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Asymmetric Total Synthesis of Caribenol A

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Abstract: A unified strategy toward the asymmetric total synthesis of carbenol A is reported, featuring intramolecular Diels−Alder (IMDA) and biomimetic oxidation reactions as key steps.

Caribenol A (**1**, Figure 1), which was isolated in 2007 by Rodríguez and co-workers from the West Indian gorgonian octocoral *Pseudopterogorgia elisabethae*, represents a family of novel norditerpenes. It possesses a unique structure and prominent biological activities.[1] Of particular interest is its strong inhibitory activity against *Mycobacterium tuberculosis* ($H_{37}Rv$), which causes tuberculosis, a disease that causes over three million deaths worldwide each year.[2]

Caribenol A has an unprecedented tricarbocyclic ring system. It carries three all-*cis* methyl groups at the C1, C4, and C8 positions and a 5-hydroxyfuran-2(5*H*)-one motif, posing a particularly synthetic challenge. Indeed, efforts have been directed toward exploring feasible strategies for the chemical syntheses of these scarce yet pharmacologically significant natural substances.[3] In our laboratories, we have aimed at identifying a pathway that allows for rapid access to such tricyclic skeletons, which provides a foundation for the total synthesis of caribenol A and the modular construction of a library of analogs for further medicinal chemistry studies.

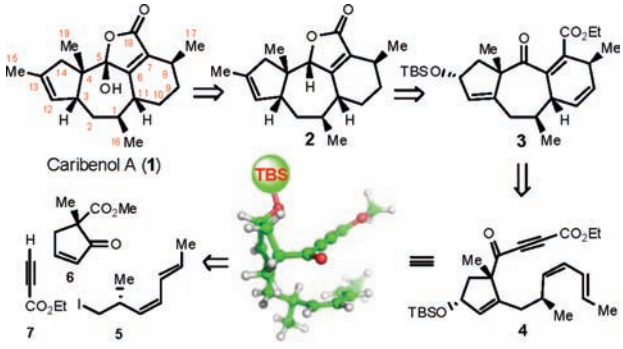
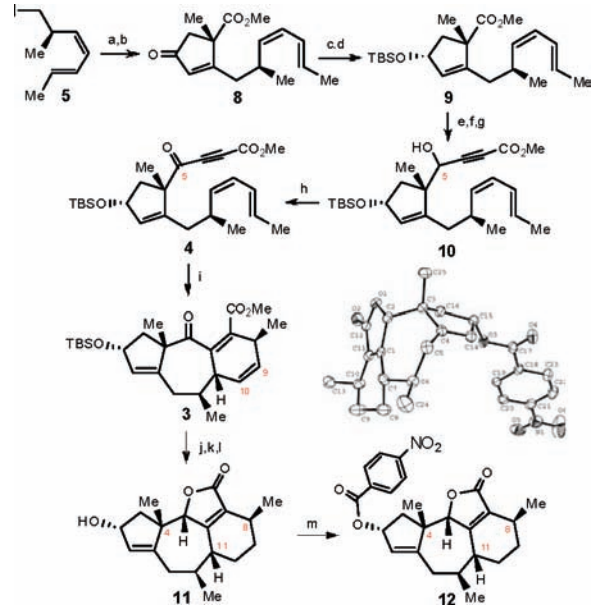


Figure 1. General Synthetic Strategy Targeting Caribenol A.

Previous investigations from our laboratories have revealed that an intramolecular Diels−Alder (IMDA) reaction[4] is an efficient method for the construction of various skeletons of natural products.[5] Herein we report our recently achieved asymmetric total synthesis of caribenol A via IMDA reaction (**4** → **3**), promoted by a preorganized favorable conformation[6] of intermedaite **4**, and a biomimetic oxidation (**2** → **1**) as key steps.

Because the reactivity and selectivity of IMDA reactions are often highly substrate-dependent,[5] particularly when 1,3-butadienes serve as the substrates,[5b] we began with examining the IMDA reaction of **4**, which could be readily prepared through the reaction sequence shown in Scheme 1. Intermediate **8** was synthesized from dienyl iodide **5**[7] and chiral enone **6**.[8] In that event, dienyl iodide **5** was first treated with *t*-BuLi in Et_2O at −78 °C to generate alkyl lithium, and the *in situ* generated alkyl lithium reacted with enone **6** to give a coupling product, which then underwent a PCC-mediated oxidative rearrangement to afford **8** in 75% overall yield.

