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Toward the Racemic Total Synthesis of Hederacines A and B: Construction of an Advanced Tricyclic Intermediate

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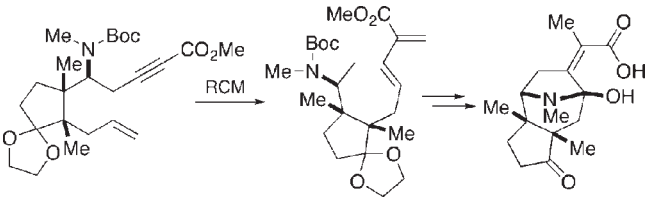
ABSTRACT



Progress toward the total synthesis of hederacines A and B is described. Our approach involves an allylic cyanate-to-isocyanate rearrangement, eneyne ring-closing metathesis, and a transannular reaction between the C-5 amino group and the C-12 position of the perhydroazuleno[5, 6-*b*]furanone intermediate.

Structurally novel tropane alkaloids, hederacines A (**1**) and B (**2**) (Figure 1), were isolated from the aerial parts of *Glechoma hederaceae* in 2003 by Sarker and co-workers[1] and were found to exhibit moderate cytotoxic activities against the colon cancer cell line, Caco-2.[2] The structures of **1** and **2** were determined by a combination of spectroscopic techniques. They each have a unique skeleton containing an 8-azabicyclo[3.2.1]octane ring system fused to a cyclopentane ring. Their unique features and biological activities prompted us to undertake a total synthesis of these natural products.

Our approach to hederacines is outlined in Scheme 1. We envisioned that both natural products could be accessed from the azuleno[5,6-*b*]furanone intermediate **3** through oxidation at C-12 (hederacine numbering system) followed by the acid-induced transannular cyclization to form a tropane ring and reductive amination in the last stage of the synthesis. The advanced intermediate **3** would be produced by lactonization of the dihydroxy ester obtained by selective olefin reduction–dihydroxylation of 1,3-dienecarboxylate **4**, which would be formed via ring-closing metathesis (RCM) of enynoate **5**.[3]

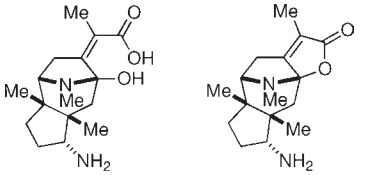


Figure 1. Structures of hederacines A (**1**) and B (**2**).

Our synthesis commenced with the reaction of the known pentalenone **6**[4] with lithium dimethyl cuprate followed by trapping of the resultant enolate with TMSOTf giving rise to silyl enol ether **7**, which upon treatment with dimethyldioxirane (DMDO)[5] followed by $Pb(OAc)_4$ generated aldehyde **8** as the sole diastereomer in 73% overall yield from **6** (Scheme 2).[6] Wittig olefination of aldehyde **8**

(1) Kumarasamy, Y.; Cox, P. J.; Jaspars, M.; Nahar, L.; Sarker, S. D. *Tetrahedron* **2003**, *59*, 6403–6407.

(2) Kumarasamy, Y.; Nahar, L.; Kong-Thu-lin, P.; Sarker, S. D. *Nat. Prod. Commun.* **2006**, *1*, 33–35.

(3) For a review on enyne metathesis, see: (a) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020–1022. (b) Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133–154. (c) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1–18. (d) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382.

(4) (a) Nakashita, Y.; Watanabe, T.; Benkert, E.; Lorenzi-Riatsch, A.; Hesse, M. *Helv. Chim. Acta* **1984**, *67*, 1204–1207. (b) Lee, H. W.; Lee., J. H.; Lee, I.-Y. C. *Bull. Korean Chem. Soc.* **1991**, *12*, 392–397.

(5) (a) Adam, W.; Prechtl, F. *Chem. Ber.* **1991**, *124*, 2369–2372. (b) Allen, J. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 351–352.

