

## Studies on the Total Synthesis of *Pseudolaric Acid A* Stereocontrolled Synthesis of the Seven-membered Lactone

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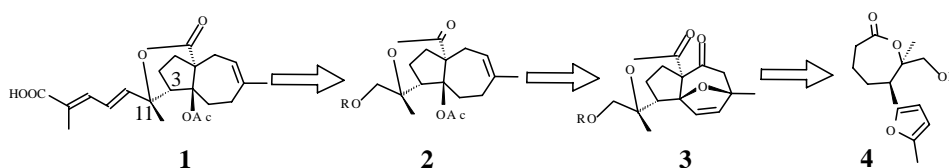
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**Abstract:** The lactone **16** was obtained stereo- and regioselectively by a reaction sequence of 9 steps in 21% overall yield.

**Keywords:** *Pseudolaric acid A*, stereocontrol synthesis, seven-membered lactone.

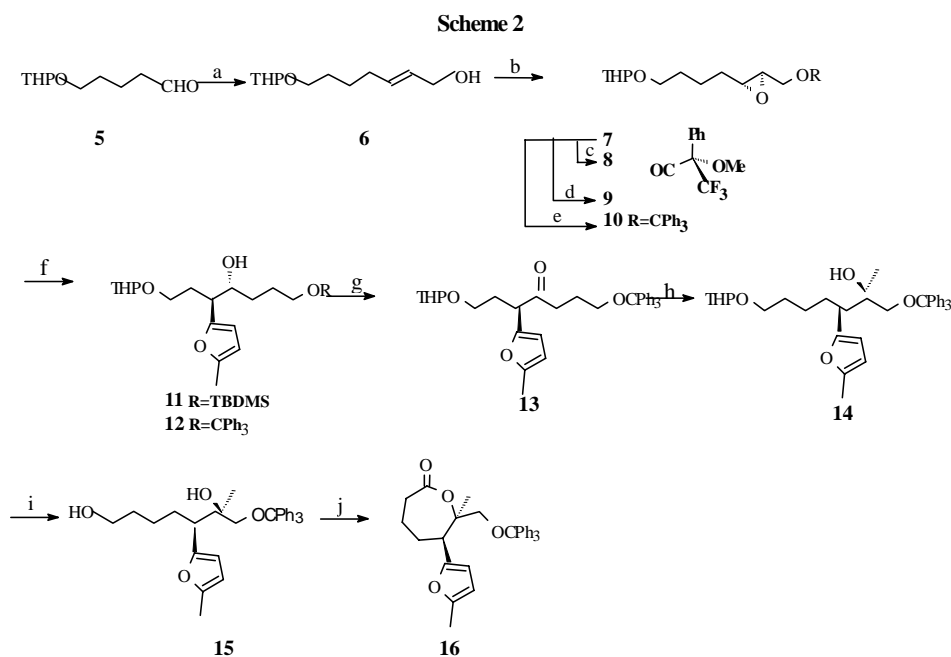
*Pseudolaric acid A* was isolated from *Pseudolarix kaempferi* Gord, a Chinese medicinal herb which exhibits antifungal and antifertility activities<sup>1</sup>. It is a diterpenic acid with a *trans* fused hydroazulene skeleton containing four chiral centers<sup>2</sup>. According to the retrosynthetic analysis, the tricyclis skeleton of **1** could be constructed by a stereoselective intramolecular [4+3] cycloaddition from a seven-membered lactone **4** (**Scheme 1**). In this communication, we would like to report an efficient, stereo- and regio-selective, synthesis of lactone **4**.

**Scheme 1**



The synthesis began with the tetrahydropyranyloxy aldehyde **5**, obtained in 70% yield from 1, 5-pentanediol monotetrahydropyranyl ether by oxidation with PCC and NaOAc in large quantities<sup>3</sup>. Aldehyde **5** was converted to the *trans*-allylic alcohol **6** by Wittig reaction, followed by DIBAL reduction of the resulting ester<sup>4</sup>. Sharpless asymmetric epoxidation of **6** in the presence of D- (-)-DIPT yielded a mixture of the epoxide **7** (3*R*, 2*S*)<sup>5</sup> and its enantiomer. The ratio of the two epoxides was determined in the form of their Mosher ester

**8**, by  $^1\text{H}$  NMR spectra. The ee value is over 95%. Since this asymmetric epoxidation of the transallylic alcohol is well-known, the absolute configuration of the epoxide **7** could be deduced unequivocally<sup>6</sup>.



