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Construction of the Core of Pseudolaric Acid A and Mechanistic Studies on Intramolecular [4+3] Cycloaddition

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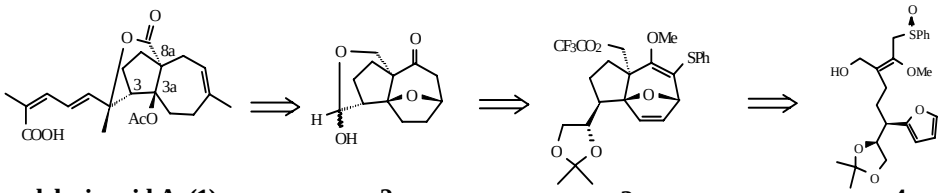
Abstracts: This paper describes the construction of hemiacetal **2**, the core of pseudolaric acid A *via* oxidative cleavage of acetonide **6** or **7** and enolization-hemiacetalization of aldehyde **8**. A plausible general mechanism for the intramolecular [4+3] cycloaddition of sulfoxide **4** to adduct **3** is suggested.

Keywords: Pseudolaric acid A, 5, 7- membered fused ring, hemiacetal, intramolecular [4+3] cycloaddition, mechanism.

Pseudolaric acid A **(1)**, which exhibits antifungal activity, cytotoxicity against several tumor cell lines *in vitro*, as well as contraceptive effects in mice, is a diterpenoid compound isolated from *Pseudolarix Kaemferi*[1]. The unusual structural feature in this molecule is a *trans* arrangement of the lactone and acetoxy group at the fused junction of 5, 7-fused ring skeleton bearing four contiguous stereogenic centers. The synthetic challenges posed by these structural elements in a rather compact molecule attract several groups to put their endeavors on the total synthesis of this molecule[2,3]. In this paper, we would like to report the construction of a 5, 7-membered fused ring hemiacetal **2** with the right configurations of the carbons corresponding to those of pseudolaric acid A based on the oxidative cleavage of acetonide **6** or **7** and enolization-hemiacetalization of aldehyde **8**.

Scheme 1

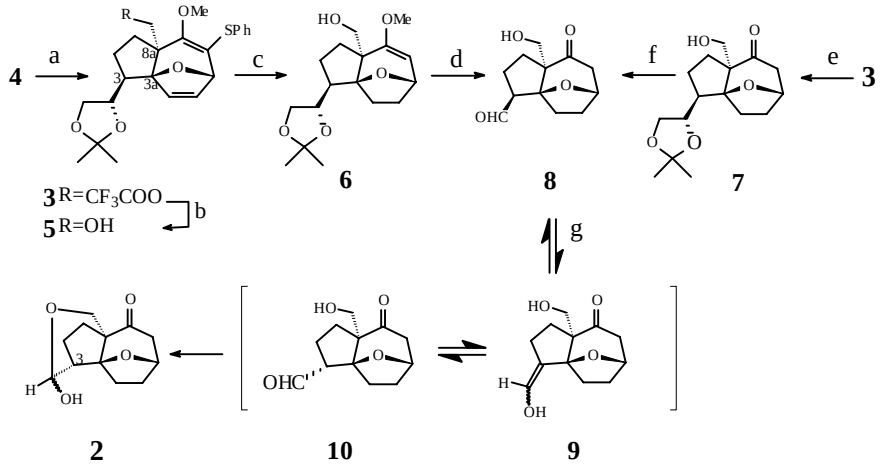


Pseudolaric acid A (1) **2** **3** **4**

The retrosynthetic analysis of pseudolaric acid A **(1)** is illustrated in. The target molecule **1** might be obtained from **2**, which was formed *via* manipulation at 5,7-

membered fused ring of acetonide **3**. Compound **3** was obtained by intramolecular [4+3] cycloaddition of **4**, which had been developed by our laboratory recently[4].