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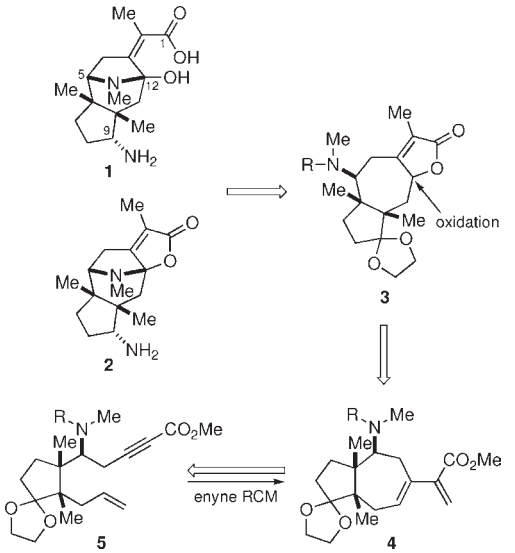
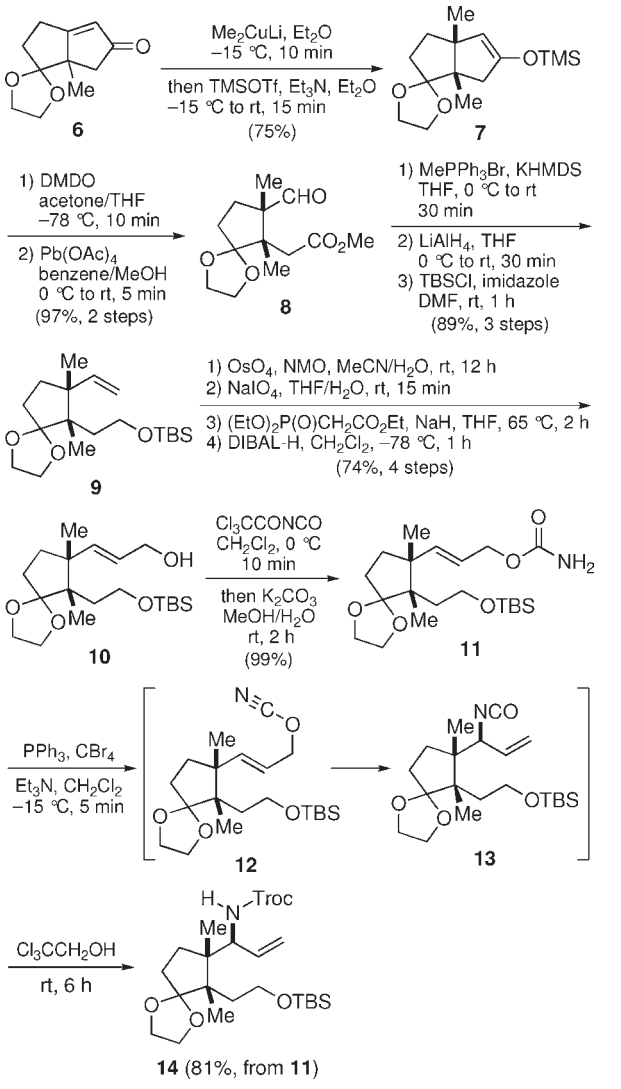
Scheme 1. Retrosynthetic Approach to Hederacines A and B



Scheme 2. Synthesis of Allylic Amine Intermediate **14**



and reduction of the ester functionality with $LiAlH_4$ followed by protection of the resultant alcohol as its TBS ether led to alkene **9** in 95% yield, which was then converted to allylic alcohol **10** in 74% overall yield in a four-step sequence involving treatment with OsO_4, cleavage of the resultant diol with $NaIO_4$, Horner–Wadsworth–Emmons reaction, and DIBAL-H reduction. The next step was stereocontrolled introduction of an amino group at the position adjacent to the quaternary carbon; this was achieved by the application of a [3,3] sigmatropic rearrangement of the allyl cyanate.[7] For this purpose, the allylic alcohol **10** was converted into carbamate **11** in 99% yield via treatment with trichloroacetyl isocyanate ($Cl_3CCONCO$) followed by hydrolysis of the trichloroacetyl group with methanolic K_2CO_3. Subsequent dehydration of **11** with PPh_3, CBr_4, and Et_3N generated an intermediate allylic cyanate **12**, which readily rearranged to give allylic isocyanate **13**. This isocyanate intermediate was trapped with 2,2,2-trichloroethanol to afford carbamate **14** as a single product in 81% yield for the two-step sequence.

