Pergamon

Tetrahedron Letters 39 (1998) 9229–9232

TETRAHEDRON LETTERS

A conjugate reduction-intramolecular aldol strategy toward the synthesis of pseudolaric acid A

Pauline Chiu,* Bin Chen, Kin Fai Cheng

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong

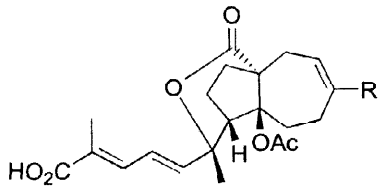
Received 24 June 1998; revised 29 September 1998; accepted 6 October 1998

Abstract

An unprecedented tandem conjugate reduction-intramolecular aldol cyclization using Stryker's reagent produced diastereomers of **5** from the ketoester precursor **8**. Compound **5c** with the *trans*-fused perhydroazulene carboskeleton as in pseudolaric acid A was formed as a minor isomer, while the all-*cis* **5b** was obtained as the major product. The structures of the two diastereomers have been determined by X-ray crystallography.

Keywords: Aldol reactions; copper and compounds; natural products

The pseudolaric acids are novel diterpenoids isolated from the bark of *Pseudolarix kaemferi Gordon*, also known as *Tujinpi* in Chinese folk medicine. Preparations from this bark has been traditionally used against skin fungal infections. Recent studies have revealed that the pseudolaric acids are promising candidates for drug development because they show *in vitro* cytotoxicity against several human tumor cell lines,[1] as well as *in vivo* antifungal activity,[2] and contraceptive effects in mice.[3]

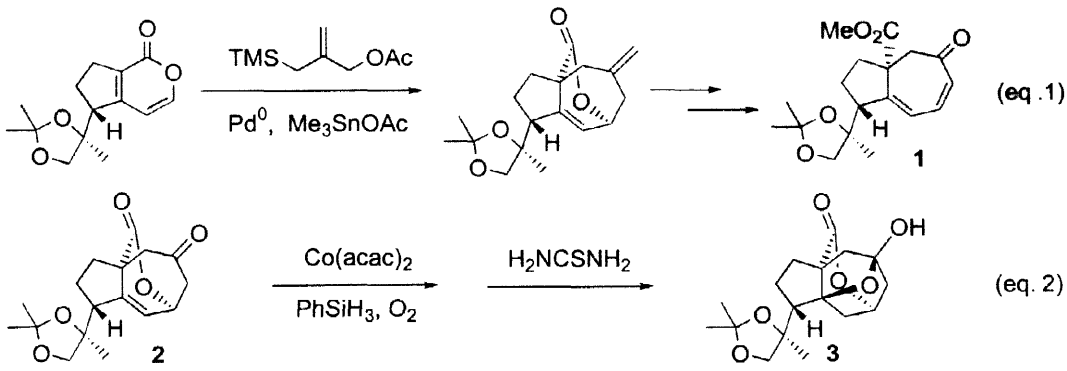


Pseudolaric Acid A (R= Me)
Pseudolaric Acid B (R= CO_2Me)

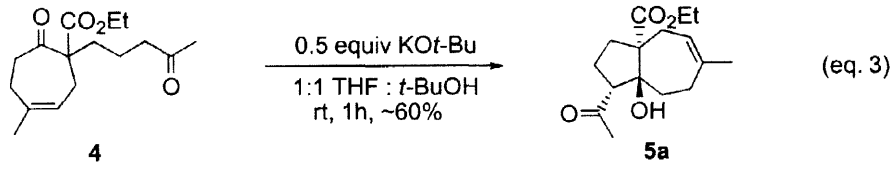
The structures and absolute stereochemistries of the pseudolaric acids have been determined by X-ray crystallography and CD studies.[4,5] Pseudolaric acid B can be obtained from the oxidation of its congener, pseudolaric acid A, which is a highly-oxygenated perhydroazulene bearing four contiguous stereocentres. The unusual structural feature, representative of this family of compounds, is a *trans* arrangement of the lactone and acetoxy group at the fused ring junction. All of these structural elements in a rather compact molecule pose quite a synthetic challenge.

