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A Facile Total Synthesis of Hainanensine via an Unusual Rearrangement−Annulation Cascade

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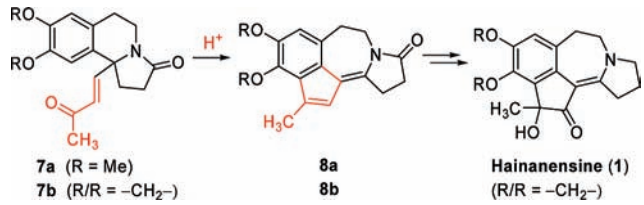
ABSTRACT



A facile total synthesis of hainanensine (1), a structurally unique *Cephalotaxus* alkaloid, via an effective acid-mediated rearrangement/Friedel−Crafts annulation cascade (7a/7b → 8a/8b), is described.

Hainanensine (**1**, racemic, Figure 1) is a structurally unique minor alkaloidal component identified from the antileukemia plant *Cephalotaxus hainanensis* and *C. fortunei* by Liang and Sun in 1981.[1] Preliminary pharmacological studies indicated that **1** possesses marginal antitumor activity.[1] Later, Liang and co-workers reported that saturated derivatives and other structural analogues of **1** have shown a range of interesting biological activity.[2] For further structural confirmation, Liang and Sun have synthesized **1** from a benzazepine derivative **2** by an acid-mediated cyclization.[1,3] Compound **2** is the key intermediate in the classic Weinreb synthesis of cephalotaxine (CET),[4] the parent member of the *Cephalotaxus* alkaloid family.[5] Liang thus postulated that **1** and CET might share a common biosynthetic origin.[1]

In connection with our continued studies[6] on the novel chemical synthesis of CET and its potent antileukemia ester derivatives (i.e., homoharringtonine), we report herein a facile total synthesis of **1** via an unusual acid-mediated rearrangement−annulation cascade of enone derivative **7a**/**7b**.

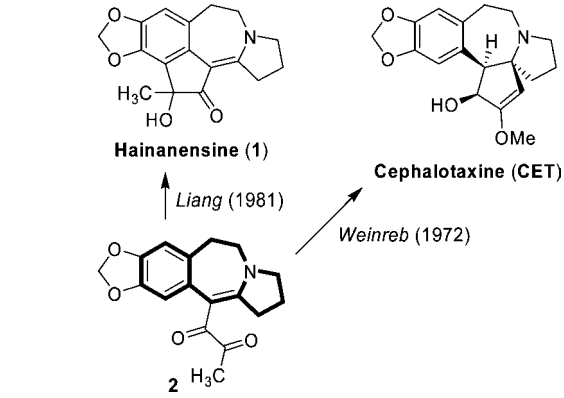


Figure 1. Hainanensine (**1**) and cephalotaxine (CET).

For the synthesis of enone **7**, an effective isoquinoline annulation approach (**3** → **4**) previously developed in our

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(1) Sun, N. J.; Liang, X. T. *Acta Pharmacol. Sin.* **1981**, *16*, 24; *Chem. Abstr.* **1981**, *95*, 175622t.

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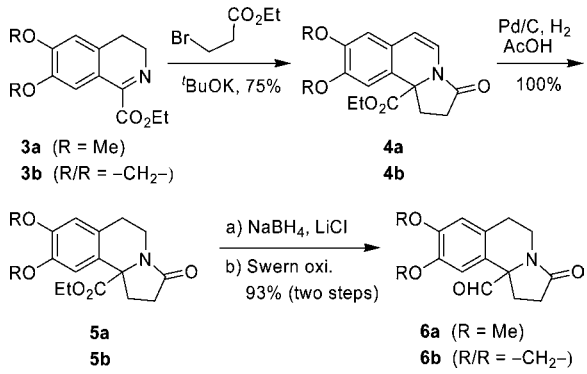
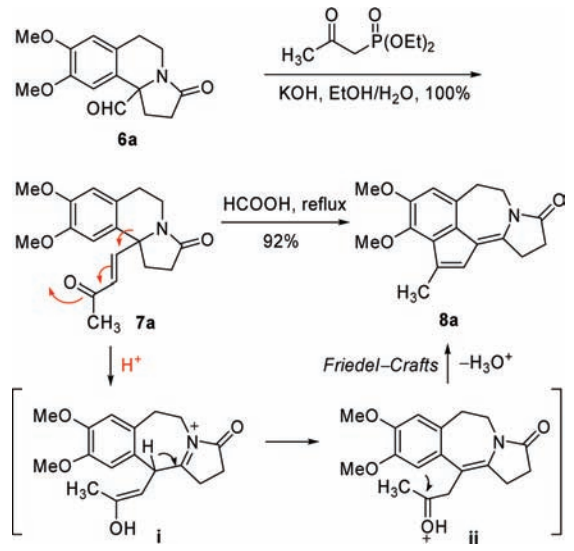
Scheme 1. Isoquinoline Annulation Approach to **6**