Scheme 1. Synthesis of Intermediate **11**[a]



[a] Reagents and conditions: (a) *t*-BuLi, Et_2O, −78 °C, then **6**, 87%; (b) PCC, CH_2Cl_2, rt, 89%; (c) $LiBEt_3H$, THF, −78 °C, 92%; (d) TBSOTf, Et_3N, CH_2Cl_2, −78 °C, 96%; (e) DIBAL-H, CH_2Cl_2, −78 °C, 94%; (f) DMP, $NaHCO_3$, CH_2Cl_2, 85%; (g) **7**, *n*-BuLi, THF, −78 °C, 97%; (h) DMP, $NaHCO_3$, CH_2Cl_2, rt, 90%; (i) BHT, toluene, 120 °C, 24 h, 92%; (j) $Rh(PPh_3)_3Cl$, H_2, PhH, 66 °C, 95%; (k) HF/Pry, THF, rt, 91%; (l) $NaBH_4$, $CeCl_3$, $7H_2O$, EtOH, 0 °C, 92%; (m) 4-nitrobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2, 90%.

The silyl ether **9** was synthesized from **8**. In this transformation, $LiBEt_3H$ demonstrated to be an efficient agent for stereoselective reduction of enone **8** to its allylic alcohol,[9] which was then protected to yield the silyl ether **9**. To achieve the key intermediate **10**, the ester group in **9** was subjected to a reduction−oxidation sequence to afford an aldehyde, which then reacted with the lithium derivative of acetylene **7** to give **10** in 78% overall yield.

Based on our experience from early model studies,[5a,c] we had predicted that **4** with an activated alkyne moiety could perform as

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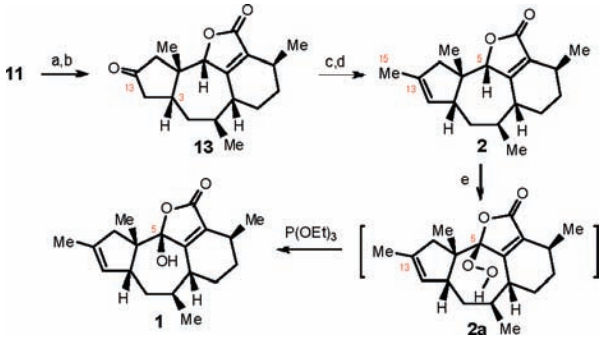
an ideal precursor for the construction of the tricyclic core of caribenol A by IMDA reaction. In our attempt to validate this prediction, **10** was oxidized to **4** with DMP in the presence of $NaHCO_3$. However, when **4** was subjected to IMDA reaction, the expected IMDA reaction did not occur, even with elevated temperature. Further attempts to carry out the IMDA reaction at lower temperature in the presence of various Lewis acids (e.g., $MgBr_2$, $ZnCl_2$, TMSOTf, $AlCl_3$, $MeAlCl_2$, and $BF_3 \cdot Et_2O$) were also unsuccessful.

With continuous effort, we subsequently found that the desired IMDA product could be generated in the presence of a catalytic amount of 2,6-di-*tert*-butyl-4-methylphenol (BHT), leading to the formation of **3** in 92% yield. **3** was converted to **11** *via* sequential hydrogenation−reduction−esterification reactions. Compound **11** was then derivatized into its 4-nitrobenzoate **12** by the treatment of **11** with nitrobenzoyl chloride in the presence of Et_3N and DMAP. The structure of **12** has been confirmed by X-ray crystal structure determination.

The pathway of achieving the total synthesis of caribenol A is outlined in Scheme 2. Intermediate **13** was generated from **11** as a sole product by an oxidation−hydrogenation sequence. The observed excellent diastereoselectivity of **13** in hydrogenation conceivably is derived from substrate conformation that possibly directs the catalyst to approach the double bond from the less hindered β-face.[10] The treatment of **13** with KHMDS generated an enolate, which reacted with Comins reagent (*N*-(5-chloro-2-pyridyl) triflimide)[11] to give an enol triflate. The enol triflate then underwent the Pd-catalyzed coupling reaction with $ZnMe_2$ to give **2** in 77% yield in two steps.