0040-4039/98/$ - see front matter
PII: S0040-4039(98)02130-3

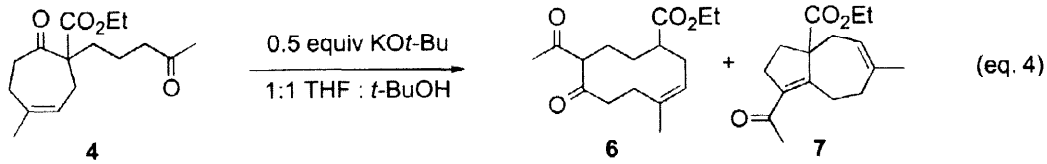
The two synthetic studies on the pseudolaric acids published to date include the contribution from Trost's group of the synthesis of **1** via a [4+3] cycloaddition (eq. 1).[6] Notably, *trans*-fused perhydroazulene **3** has been obtained from a related intermediate **2** (eq. 2); however, **3** was resistant to many bridge-opening attempts.



The report by Pan *et al* towards the synthesis of pseudolaric acid A outlined the construction of the perhydroazulene intermediate **5a** from a base-catalyzed aldol condensation of ketoester **4** (eq. 3).[7]



However, in our efforts to synthesize pseudolaric acid A, cyclization under the reported reaction conditions as well as a number of different basic conditions failed to generate **5a**.[8] By far, the major product consistently obtained with KO*t*-Bu was the diketoester **6** as a 1:1 mixture of diastereomers (eq. 4). The formation of the interesting ten-membered carbocycle **6** is a due to a known base-induced retro-aldol fragmentation of **5**.[9,10,11] This implied that **5** was formed but also underwent subsequent decomposition to **6** under these conditions. Compound **6** and the dehydrated product **7** together accounted for over 70% of the product mixture.[12]

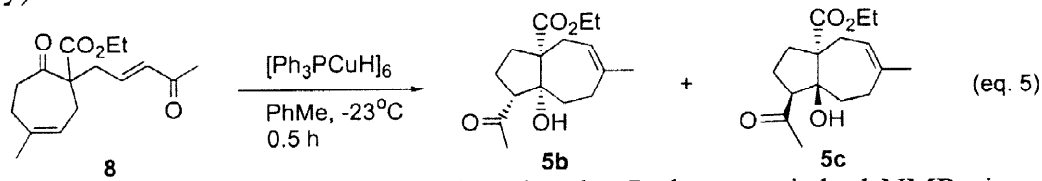


We then sought to perform the intramolecular aldol condensation in a quantitative and kinetic fashion, under conditions which allow **5** to be isolated, and arresting its conversion to **6**. Our strategy was to induce the conjugate reduction of **8** to produce the internal enolate whose subsequent aldol reaction would provide access to **5**. The reduction must be chemoselective for the α,β-unsaturated ketone due to the presence of another isolated alkene. We also needed a reasonably non-basic reagent to induce this transformation to prevent the decomposition of **5**.

A survey of the available methods of conjugate reduction revealed that Stryker's reagent, $[Ph_3PCuH]_6$, fulfills these criteria.[13,14,15] Enolates resulting from the copper hydride reduction of α,β-unsaturated ketones and aldehydes were recognized to be able to participate in subsequent aldol condensations, but these were regarded as undesirable side-reactions resulting in the

consumption of the starting material, and were actively suppressed by the addition of deaerated water to quench the enolate.[16] It was our intention, however, to exploit this conjugate reduction to produce one enolate regioselectively for intramolecular reaction with the ketone.[17] We also believed that the copper cation would function as a chelator for the intermediate β-oxyketoester which would enable it to survive until workup, therefore impeding the retro-aldol reaction to yield **6** or dehydration to give **7**.

