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The Synthesis of a 5,7-Membered Fused-Ring Compound by a Tandem Pummerer Rearrangement and Intramolecular [4+3] Cycloaddition

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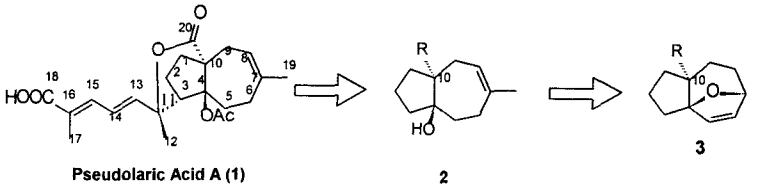
Abstract: A 5, 7-membered fused-ring compound with a functionalized angular substituent, 8-methoxy-8aα-methoxymethyl-7-phenylthio-1, 2, 3, 6-tetrahydro-3aα, 6β-epoxyazulene, was synthesized *via* a tandem Pummerer rearrangement and intramolecular [4+3] cycloaddition.

The [4+3] cycloaddition of allylic cations and dienes is a novel method for the construction of seven-membered rings.[1] Of particular interest is the intramolecular [4+3] cycloaddition for the formation of 5,7-membered fused rings by the generation of the appropriate alkoxyallylic cations or their equivalents such as polyhaloketones,[2] allylic alcohols or their derivatives,[3] α-chloroketones,[4] alkoxyallylic sulfones[5] and sulfoxides.[6] This intramolecular process has shown its potential for construction of complex polycyclic systems from simple precursors. However, this reaction has not yet been widely applied in the synthesis of natural products, because in most cases reported in the literature, [4+3] cycloaddition occurred only to not fully functionalized allylic cations. During the course of our study on the total synthesis of pseudolaric acid A (**1**), our major efforts are focused on the preparation of the 5, 7-membered fused ring compound **3** with a carboxyl group at C-10 *via* an intramolecular [4+3] cycloaddition (**Scheme 1**).



Pseudolaric Acid A (1) **2** **3**

Scheme 1

In a model study, 1-chloro-6-(2-furyl)-3-methoxycarbonyl-2-hexanone (**4**) was used as the functionalized precursor and treated with $LiClO_4$/TEA in ether at room temperature for 22h.[4] The desired intramolecular [4+3] cycloadduct **5** was not obtained. Reasoning that the methoxycarbonyl group in **4** inhibits the formation of the allylic cation, the ester group was transformed into a hydroxymethyl group which was further protected as ethers **9, 10, 11** or ester **12 (Scheme 2)**.

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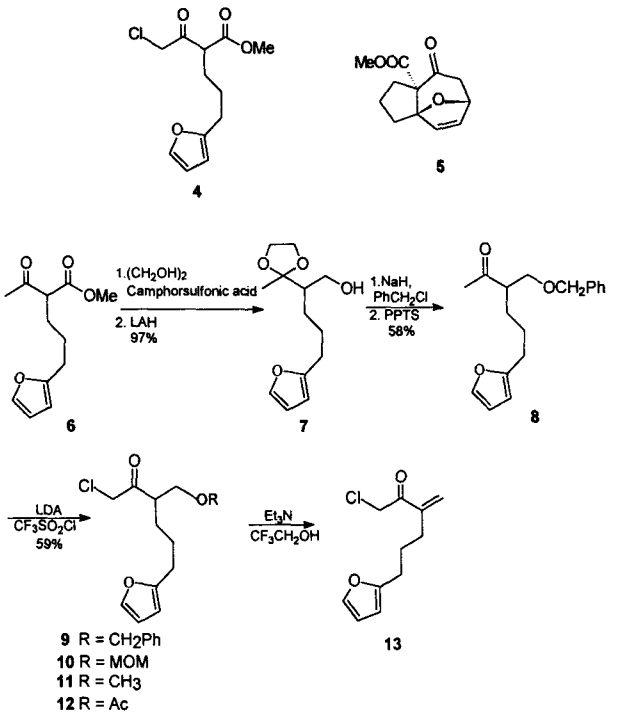
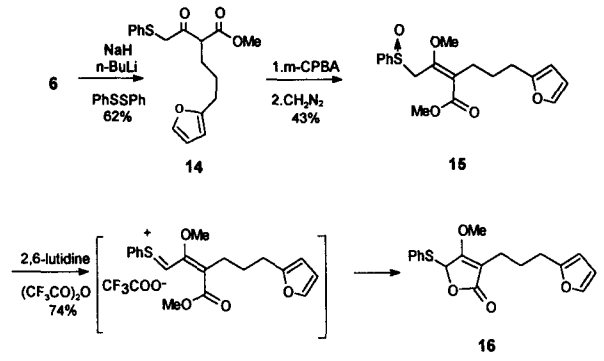


Scheme 2

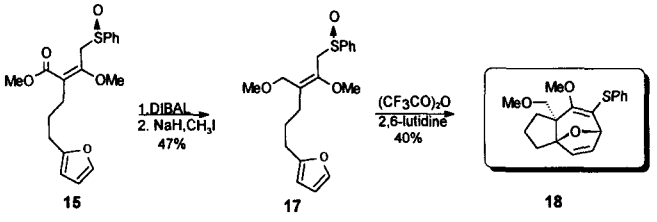
Compound **6** was converted to its ketal followed by reduction with LAH to give its alcohol **7**. Compound **7** was further protected as a benzyl ether with $NaH/PhCH_2Cl$ and removal of the ketal group afforded compound **8**.[7] Chlorination of **8** with LDA/CF_3SO_2Cl gave **9**. When **9** was subjected to intramolecular [4+3] cycloaddition under various conditions (CF_3CH_2OH/Et_3N, $LiClO_4/Et_3N$, CF_3CH_2ONa/ CF_3CH_2OH), an elimination occurred instead of cycloaddition, and the α,β–unsaturated ketone **13** was formed. In addition, compounds **10, 11** and **12** with different protecting groups were also tested, and the same product **13** was obtained.