Reagents and conditions: **a.**  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOEt}$ , NaH, THF, reflux, 1.5 h, 74 %. **ii.** DIBAL,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 2 h, 95 %. **b.** 1.5 eq.  $t\text{-BuOOH}$ , 0.08eq.  $\text{Ti}(\text{O}i\text{Pr})_4$ , 0.1 eq. D-(-)-DIPT,  $4\text{\AA}$  MS,  $\text{CH}_2\text{Cl}_2$ ,  $-20^\circ\text{C}$ , 4 h, 85 %. **c.** (*S*)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl) phenylacetyl chloride, DMAP,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , r.t., 24 h, 95 %. **d.** TBDMSCl, imidazole, DMF,  $0^\circ\text{C}$ , 12 h, 93 %. **e.** 1.1 eq.  $\text{Ph}_3\text{CCl}$ , 1.2 eq. DBU,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  to r.t., 7 h, 85 %. **f.** 4 eq.  $(\text{Methylfuryl})_2\text{CuCNLi}_2$ , 4 eq.  $\text{BF}_3\cdot\text{Et}_2\text{O}$ ,  $\text{Et}_2\text{O}$ ,  $-78^\circ\text{C}$ , 4 h, 70%. **g.** Dess-Martin Periodide,  $\text{CH}_2\text{Cl}_2$ , r.t., 3 h, 83 %. **h.**  $\text{CH}_3\text{MgBr}$ , THF,  $-78^\circ\text{C}$ , 12h, 88 %. **i.** PPTS, EtOH,  $55^\circ\text{C}$ , 3 h, 85 %. **j.** PDC, DMF, r.t., 2 d, 95 %.

In order to improve the regioselectivity in a cuprate opening of the epoxide **7**, a bulky group for the protection of the hydroxyl was favorable<sup>7</sup>. Consequently, **9** was obtained in 93% yield using TBDMSCl as the protecting reagent. However, the ring opening of epoxide **9** by a variety of cuprates (furyl cuprate, furyl lithium cuprate, (5-methyl-2-furyl)<sub>2</sub>CuLi<sub>2</sub>) was unsuccessful. Finally, compound **11** was obtained by the reaction of **9** with 4eq. of each (5-methyl-2-furyl)<sub>2</sub>CuCNLi<sub>2</sub><sup>8</sup> in the presence of  $\text{BF}_3\cdot\text{Et}_2\text{O}$  at  $-78^\circ\text{C}$  in  $\text{Et}_2\text{O}$  in 55% yield. However, when the hydroxy group of **7** was protected as trityl ether **10**, the regioselective

cleavage of **10** epoxide under the same conditions gave the sole product compound **12** (3S, 2S)<sup>9</sup> in a satisfactory yield (70%).

Dess-Martin oxidation of **12** gave the ketone **13** in 83% yield<sup>10</sup> Because of the bulky trityl group, no chelation occurred at ether oxygen with organometallic reagents in this molecule<sup>11</sup>. Therefore according to the Cram or Felkin-Anh models, the addition of CH<sub>3</sub>MgBr to ketone **13** at -78°C afforded the major adduct **14** (3S, 2R)<sup>12</sup> in 88% yield. The ratio of two diastereomers are about 10 : 1 by <sup>1</sup>H NMR analysis. Selective removal of the THP group of **14** with PPTS in ethanol at 55°C gave 1,6-diol **15**<sup>13</sup>, and oxidation of the diol **15** with PDC in DMF<sup>14</sup> yielded the expected lactone **16** (3S, 2S)<sup>15</sup> directly.

Thus lactone **16** with two chiral centers at C<sub>11</sub> and C<sub>3</sub> in pseudolaric acid A was synthesized in 9 steps and in 21% overall yield. The 4π component in lactone **16** could be used for the intramolecular [4+3] cycloaddition for the construction of the ring skeleton of the target molecule **1**.