Typically, Stryker's reductions are conducted at room temperature. Under these conditions, substrate **8** was consumed within a few minutes.[18] We found that better results were obtained at lower temperatures. Thus when **8** was treated with Stryker's reagent (2 equivs) in THF at -23°C, conjugate reduction-aldol cyclization occurred as proposed to give cleanly **5b** and **5c** (vide infra) in a ratio of 6:1, without any formation of **6** or **7**.[19] When the reaction was done in a non-coordinating solvent, toluene, the product ratio further increased in favour of **5c** to give **5b**:**5c** in a ratio of 2.4-3:1, as determined from the crude NMR (isolated yields 66% and 16% respectively).



8 **5b** **5c**

The major diastereomer was initially believed to be **5a** because it had NMR signals which appeared to correspond to that of the product described in Pan's report, based on the limited characterization provided.[20] However, the IR spectrum of this isomer showed no change in the hydroxyl region with dilution. The stretching frequencies for the ketone as well as the ester carbonyl functionalities are lowered, both being at 1708 cm^{-1}. These observations suggest strong intramolecular hydrogen bonding, which would not be expected for the desired stereoisomer **5a**. The crystalline 2,4-dinitrophenylhydrazone derivative, subjected to X-ray analysis, definitively showed the structure to be **5b**, containing *cis*-fused rings rather than *trans* (Figure 1).[21]

The second diastereomer was cofirmed to have structure **5c** by X-ray crystallographic analysis of its dinitrophenylhydrazone derivative (Figure 2).[21,22] Gratifyingly, **5c** contains the unusual *trans*-ring junction of quaternary carbon atoms as in pseudolaric acid A, and is a possible candidate for further elaborations toward its total synthesis.

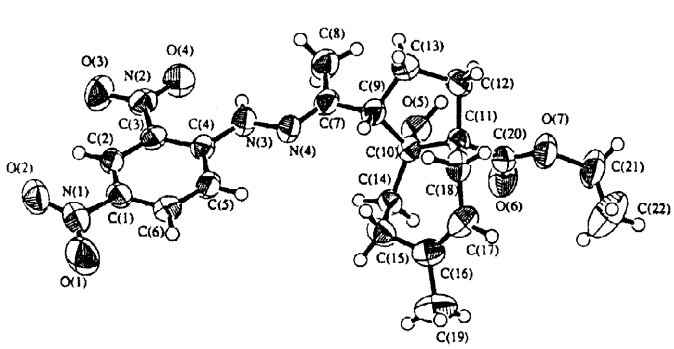


Figure 1. ORTEP of **5b**-2,4-dinitrophenylhydrazone

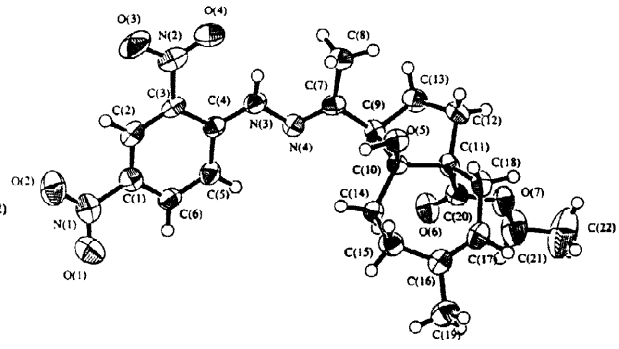


Figure 2. ORTEP of **5c**-2,4-dinitrophenylhydrazone

Studies to increase the diastereomeric ratio in favour of **5c**, and to achieve the epimerization of **5c** to **5a** are in progress. Investigations on the use of Stryker's reagent for aldol cyclizations and toward completing the total synthesis of pseudolaric acid A are also being actively pursued.

Acknowledgements

We thank the University of Hong Kong and the Hong Kong Research Grants Council (HKU 7098/97P) for financial support. B. C. thanks the University of Hong Kong for an exchange student scholarship. We are also grateful to Dr. W. T. Wong for the X-ray crystallographic analyses, and Dr. G. D. Brown for helpful discussions.

