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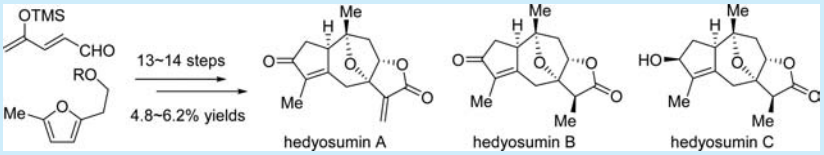
Catalytic Asymmetric Total Synthesis of Hedyosumins A, B, and C

Wang-Bin Sun,[†,‡,§] Xuan Wang,[†,§] Bing-Feng Sun,[*,†] Jian-Ping Zou,[‡] and Guo-Qiang Lin[†]

[†]CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, 345 Lingling Road, Shanghai 200032, China

[‡]Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry and Chemical Engineering, Soochow University, Suzhou, Jiangsu 215123, China

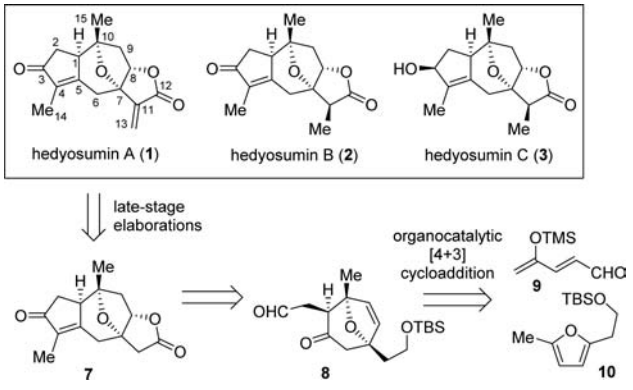
Supporting Information



ABSTRACT: The first and asymmetric total synthesis of hedyosumins A, B, and C was accomplished in 13−14 steps from simple starting materials. The essential tools that allow us to access the tetracyclic skeleton include an organocatalytic [4 + 3] cycloaddition reaction, an intramolecular aldol condensation, and an intramolecular carboxymercuration/demercuration enabled lactonization. A CBS-catalyzed asymmetric reduction was employed to boost the ee of the synthetic natural products to an excellent level. This synthesis established the absolute configurations of hedyosumins A, B, and C.

Guaianolides have attracted much attention from the chemistry community on account of their intriguing molecular structures as well as their significant biological activities.[1] Hedyosumins A−C (**1**−**3**) are scarce guaianolides isolated from *Hedyosmum orientale*, the sole species of *Hedyosmum* genus that grows in China (Scheme 1).[2] The extremely low contents of these natural products in the plants, i.e., 7 ppm for **1**, 3.5 ppm for **2**, and 3.0 ppm for **3**, have hampered the efforts to identify their full biological profiles. Structurally, these tetracyclic natural products represent the rare examples of guaianolides that contain a characteristic 7,10-epoxy bridge. The exquisite polycyclic architecture decorated with a dense array of stereogenic centers presents significant synthetic challenge. So far, these natural products have not succumbed to total synthesis.

Scheme 1. Retrosynthetic Analysis of 1−3



The past decades have witnessed significant achievements in the total synthesis of guaianolides.[3] Nevertheless, to the best of our knowledge, no catalytic enantioselective approach to guaianolides has been reported. The development of a catalytic enantioselective synthetic strategy for guaianolides, albeit challenging, is highly desirable. Herein, we report our efforts in the development of the first organocatalytic enantioselective strategy for guaianolides that allows the asymmetric total synthesis of hedyosumins A−C (**1**−**3**).

To accomplish the asymmetric total synthesis of **1**−**3**, tetracycle **7** was envisioned to be a common synthetic precursor which, through late-stage elaborations, could produce all the targets (Scheme 1). By disassembling the two flanking five-membered rings, **7** could be reduced to **8**. This retrosynthetic analysis demanded us to develop an approach to oxa-bridge cycloheptenone **8**. Encouraged by our recent success in realizing the first application of Harmata's organocatalytic [4 + 3] cycloaddition reaction in the total synthesis of natural products,[4,5] we anticipated that **8** could be directly assembled from the [4 + 3] cycloaddition reaction of **9** and **10**.