Although the stereochemistry of the newly generated stereogenic center in **14** could not be determined at this stage, it was elucidated by NOESY correlation studies performed on **15**, an unexpectedly formed bicyclic hemiaminal by treatment of **14** with $LiAlH_4$ in refluxing ether (Scheme 3). On the other hand, when the reduction was conducted at 0 °C and gradually warmed to room temperature, the desired secondary amine was produced, which was converted to the desired corresponding *N*-Boc carbamate **16** in 55% overall yield.

Having obtained the allylic amine with the desired stereochemistry, we focused on the synthesis of the octahydroazulene intermediate **4** in Scheme 1. The requisite enyne for the RCM strategy was prepared as follows.

Hydroboration of the allylic methylene group in **16** proved troublesome and was best achieved by employing thexylborane ($ThxBH_2$) at 0 °C to room temperature. It provided alcohol **17** in 89% yield, which was subjected to IBX oxidation[8,9] and Corey–Fuchs homologation[10] of the resulting aldehyde to give alkyne **18** (Scheme 4). Subsequent removal of the TBS group of **18** with TBAF gave the primary alcohol which, in turn, was subjected to IBX

(6) Rubottom oxidation of **7** with *m*-chloroperbenzoic acid or osmium tetraoxide provided the corresponding α-hydroxy ketone in an unacceptable low yield.

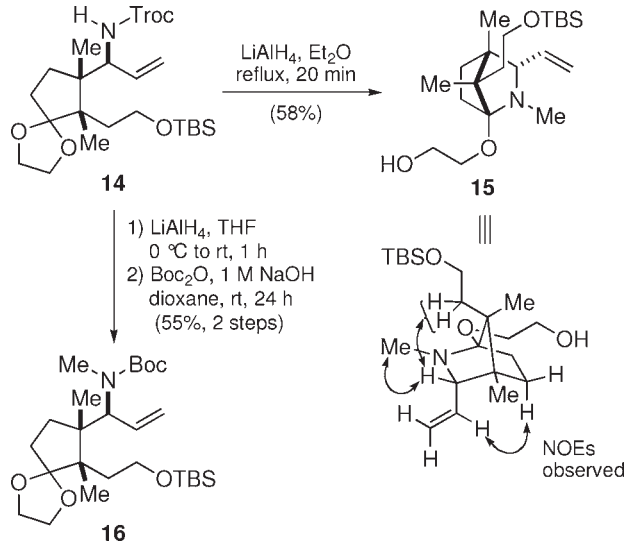
(7) (a) Ichikawa, Y. *Synlett* **1991**, 238–240. (b) Ichikawa, Y.; Tsuboi, K.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2791–2796. (c) Ichikawa, I.; Kobayashi, C.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 377–382. (d) Ichikawa, I.; Osada, M.; Ohtani, I. I.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1449–1455. (e) Ichikawa, Y.; Ito, T.; Nishiyama, T.; Isobe, M. *Synlett* **2003**, 1034–1036. (f) Ichikawa, Y. *Synlett* **2007**, 2927–2936.

(8) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272–7276.

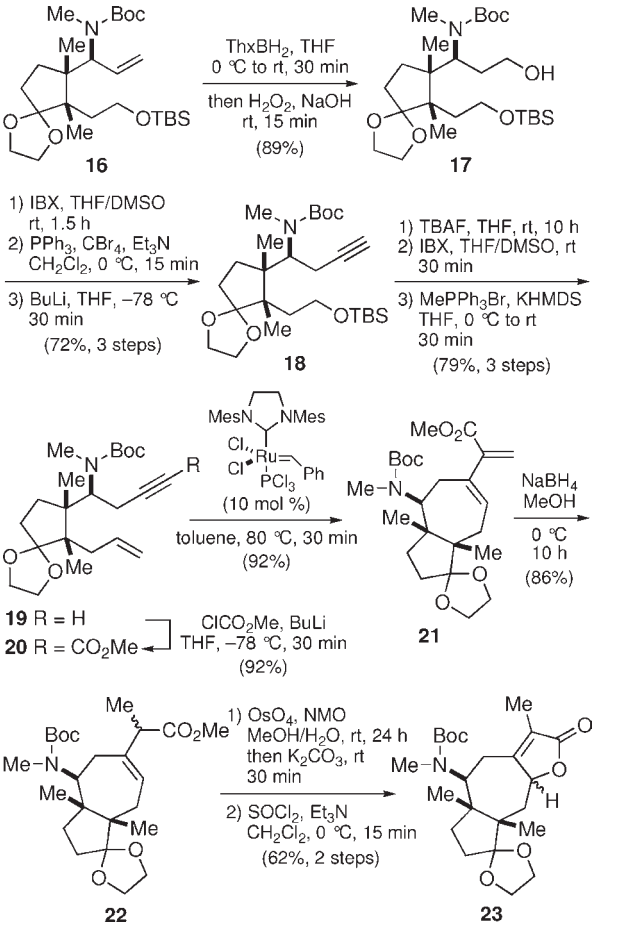
(9) Oxidation of the alcohol **17** with Dess–Martin periodinane or a pyridine–sulfur trioxide complex led to the formation of undesired byproducts, probably due to the acetic acid formed in the reaction.