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### References

1. B. N. Zhou; B. P. Ying; G. Q. Song; Z. X. Chen; J. Han; Y. E. Yan. *Planta Medica*, **1983**, *47*, 35.  
B. C. Pan; H. Y. Chang; G. L. Cai; Y. S. Guo. *Pure & Appl. Chem.*, **1989**, *61*, 389.  
E. Li; A. M. Clark; C. D. Hufford. *J. Nat. prod.* **1995**, *58*, 57.
2. B. P. Ying; R. S. Xu; J. F. Mi; M. Han. *HUAXUEXUEBAO*, **1988**, *46*, 85.
3. K. F. Bernaday; M. B. Floyd; J. F. Poletto; M. J. Weiss. *J. Org. Chem.*, **1979**, *44*, 1438.  
J. C. Collins; W. W. Hess; F. J. Frank. *Tetrahedron Lett.*, **1968**, 3363.  
E. J. Corey; H. Yamamoto; D. K. Herron; K. Achiwa. *J. Am. Chem. Soc.*, **1970**, *92*, 6636.
4. H. Nagaoka; Y. Kishi. *Tetrahedron*, **1981**, *37*, 3873.
5. Selected data of compound **7**: oil, <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): 4.50 (t, 1H), 3.00-3.80 (m, 4H), 2.70 (m, 2H), 1.00-2.00 (m, 14H); MS (m/z): 177 (6), 145 (12), 129 (35), 101 (32), 85 (100); IR (film): 3500, 3000, 1720, 1454, 1201, 1031cm<sup>-1</sup>.
6. T. Katsuki; K. B. Sharpless. *J. Am. Chem. Soc.*, **1980**, *102*, 5974.  
Y. Gao; R. M. Hanson; J. M. Klunder. *J. Am. Chem. Soc.*, **1987**, *109*, 5765.
7. R. D. Tung; D. H. Rich. *Tetrahedron Lett.*, 1987, *28*, 1139.  
W. W. Mcwhorter, Jr. S. H. Kang; Y. Kishi. *Tetrahedron Lett.*, **1983**, *24*, 2243.
8. J. S. Ng; J. R. Behling; A. L. Campbell; D. Nguyen; B. Lipshutz. *Tetrahedron Lett.*, **1988**, *29*, 3045.
9. Selected data of compound **12**: oil, <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): 7.20~7.50 (m, 15H), 5.80 (d, 1H), 4.52 (m, 1H), 3.8~3.90 (m, 2H), 3.45 (m, 1H), 3.32 (m, 1H), 3.06 (m, 2H), 2.78 (m, 1H), 2.15 (s, 3H), 1.60~1.80 (m, 12H); MS (m/z): 554 (M+, 0.2), 536 (1), 243 (100), 165 (59), 85 (100); Anal. Calcd for C<sub>36</sub>H<sub>42</sub>O<sub>5</sub>: C, 77.89; H, 7.79. Found: C, 77.95; H, 7.63.
10. S. D. Meyer; S. L. Schreiber. *J. Org. Chem.*, **1994**, *59*, 7549.
11. S. V. Frye; E. L. Elliel. *J. Am. Chem. Soc.*, **1988**, *110*, 484.

12. Selected data of compound **14** : oil,  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ): 7.20~7.45 (m, 15H), 5.85 (d, 1H), 5.79 (d, 1H), 4.50 (t, 1H), 3.80 (m, 1H), 3.65 (m, 1H), 3.45 (m, 1H), 3.28 (m, 1H), 3.00 (dd, 2H,  $J = 9.0\text{Hz}$ ), 2.98 (m, 1H), 2.40 (s, 1H), 2.18 (s, 3H), 1.40~1.57 (m, 12H), 1.15 (s, 3H); MS ( $m/z$ ): 384 (2), 260 (23), 243 (28), 183 (100), 154 (24), 105 (92). IR (film) : 3458, 3050, 2995, 1597, 1491, 1448, 1353, 1074, 1024, 902, 765,  $704\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{37}\text{H}_{44}\text{O}_5$ : C, 77.95; H, 8.16. Found: C, 78.14; H, 7.80.
13. M. Miyashita; A. Yoshikoshi; P. A. Grieco. *J. Org. Chem.*, **1977**, 42, 3772.
14. E. J. Corey; G. Schmidt. *Tetrahedron Lett.*, **1979**, 399.
15. Selected data of compound **16** :  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ): 7.10 ~7.45 (m, 15H), 5.89 (d, 1H,  $J = 3.1\text{Hz}$ ), 5.80 (d, 1H,  $J = 3.1\text{Hz}$ ), 3.50 (t, 2H), 3.00 (dd, 2H,  $J = 9.2\text{Hz}$ ), 2.98 (m, 1H), 2.18 (s, 3H), 1.20 ~ 1.60 (m, 4H), 1.15 (s, 3H); MS ( $M/Z\%$ ): 243 (100), 167 (30), 95 (18); IR (film) : 1739, 1448, 1373, 1244, 1074,  $1047, 708\text{cm}^{-1}$ .  $[\alpha]_{\text{D}}^{25} = -4.41$ ; Anal calcd for  $\text{C}_{32}\text{H}_{32}\text{O}_4$ : C, 80.00%; H, 6.67. Found: C, 79.73; H, 6.69.

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