The synthetic journey commenced with the critical [4 + 3] cycloaddition reaction. In light of the stereochemical course as established by us[5] and confirmed recently by Harmata's computational analysis,[6] (*S*,*S*)-**A** was chosen as the catalyst for the reaction to deliver the anticipated absolute stereochemistry (Scheme 2). Dienal **9** and furan **10** were prepared before being subjected to the reaction. To our delight, the [4 + 3] reaction in nitromethane went smoothly in the presence of 20 mol % of (*S*,*S*)-**A**/TFA at −20 °C, furnishing a regioisomeric mixture of **8** and **8′** in a ratio of 1.8/1. The relative stereochemistries of **8** and **8′** were established through 2D NMR studies. Although the overall yield for **8** and **8′**

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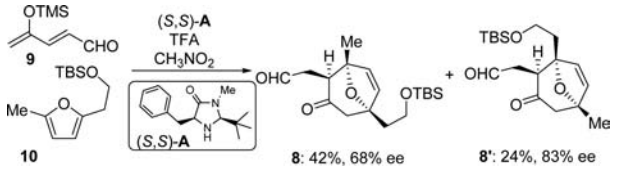
Scheme 2. [4 + 3] Cycloaddition Reaction of 9 and 10 Catalyzed by (*S*, *S*)-A[a]

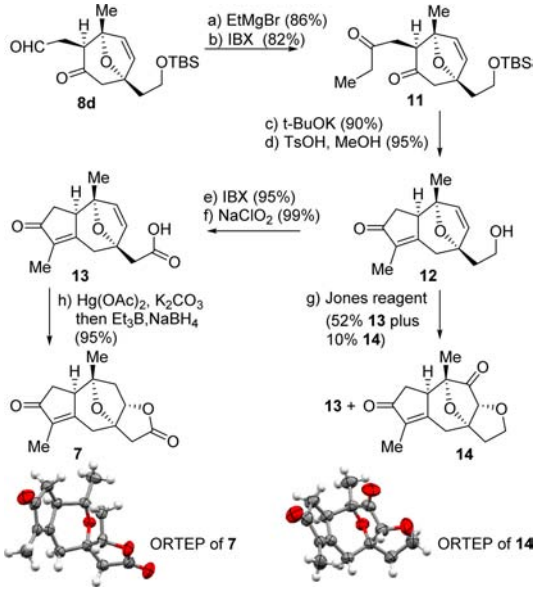


[a]Reagents and conditions: **9** (1 equiv), (*S*,*S*)-**A** (0.2 equiv), TFA (0.2 equiv), **10** (3 equiv), CH_3NO_2, − 20 °C.

reached a good level (68%), the yield for the desired regioisomer **8** was obtained in a modest yield of 42%. Nevertheless, the reaction is fairly efficient considering that two rings and three stereogenic centers have been fostered in only one step. The modest enantiopurity (68% ee) would be further enhanced to an excellent level at a later synthetic stage.

With an efficient asymmetric synthesis of **8** established, we moved on to construct the two flanking five-membered rings (Scheme 3). Treatment of **8** with EtMgBr followed by

Scheme 3. Synthesis of 7[a]

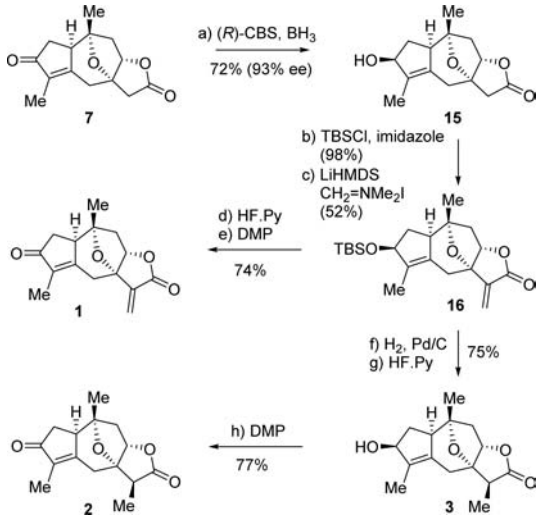


[a]Reagents and conditions: (a) EtMgBr, THF, 0 °C, 86%; (b) IBX, DMSO, 40 °C, 82%; (c) *t*-BuOK, Na_2SO_4, *t*-BuOH, 40 °C, 90%; (d) TsOH, MeOH, rt, 95%; (e) IBX, DMSO, 45 °C, 95%; (f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, MeCN, H_2O, rt, 99%; (g) Jones' reagent, acetone, 0 °C, 52% **13** plus 10% **14**; (h) $Hg(OAc)_2$, K_2CO_3, THF; then Bu_3SnH, 90%.