(10) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769–3772.

Scheme 3. Preparation of *N*-Methyl Allyic Amine **16**



Scheme 4. Synthesis of Azuleno[5,6-*b*]furanone **23**



oxidation and Wittig olefination ($MePPh_3Br$, KHMDS) providing enyne **19** in 79% yield in three steps. Methoxycarbonylation of the terminal alkyne was achieved by employing butyllithium as a base followed by addition of methyl chloroformate to afford the desired ester **20** in 92% yield. The enyne ester **20** thus obtained was then subjected to RCM using Grubbs second-generation catalyst to form 1,3-dienecarboxylate **21** in 92% yield, which contains the complete carbon skeleton of the natural products.

The next task was construction of the butenolide moiety bearing a methyl group. Thus, 1,3-dienecarboxylate **21** was treated with $NaBH_4$ to reduce the α,β-unsaturated ester selectively to afford ester **22** in 86% yield. Dihydroxylation of the resulting ring alkene of **22** with OsO_4 and *N*-methylmorpholine *N*-oxide (NMO), followed by treatment of the resulting crude mixture with $SOCl_2$ and Et_3N, provided the desired azuleno[5,6-*b*]furanone **23** efficiently in 62% yield.

The final stage in the synthesis of the common core framework of the target natural products involved selective conversion of the butenolide to the γ-hydroxybutenolide. For this purpose, the azuleno[5,6-*b*]furanone intermediate **23** was treated with *tert*-butyldimethylsilyl triflate (TBSOTf, 1.3 equiv) in the presence of Et_3N to afford trialkylsilyloxyfuran **24** in 59% yield together with the corresponding TBS carbamate **25** in 7% yield.[11] The best result was obtained when the reaction was carried out by employing 5.0 equiv of TBSOTf; only the TBS carbamate **25** was produced in 79% isolated yield (Scheme 5). Treatment of **25** with DMDO at −15 °C by the Boukouvalas protocol[12] gave rise to γ-hydroxybutenolide **26**, which, without purification, was treated with TBAF in THF. The resulting amine **27** was then exposed to mild acidic conditions (heating at 60 °C in acetonitrile solution containing 5% water in the presence of $LiBF_4$) in order to remove the 1,3-dioxolane protecting group, to give bisacetal **28** in 74% yield with a fused tetracyclic ring system derived from intramolecular transacetalization from **25**. The bisacetal **28** thus formed was found to undergo transannular hemiaminal formation by prolonged heating at increased temperature (ca. 100 °C), giving the desired 8-azabicyclo[3.2.1]octane **29**, albeit in modest yield (36%).