References and Notes

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8. With a variety of potassium bases (*t*-BuOK, K_2CO_3, KOH, KHMDS) in THF and THF/MeOH from -78°C to 25°C, **6** was the major product. With lithium bases (LDA, LHMDS) at -78°C, the bicyclo[5.5.0] aldol product was formed via the kinetic enolate.
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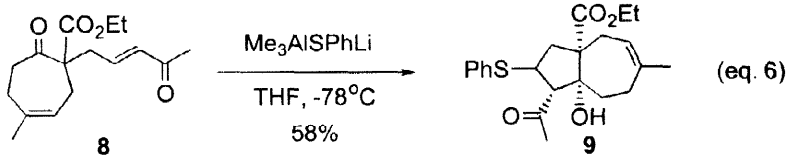
11. **5** represents any of the diastereomers of **5a**
12. **6** and **7**, along with minor amounts of **5b**, **5c** were obtained in a ratio of about 58:24:12:6.
13. Mahoney WS, Brestensky DM, Stryker JM. J. Am. Chem. Soc. 1988; 110:291-293.
14. **8** was totally unreactive toward conjugate reduction using catecholborane either with or without Wilkinson's catalyst.[23]
15. A tandem conjugate addition-intramolecular aldol sequence was also attempted using $Me_3AlSPhLi$ in THF,[24] yielding **9** as a single diastereomer (eq. 6). Reduction of **9** by Raney-Nickel generated **5b**.



8 9 (eq. 6)

16. Koenig TM, Daeuble JF, Brestensky DM, Stryker JM. Tetrahedron Lett. 1990; 31:3237-3240.
17. Tandem reduction-intramolecular alkylation reaction has been attempted in related systems, but was largely unsuccessful.[16]
18. When excess Stryker's reagent was used, or when the reaction temperature was raised, **6** and **7** also appear as products.
19. All new compounds were purified and fully characterized by IR, NMR and mass spectral analysis.
20. **5b**: colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (1H, br t, *J*= 6.3 Hz), 4.77 (1H, s), 4.15 (2H, m), 3.00 (1H, t, *J*= 8.7 Hz), 2.45 (m, 1H), 2.24 (3H, s), 2.21 (3H, m), 2.17 (2H, m), 2.02 (1H, m), 1.87 (1H, m), 1.68 (3H, s), 1.64 (2H, m), 1.25 (3H, t, *J*= 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.9, 176.6, 141.7, 120.4, 85.4, 60.56, 58.7, 57.8, 35.5, 34.4, 33.7, 30.9, 29.3, 25.2, 23.8, 14.1; IR (CCl_4, cm^{-1}) 3454, 2969, 2938, 1708, 1193; HRMS: Calculated for $C_{16}H_{24}O_4$: 280.1674; Obtained: 280.1672.
21. Full crystallographic data for the 2,4-dinitrophenylhydrazone derivatives of **5b** and **5c** can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ , UK.
22. **5c**: colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36 (1H, br m), 4.24 (1H, s), 4.14 (1H, dq, *J*= 10.7, 7.1 Hz), 4.03 (1H, dq, *J*= 10.8, 7.1 Hz), 3.68 (1H, t, *J*= 9.6 Hz), 2.69 (2H, m), 2.16 (3H, s), 2.15 (4H, m), 1.94 (2H, m), 1.74 (2H, m), 1.68 (3H, s), 1.23 (3H, t, *J*= 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.2, 175.5, 141.1, 122.4, 82.3, 59.9, 59.1, 57.3, 34.4, 31.5, 30.9, 27.4, 26.9, 26.7, 24.7, 14.2; IR (CCl_4, cm^{-1}) 3470, 2959, 2932, 1723, 1700, 1190. HRMS: Calculated for $C_{16}H_{24}O_4$: 280.1674; Obtained: 280.1674.
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