laboratory[7] was employed. As shown in Scheme 1, isoquinoline aldehyde derivative **6** was prepared from readily available 3,4-dihydroisoquinoline **3** in 70% overall yield. As illustrated in Scheme 2, enone **7a** was elaborated by the Horner−Wadsworth−Emmons olefination[8] of aldehyde **6a**.

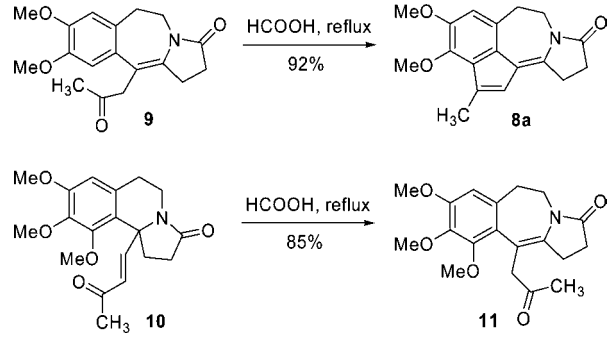
Scheme 2. Rearrangement−Annulation Cascade of **7a** → **8a**



With readily available enone **7a** in hand, we anticipated an acid-promoted ring-expansion process as indicated (arrows, Scheme 2) leading to the benzazepine ring system of **1**. Upon refluxing enone **7a** in formic acid for 6 h, a crystalline product (mp 152−154 °C) was isolated in 92% yield, which was characterized spectroscopically as compound **8a**, bearing the exact ring skeleton of **1**. Apparently, the formation of rearranged annulation product **8a** is resulted from further Friedel−Crafts-type cyclization−dehydration of the initial ring-expansion intermediates **i** and **ii** (Scheme 2).[9]

Further confirmation of the above rearrangement−annulation pathway (**7a** → **8a**) was provided by the clean transformation of a previously synthesized benzazepine ketone **9**[7] into **8a** in refluxing formic acid (Scheme 3). Furthermore, the

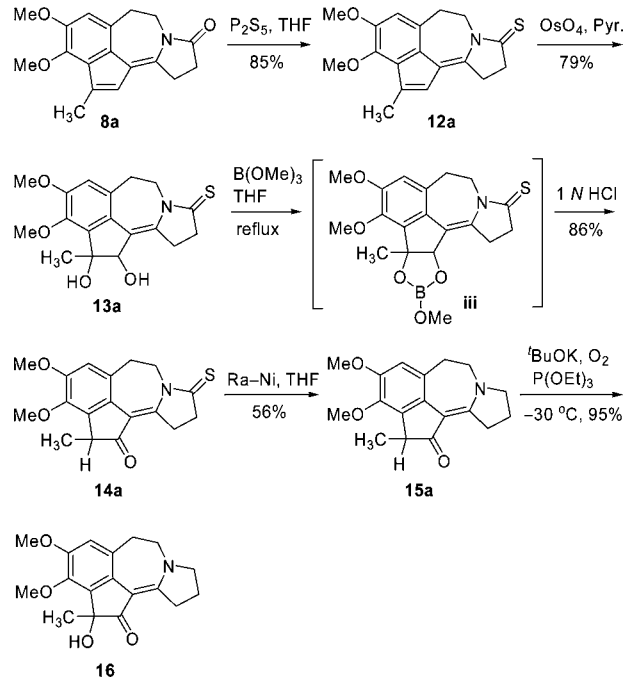
Scheme 3



trimethoxy enone derivative **10**[10] was found to give the corresponding ring-expansion product **11** in good yield.