In search of other means of generating allylic cations, sulfoxides have been reported by Harmata and his co-workers.[6] Therefore, sulfoxide **15** was considered as an appropriate intermediate for intramolecular [4+3] cycloaddition to construct the 5, 7-fused ring system. Compound **6** was treated with NaH and n-BuLi successively, and the resulting dianion reacted with diphenyl disulfide to give its sulfide **14** in 62% yield.[8] Oxidation of sulfide **14** with m-CPBA gave a sulfoxide [9] and treatment with etheral diazomethane can gave the E-isomer of the enol ether **15** in 43% overall yield. When **15** was treated with Tf_2O and 2,6-lutidine in methylene chloride at room temperature,[6] an α,β–unsaturated five-membered lactone **16** was obtained[10] (**Scheme 3**). The mechanism of this reaction may involve a Pummerer rearrangement[11] followed by intramolecular attack on the Pummerer intermediate.



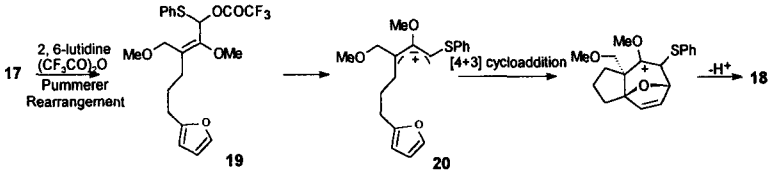
Scheme 3

In order to avoid the formation of lactone **16**, the ester **15** was reduced with DIBAL to the alcohol which was protected as a methyl ether with NaH/CH_3I giving the precursor **17** for intramolecular [4+3] cycloaddition in an overall yield of 47 %. The functionalized 5, 7-membered fused ring adduct **18** was finally obtained by the treatment of **17** with Tf_2O and 2, 6-lutidine in methylene chloride in 40% yield .[12] The relative configuration of **18** was assigned on the basis of Harmata reports **(Scheme 4)**.[5]



Scheme 4

The whole reaction mechanism from **17** to **18** could be rationalized as follows **(Scheme 5).**



Scheme 5

Intermediate **19** may be formed from sulfoxide **17** *via* Pummerer rearrangement in the presence of Tf_2O and 2, 6-lutidine, and converted to **18** *via* the alkoxyallylic cation **20** by an intramolecular [4+3] cycloaddition.

Application of this tandem Pummerer rearrangement and [4+3] cycloaddition reaction to the synthesis of polycyclic natural products such as pseudolaric acid A is under way and the results will be reported in due course.

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10. Selected Data of Compound **16**: ^{1}H NMR (400MHz, $CDCl_3$) : 7.50 (m, 2H), 7.28 (m, 4H), 6.28 (dd, 1H, J = 1.9, 3.0Hz), 5.90 (d, 1H, J = 3.0Hz), 5.82 (s, 1H), 4.02 (s, 3H), 2.38 (t, 2H, J = 7.4Hz), 2.12 (m, 2H), 1.40 (m, 2H); ^{13}C NMR ($CDCl_3$) : 172.1, 168.8, 155.3, 140.7, 135.6, 129.8, 129.0, 127.4, 110.1, 105.9, 105.0, 81.4, 58.2, 27.3, 26.8, 21.6; MS (m/z) : 330 (M^+, 6), 236 (100), 221 (27), 189 (30), 149 (46), 127 (24), 81 (36); IR(film) : 3050, 1755, 1660, 1365, 1350, 1005, 738, 692cm^{-1}; HRMS (EI) Calcd for $C_{18}H_{18}O_4S$: 330.09214 (M^+). Found: 330.09259.
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12. Selected Data of Compound **18**: ^{1}H NMR (600MHz, $CDCl_3$) : 7.36 (d, 2H, J = 7.4Hz), 7.02 (t, 2H, J = 7.5Hz), 6.87 (t, 1H, J = 7.4Hz), 6.32 (dd, 1H, J = 1.8, 5.7Hz), 5.96 (d, 1H, J = 5.7Hz), 4.80 (d, 1H, J = 1.8Hz), 3.74 (s, 3H), 3.29 (d, 1H, J = 9.2Hz), 3.19 (d, 1H, J = 9.2Hz), 2.95 (s, 3H), 2.31 (m, 2H), 2.10 (m, 1H), 1.97 (m, 2H), 1.80 (m, 1H); ^{13}C NMR (600MHz, $CDCl_3$) : 137.4, 136.9, 132.8, 129.4, 129.2, 128.2, 127.8, 127.2, 125.4, 108.8, 96.3, 80.9, 75.4, 59.9, 58.8, 56.6, 33.8(2C), 22.0; MS (m/z) : 330 (M^+, 58), 285 (100), 257 (14), 207 (46), 176 (38), 148 (32), 121 (26), 91 (38), 75 (88); IR (film) : 2982, 1735, 1601, 1450, 1211, 1132, 1047, 1022, 740, 692cm^{-1}; HRMS (EI) Calcd for $C_{19}H_{22}O_3S$: 330.12884 (M^+). Found: 330.12897.