CH_3O-ratio is 2:1. For the minor product 4 this ratio is 1:1. Neither compound shows a hydroxyl group in the infra-red, thus ruling out the alternative diol products.



3 4

Since it is known that acetals react with enol silyl ethers under activation by titanium tetrachloride[4], we have examined the reaction of 1 with 2,5-dimethoxytetrahydrofuran (5)[5] as a facile route to the 8-oxabicyclo[3.2.1] octyl system. We were pleased to find that 1 did indeed condense with 5 in the presence of titanium tetrachloride to give the bicyclic product 6 (79%)[6].



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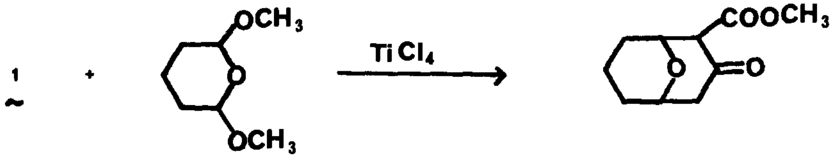
Similarly, we have synthesized the 9-oxabicyclo[3.3.1]nonyl compound 8 (yield 74%) by titanium tetrachloride catalysed condensation of 1 with 2,6-dimethoxytetrahydropyran (7)[7].



7 8

We have utilized this approach to synthesize compound 9, the 8-oxa analog of cocaine (10). The bicyclic product 6 was reduced by sodium borohydride to give the hydroxy compound 11 as a mixture of stereoisomers. Benzoylation of 11 with benzoyl chloride in pyridine gave the benzoate derivative also as a mixture of stereoisomers, of which 9 was present as the major component. The stereochemistry of 9 is deduced on the basis of its pmr spectrum. The chemical shift (δ = 5.3 ppm) and coupling constants with neighbouring hydrogens of the proton at C-3 are nearly identical with those of cocaine (H_3: δ 5.27 ppm, $J_{2,3}$ = 6.0 Hz, $J_{3,4\ ax}$ = 11.6 Hz, $J_{3,4\ eq}$ = 6.0 Hz)[8] and quite different from the other isomers of cocaine.

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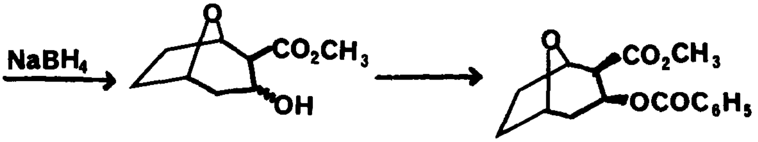

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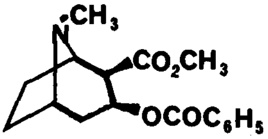

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Previously, the 8-oxabicyclo[3.2.1]octyl system has been constructed by the [4 + 3] cycloaddition of furan with oxyallyl[9] or cyclopropanone[10]. 8-Oxabicyclo[3.2.1]octyl compounds also serve as valuable precursors for tropones[11]. Our method of construction of this system has the advantage that the product does not have a plane of symmetry and the three-carbon bridge can be cleaved and converted into other tetrahydrofuran derivatives, e.g. the C-nucleosides. The facile entry into the 9-oxabicyclo[3.3.1]nonyl system 8 is rather unprecedented. It is clear that compound 1 can be usefully exploited for the construction of six,[2,3] seven and eight membered rings.

Acknowledgement: We thank the NSERC of Canada and the Ministry of Education, Government of Quebec, for financial support of this work.

References and Footnotes

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6. Experimental procedure. To the acetal **5** (ca. 5 mmol) in dry CH_2Cl_2 (15 ml) at -78° under nitrogen was added titanium tetrachloride (1 equivalent). A solution of **1** in CH_2Cl_2 (1 equiv. in 25 ml) was added dropwise over 20 min, and stirring at -78 continued for 3h. The dark red solution was then poured into excess aqueous $NaHCO_3$ and extracted with ether, the extracts dried ($MgSO_4$), evaporated, and the product purified by column chromatography on silica gel.
7. Compound **7** was prepared by toluenesulfonic acid-catalysed methanolysis of 2-methoxy-3,4-dihydro-2*H*-pyran[5].
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