As depicted in Scheme 4, a sequence of functional group transformations was developed for the facile assembling of

Scheme 4. Synthesis of Dimethyl Analogue **16**



the dimethyl analogue **16** of hainanensine (**1**) from readily available **8a**, which involves (1) converting **8a** into the corresponding thiocarbonyl derivative **12a**; (2) regioselective dihydroxylation to diol **13a**; (3) acid-mediated pinacol-type rearrangement of diol **13a** to ketone **14a** facilitated via a

(2) (a) Yin, D. L.; Xu, C. X.; Gao, Y. S.; Liu, D. K.; Wen, S. Y.; Guo, J. Y. *Acta Pharmacol. Sin.* **1992**, *27*, 824; *Chem. Abstr.* **1993**, *118*, 160544p. (b) Guo, J. Y.; Yin, D. L.; Gao, Y. S.; Liu, D. K.; Liang, X. T. *Youji Huaxue* **1993**, *13*, 195; *Chem. Abstr.* **1993**, *119*, 72895. (c) Ye, Y. M.; Xu, C. X.; Sui, R. H.; Guo, J. Y.; Cui, G. J. *Acta Pharmacol. Sin.* **1995**, *30*, 12; *Chem. Abstr.* **1995**, *123*, 414w. (d) Zhang, W. J.; Zhou, T. H. *Acta Pharmacol. Sin.* **1998**, *33*, 212; *Chem. Abstr.* **1998**, *129*, 269913m.

borate intermediate **iii**;[11] (4) reductive desulfurization of **14a** to ketone **15a**; and (5) basic autoxidation[12] of **15a** to the hydroxyl ketone **16**. The structure of **16** was established by X-ray crystallographic analysis (Figure 2).[13] It is worthy to note that attempted direct oxidation of diol **13a** led to the corresponding dicarbonyl product (C−C cleavage) exclusively.

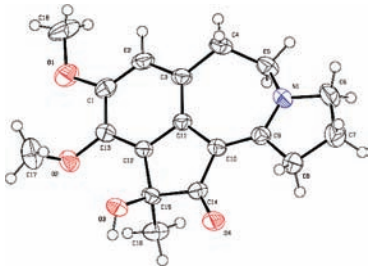
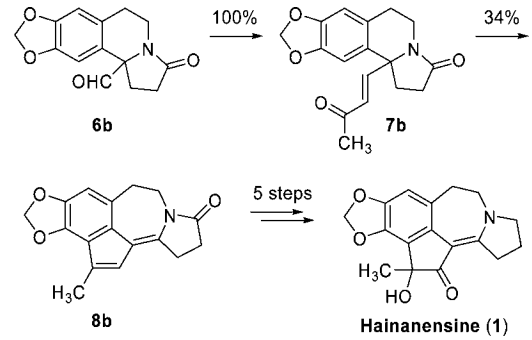


Figure 2. X-ray structure of compound **16** (ORTEP drawing).

Hainanensine (**1**) was analogously synthesized from aldehyde **6b** via the enone intermediate **7b** and rearranged annulation product **8b** as shown (Scheme 5).[14] The synthetic product **1** (racemic) is identical spectroscopically with the natural hainanensine reported.[1,15]

Scheme 5. Synthesis of Hainanensine (**1**) from **6b**



In summary, we have achieved a facile total synthesis of unique natural alkaloid **1** via an unusually effective rearrangement−annulation cascade, which may facilitate the synthesis of structural analogues of **1** and further biological evaluation.

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Supporting Information Available: Experimental procedures; spectral data; copies of spectra for compounds **3b**−**8b**, **7a**, **8a**, **10**, **11**, **12a/b**−**15a/b**, **16**, and **1**; and CIF file for **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) For a similar synthetic method, see also: Japanese Patent JP58059984, 1983; *Chem. Abstr.* **1983**, *99*, 140218w.
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(9) Other protic or Lewis acid conditions led to decomposition of **7** or very sluggish reaction.
(10) For preparation, see Supporting Information.
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(13) For detailed data, see Supporting Information.
(14) For experimental details, see Supporting Infromation.
(15) No authentic sample available for direct comparison.