Synthetic studies on pseudolaric acid A

FAN Bai-Chuan, Chang Hong-Yue, Cai Guo-Lin and Guo Yi-Sheng

Shanghai Institute of Meteria Medica, Academia Sinica
319 Yue-Yang Road, Shanghai 200031, China

Abstract - Pseudolaric acid A is a diterpenic acid with a hydroazulene skeleton. Work on its total synthesis is nearing completion; the steps completed are presented herein.

The root bark of Pseudolarix Kaempfer Gorden is a Chinese traditional medicinal herb, called Tu Jin Pi, which has been used for many years for the treatment of some kinds of fungus disease such as tinea pedis. Three acidic active principles [1,2,3] were isolated from it, namely pseudolaric acid A (1), B (2) and C (3). They have not only antifungal activity but also a significant effect on the termination of early pregnancy in rats, rabbits and dogs [4]. The structures of the three pseudolaric acids were elucidated by spectroscopic analysis and X-ray diffraction, and found to be diterpenic acids with a trans fused hydroazulene skeleton. It is of special interest that the tertiary acetoxy group (or hydroxyl group) was trans to the lactonyl group. No other natural hydroazulene with this type of structure has previously been found.

A total synthesis of pseudolaric acid A (1) is proceeding as follows. By retrosynthetic analysis, compound (4) would appear to be the key intermediate for the synthesis of pseudolaric acid A, and compound (4) presumably could be prepared from the seven-membered ring (5).
1 SYNTHESIS OF THE SEVEN-MEMBERED RING (5)

Ethyl acetate was first metalated with LDA and then condensed with lactone (6) to form the hydroxy-lactone (7). Compound (7) was dehydrated with TsOH to give the unsaturated ester (8). A Claisen rearrangement of (8) at high temperature then gave the desired seven-membered keto-ester (5). Compound (7) could be obtained more conveniently by the reaction of the epoxide (9) with the dianion of ethyl acetoacetate.

2 SYNTHESIS OF KEY INTERMEDIATE (4) FROM THE SEVEN-MEMBERED β-KETO ESTER (5)

2.1 Model test of the formation of hydroazulene by pinacol coupling

A Michael addition of compound (10) to acrolein gave keto-aldehyde (11), which was subjected to pinacol coupling to afford the diol (12). Diol (12) was oxidized to the hydroxy-ketone (13) with DMSO and trifluoroacetic anhydride. However, oxidation of (12) with PPC gave (13) in very poor yield, the major product being the open-ring compound (11). Compound (13) proved to be a mixture of trans and cis isomers, in about a 1:1 ratio, which could be separated by chromatography after acetylation with acetic anhydride in the presence of dimethylaminopyridine.

Because the pinacol coupling reaction of the model compound did form a hydroazulene, the same method was applied to compound (5). By the Michael addition of acrolein, compound (5) was converted into the keto-aldehyde (14) in nearly quantitative yield. However, pinacol coupling of (14) under the conditions used for the model compound did not give the desired product (15).

2.2 Formation of the hydroazulene by aldol condensation

Because the pinacol coupling reaction of (14) did not form the desired hydroazulene (15), an aldol condensation was investigated for the synthesis of the hydroazulene. The keto-aldehyde (14) was reacted with ylide (16) to yield (17), which was then converted into the di-keto compound (18), by hydrolysis with glycol-PPTS-benzene. β-Keto-ester (5), on treatment with iodo compound (19), potassium carbonate and 18-crown-6 in toluene gave (20), which was hydrolysed to compound (18) in dilute acetic acid. The second method gave the better yield.
Diketo compound (18) was treated with freshly sublimed potassium t-butoxide in t-butanol at room temperature, to afford a 25% yield of unsaturated hydroazulene (21). Treatment of (18) with LDA yielded a small amount of the desired hydroxyhydroazulene (4) and a considerable quantity of unidentified by-products. The same result could be obtained using potassium t-butoxide in THF at room temperature. By treatment of (18) with 0.5 equivalent of potassium t-butoxide in THF-t-BuOH (1:1) at room temperature for 1 hr, compound (4) could be obtained in about 60% yield. The structure was confirmed by IR, $^1$H NMR (400 MHz), $^{13}$C NMR, and MS. IR: 3450 cm$^{-1}$ (OH), 1705 cm$^{-1}$, 1715 cm$^{-1}$ (CO, COOEt); MS: 280 (m+), 262 (m$^+$ - H$_2$O); $^1$H NMR: 5.30 (t, 1H, CH=), 4.75 (br s, 1H, OH); $^{13}$C NMR: 208.90 (CO), 176.4 (COOEt), 141.07 ppm, 120.46 ppm (olefin carbon), 85.7 ppm (tertiary hydroxy carbon), 58.73 ppm (quartenary carbon).

3 FORMATION OF LACTONE

The key intermediate (4) was reduced with sodium borohydride to give lactone (22) and a small amount of unsaturated compound. The formation of lactone (22) showed that the carboethoxy group and the acetyl group of (4) were on the same side. Because the acetyl group was easily epimerized, the acetyl group and tertiary hydroxyl group must be on opposite sides. The relative configuration of (4) was found to be identical with that of the pseudolaric acids.

Compound (4) was reacted with vinyl magnesium chloride at -50°C to give diol (23), which was lactonized to (24) by treatment with sodium hydride. The tin compound (25), after treatment of n-butyl lithium, was reacted with (4) to form the diol (26). The reaction of (26) with sodium hydride then gave the $\delta$-lactone (27). The remaining steps in the synthesis of pseudolaric acid A from (27) are in progress.
REFERENCES