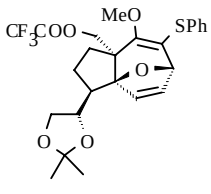
Scheme 2



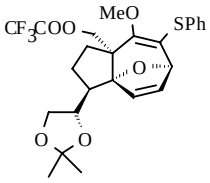
Reagents and conditions: a) $(CF_3CO)_2O$, 2, 6-lutidine, CH_2Cl_2, r.t., overnight, 50%; b) silica gel pretreated with Et_3N, 95%; c) Raney Ni (W-2), H_2, EtOH, r.t., 12h, 96%; d) H_3IO_5, EtOAc, r.t., 3h, 90%; e) Raney Ni (H-1), H_2, EtOH, r.t., 12h, 65%; f) H_3IO_5, EtOAc, r.t., 3h, 85%, g) CF_3COOH, $CHCl_3$, reflux, 12h, 33% (recovery of the starting material, 60%).

The synthesis of **2** is described in **Scheme 2**. Intramolecular [4+3] cycloaddition of sulfoxide **4** afforded cycloadduct **3** as a single isomer. The absolute configurations of the newly formed stereogenic centers in **3** were determined to be 3aR and 8aS based on 1D NOE difference spectrum and 2D NOESY experiments of its detrifluoroacetylated compound **5**[4]. However the configuration of C-3 in **3** is opposite to that of pseudolaric acid A, the inversion of the configuration of C-3 to meet the stereochemistry of the skeleton of pseudolaric acid A was thus executed.

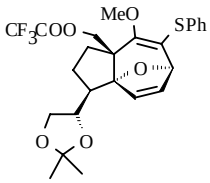
Detrifluoroacetylation of **3** was achieved by a short column of silica gel pretreated with triethylamine to give alcohol **5** in 95% yield[5]. Hydrogenation of double bond and desulfidation of **5** with Raney Ni (W-2)[6a] in ethanol at room temperature afforded enol ether **6** in 96% yield. Oxidative cleavage of acetonide **6** with H_3IO_5 at room temperature concomitant with hydrolysis of enol ether obtained aldehyde **8** in 90% yield. Alternatively, reduction of double bond, desulfidation, hydrolysis of enol ether and detrifluoroacetylation of **3** were also accomplished in one pot using H_2 - Raney Ni (H-1)[6b] in 95% ethanol at room temperature to afford acetonide **7** in 65% yield. Oxidative cleavage of acetonide **7** with H_3IO_5 in a similar manner as the preparation of **8** from **6** gave aldehyde **8** in 85% yield. Inversion of the C-3 configuration in aldehyde **8** was achieved *via* equilibration between aldehyde **8**-enol **9**-aldehyde **10** followed by intramolecular hemiacetalization of **10** in refluxing acidic $CHCl_3$ to give hemiacetal **2** in 33% yield.



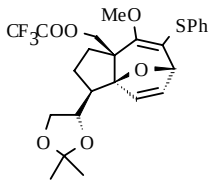
3



3a

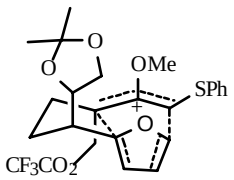


3b

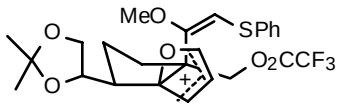


3c

In order to investigate the reaction mechanism from **4** to **3**, the energy calculation of the product **3** and three other diastereomers **3a**, **3b**, and **3c** was carried out with Gaussian 94 program. The minimized energy of **3**, **3a**, **3b**, and **3c** are -1249.7, -1243.8, -1207.8 and –1205.0 kJ/mol, respectively. If the intramolecular [4+3] cycloaddition of **4** was of thermodynamic control, the ratio of four adducts should have been 1 **(3)** : 9.23 x 10^{-2} **(3a)** : 4.67 x 10^{-8} **(3b)** : 1.49 x 10^{-9} **(3c)**. However, adducts **3a** was not detected.