oxidation of the resultant alcohol with IBX produced diketone **11** in 74% yield. The intramolecular aldol condensation reaction of **11** was next examined with various conditions, and an optimal yield of 90% was obtained with *t*-BuOK in the presence of anhydrous Na_2SO_4.[7] Exposure of the resultant enone to TsOH/MeOH furnished alcohol **12** in 95% yield. The subsequent two-step oxidation procedure converted **12** to carboxylic acid **13** in an excellent overall yield. In comparison, direct oxidation of **12** with Jones' reagent afforded **13** in 52% yield along with a minor amount of **14** whose structure was confirmed by the X-ray crystallographic analysis.[11] The annulation of **13** was subsequently investigated. Although various conditions failed to give any cyclization product, to our delight, treatment of **13** with $Hg(OAc)_2$ followed by reduction with $Et_3B/NaBH_4$ generated **7** in a yield of 95%.[8,9] The stereochemistry of **7** was established unambiguously through the X-ray crystallographic analysis.[11]

With tetracycle **7** in hand, we entered the stage to finish the total synthesis of hedyosumins A−C (**1**−**3**) (Scheme 4). The

Scheme 4. Total Synthesis of 1−3[a]



[a]Reagents and conditions: (a) (*R*)-CBS, BH_3·THF, DCM, 72%, 92% ee; (b) TBSCl, imidazole, DCM, 98%; (c) LiHMDS, THF, −78 °C, CH_2═Me_2NI, 52%; (d) HF·Py; (e) Dess-Martin periodinane, 74% from **16**; (f) H_2, Pd/C; (g) HF·Py, 75% from **16**; (h) Dess-Martin periodinane, 77%.

asymmetric reduction of enone **7** catalyzed by (*R*)-CBS[10] furnished **15** in 72% yield while enhancing the enantiopurity of the product to an excellent level (93% ee). Masking the hydroxyl group was found necessary before methylenating the α-carbon of the lactone to afford **16**. Removal of the silyl group and oxidation of the resultant hydroxyl group transformed **16** to **1**. On the other hand, catalytic hydrogenation of **16** followed by desilylation generated **3**, from which **2** was easily garnered by an oxidation reaction.

The synthetic samples of **1**−**3** exhibited identical ^1H and ^{13}C NMR spectroscopic data to those reported for hedyosumins A−C, respectively, thereby confirming the structures as well as the relative stereochemistries of these natural products. Synthetic **1** and **2** also possess the same sense of specific optical rotation ($[\alpha]_D$ = +192.7 (*c* = 0.20, MeOH) for **1**, $[\alpha]_D$ = +143.1 (*c* = 0.83, MeOH) for **2**) as reported for natural hedyosumins A and B ($[\alpha]_D$ = +70.0 (*c* = 0.16, MeOH) for hedyosumin A, $[\alpha]_D$ = +183.0 (*c* = 0.11, MeOH) for hedyosumin B),[2] indicating they possess the same absolute configurations as their natural counterparts. The synthetic sample of **3** exhibited a different sense of specific optical rotation ($[\alpha]_D$ = −1.53 (*c* = 0.25, MeOH) as compared to that of the natural hedyosumin C ($[\alpha]_D$ = +6.0 (*c* = 0.08, MeOH)).[2] However, on the basis of these two facts: (1) the absolute values of these two data are relatively small, and (2) hedyosumins A, B, and C are congeners isolated from the same plant, we believe the synthetic sample of **3** possesses the same absolute configuration as the natural one.

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In summary, the first catalytic enantioselective synthetic strategy for guaianolides was successfully developed that allowed the first and asymmetric total synthesis of hedyosumins A, B, and C in 13 steps, 14 steps, and 13 steps, respectively. The synthetic route is quite efficient, with hedyosumins A, B, and C being obtained in 6.1%, 4.8%, and 6.2% overall yield, respectively. Salient transformations include an organocatalytic [4 + 3] cycloaddition reaction, an intramolecular aldol condensation reaction, an intramolecular carboxymercuration/demercuration-enabled lactonization, and a CBS-catalyzed ee-boosting reduction. Through this total synthesis, the absolute configurations of hedyosumins A, B, and C are successfully established. The total synthesis has paved the way toward a detailed biological profiling of these scarce natural products. The newly demonstrated synthetic strategy can readily lend itself to the total synthesis of a broad scope of natural products. Studies along this line are currently actively pursued in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00150.

Experimental procedures and spectroscopic data for new compounds (PDF)
Crystallographic data for **7** (CIF)
Crystallographic data for **14** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bfsun@sioc.ac.cn

Author Contributions

§These authors contributed equally.

Notes

The authors declare no competing financial interest.

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(11) CCDC 1445342 (**7**) and CCDC 1445343 (**14**) contain the supplementary crystallographic data for this paper.

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