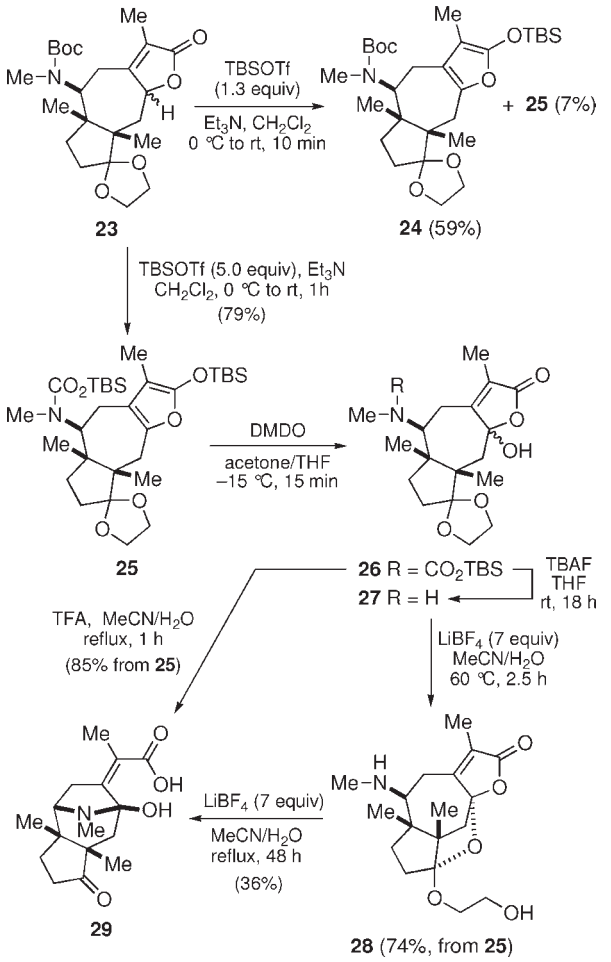
After testing several reaction conditions, we finally succeeded in optimizing the reaction by use of TFA in aqueous acetonitrile to provide **29** in 93% yield, the structure of which was confirmed by single-crystal X-ray analysis (Figure 2).[13] The best result was obtained when the γ-hydroxybutenolide **26** resulting from oxidation of **25**

(11) (a) Jefford, C. W.; Sledeski, A. W.; Rossier, J.; Boukouvalas, J. *Tetrahedron Lett*. **1990**, *31*, 5741–5744. (b) Maltais, F.; Lachance, N.; Boukouvalas, J. *Tetrahedron Lett*. **1994**, *35*, 7897–7900. (c) Jefford, C. W.; Rossier, J. C.; Boukouvalas, J.; Sledeski, A. W.; Huang, P. Z. *J. Nat. Prod*. **2004**, *67*, 1383–1386. (d) Bagal, S. K.; Adlington, R. M.; Baldwin, J. E.; Marquez, R. *J. Org. Chem*. **2004**, *69*, 9100–9108.

(12) (a) Boukouvalas, J.; Lachance, N. *Synlett* **1988**, 31–32. (b) Marcos, I. S.; Pedrero, A. B.; Sexmero, M. J.; Diez, D.; García, N.; Escola, M. A.; Basabe, P.; Conde, A.; Moro, R. F.; Urones, J. G. *Synthesis* **2005**, 3301–3310.

(13) Crystallographic data for structure **29** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 813340.

Scheme 5. Synthesis of Azabicyclo[3.2.1]octane **29**



was treated with TFA in aqueous acetonitrile at reflux; under these conditions, **29** was obtained in 85% yield over two steps from **25**.

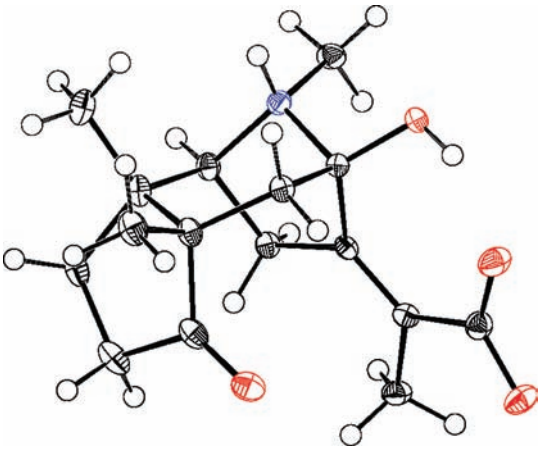


Figure 2. X-ray crystal structure of compound **29**.

In conclusion, we have developed a synthetic pathway to the azabicyclo[3.2.1]octane **29**, an advanced key intermediate for the total synthesis of both **1** and **2**, using an allylic cyanate-to-isocyanate rearrangement, eneyne ring-closing metathesis, and a transannular aminal formation. Further studies directed toward the completion of hederacines A and B continue in our laboratory.

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Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.