11a



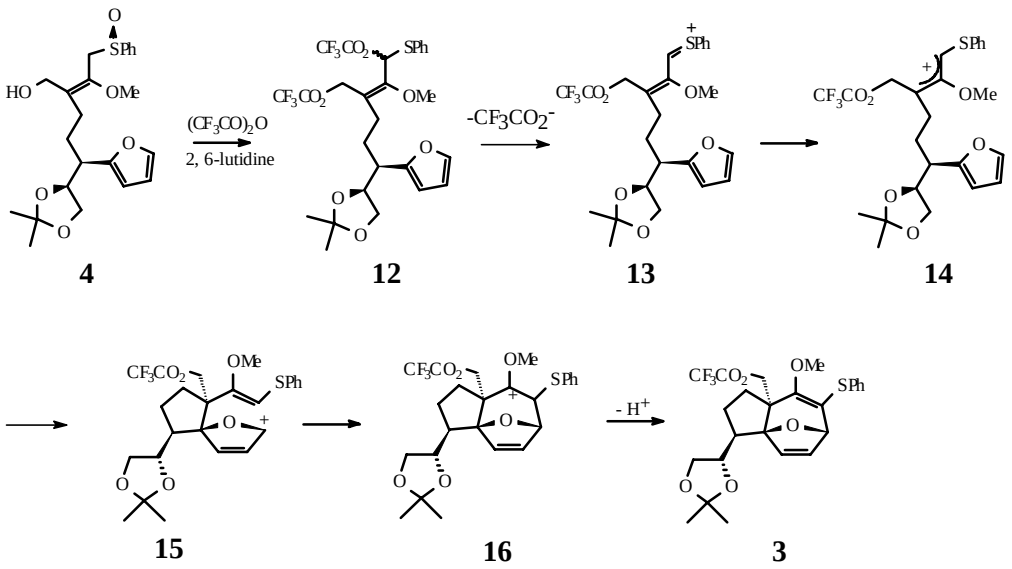
11b

In general, the [4+3] cycloaddition proceeds *via* two models, the concerted and step-wise one[7]. Both the transition states of the concerted model **11a** and step-wise model **11b** will lead to adduct **3**. It is obvious that transition state **11b** is energetically more favorable than **11a** because the acetonide and trifluoroacetate moieties are equatorial in **11b** while they are axial in **11a**. Thus **11b** rather than **11a** may be involved in the above mentioned [4+3] cycloaddition. We proposed that the intramolecular [4+3] cycloaddition of **4** is of kinetic control and *via* a step-wise transition state.

A plausible general mechanism for the transformation from **4** to **3** is suggested (**Scheme 3**). The Pummerer rearrangement accompanied by trifluoroacetylation of hydroxyl group of **4** yielded diester **12**. Detrifluoroacetoxylation of **12** to sulfonium ion **13** followed by delocalization led to oxallylic cation **14**. The oxocarbonium ion **15** was formed after intramolecular electrophilic addition of cation in **14** to the furan ring. Ring closure of **15** followed by deprotonation of **16** gave the intramolecular [4+3] cycloadduct **3**.

In summary, using diastereoselective intramolecular [4+3] cycloaddition of **4** as a key step to construct the 5,7-membered fused ring skeleton in compound **3** and further modification of this cycloadduct, the core of pseudolaric acid A, compound **2** was synthesized with three contiguous stereogenic centers corresponding to those of the target molecule. Further works on this project is underway.

Scheme 3



Acknowledgment

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References and Notes

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8. Selected data for compound **2**: ^{1}HNMR (300MHz, $CDCl_3$): δ 4.60 (m, 2H), 3.71 (m, 1H), 3.40 (dd, 1H, J=6.9, 15.9Hz), 2.30-1.60 (m, 9H). IR (film): 3300, 1705, 1462, 1327, 1045, 802 cm^{-1}. MS (m/z): 223(M^+-1), 207 (100), 149, 122, 105. HREIMS for $C_{12}H_{16}O_4$: calcd: 224.1021; found: 224.1035.
9. Selected data for compound **8**: ^{1}HNMR (300MHz, $CDCl_3$): δ 9.75 (d, 1H, J = 2.2Hz), 4.65 (m, 1H), 3.74 (m, 1H), 3.50 (m, 1H), 2.80-3.00 (m, 2H), 1.85-2.50 (m, 7H), 1.50-1.70(m, 2H). ^{13}CNMR (75MHz, $CDCl_3$): δ 213.9, 201.4, 94.4, 73.8, 64.4, 63.1, 54.3, 46.5,5, 29.0, 28.6, 21.9. IR (film): 3446, 1701, 1466, 1350, 1059, 756 cm^{-1} MS (*m/z*): 224(M^+), 223, 206, 196, 178, 91(100), 55. HREIMS for $C_{12}H_{16}O_4$: calcd: 224.1049; found: 224.1040.

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