Scheme 2. Total Synthesis of Caribenol A (**1**)[a]



[a] Reagents and conditions: (a) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 92%; (b) Pd/C, H_2, THF, 93%; (c) KHMDS, THF, Comins reagent, −78 °C, 92%; (d) $Pd(PPh_3)_4$, Me_2Zn, THF, rt, 84%; (e) O_2, DMF, K_2CO_3, $P(OEt)_3$, 60 °C, 80 h, 66%.

At the end of this total synthesis, there arose a need for identifying a viable method to complete C-5 hydroxylation of **2**. To this end, various oxidative methods[12] were screened in an attempt to achieve this goal. It was found that sequential formation−reduction of the 5-hydroperoxy-furan-2(5*H*)-one[12d] of **2a** by the treatment of compound **2** with O_2 in the presence of $P(OEt)_3$ under basic conditions, originally developed by Corey and Ensley,[13] could successfully lead to the formation of caribenol A (**1**) in 66% yield.

The synthesized compound **1** has been proven to be identical to the natural product caribenol A on the aspects of ^1H NMR and ^{13}C NMR.[1] The optical rotation is also consistent with that of the reported natural product ($[\alpha]^{20}_D = +47°$ (*c* 0.4, $CHCl_3$); lit.: $[\alpha]^{20}_D = +40.0°$ (*c* 1.0, $CHCl_3$)).[1]

In summary, we have successfully applied an IMDA reaction to construct the 5−7−6 tricyclic core of caribenol A (**1**) and have effectively incorporated a hydroxyl group into its unique butenolide moiety through a biomimetic oxidation. This strategy allows us to achieve the total synthesis of caribenol A for the first time. We are currently applying the same synthetic strategy to the synthesis of a diversified caribenol-like library.

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

References

(1) Wei, X.; Rodríguez, I. I.; Rodríguez, A. D.; Barnes, C. L. *J. Org. Chem.* **2007**, *72*, 7386.
(2) Bloom, B. R.; Murray, C. J. L. *Science* **1992**, *257*, 1055.
(3) (a) Kaloko, J. J.; Teng, Y-H. G.; Ojima, I. *Chem. Commun.* **2009**, 4569. (b) Mondal, S.; Yadav, R. N.; Ghosh, S. *Tetrahedron Lett.* **2009**, *50*, 5277.
(4) (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5, p 513. (b) Brieger, G.; Bennet, J. N. *Chem. Rev.* **1980**, *80*, 63. (c) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167. (d) Juhl, M.; Tanner, D. *Chem. Soc. Rev.* **2009**, *38*, 2983. (e) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779.
(5) (a) Li, C.; Liang, S.; Zhang, X.-H.; Xie, Z.; Chen, J.-H.; Yun-Dong Wu, Y.-D.; Yang, Z. *Org. Lett.* **2005**, *7*, 3709. (b) Li, C.-C.; Wang, C.-H.; Liang, B.; Xin-Hao Zhang, X.-H.; Lu-Jiang Deng, L.-J.; Liang, S.; Chen, J.-H.; Wu, Y.-D.; Yang, Z. *J. Org. Chem.* **2006**, *71*, 6892. (c) Liu, L.; Gao, Y.; Che, C.; Wu, N.; Wang, D. Z.; Li, C.-C.; Yang, Z. *Chem. Commun.* **2009**, 662. (d) Che, C.; Liu, L.; Gong, J.; Yang, Y.; Wang, G.; Quan, J.; Yang, Z. *Org. Lett.* **2010**, *12*, 488.
(6) (a) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (b) Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16. (c) Diedrich, M. K.; Klarner, F.-G.; Beno, B. R.; Houk, K. N.; Senderowitz, H.; Still, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 10255.
(7) **5** is prepared in 7 steps from the Roche ester; see the Supporting Information for details.
(8) Kato, K.; Suzuki, H.; Tanaka, H.; Miyasaka, T. *Tetrahedron: Asymmetry* **1998**, *9*, 911. The reference describes the preparation of **6** in 5 steps.
(9) The rationale for the diastereoselective reduction is provided in the Supporting Information.
(10) The stereochemistry at C3 in **13** could not be established at this stage, and its structure was eventually assigned on the basis of conversion of **2** to **1**, which was compared with the reported data of caribenol A.
(11) Comins, D. L.; Dheghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.
(12) (a) Lacey, R. N. *J. Chem. Soc.* **1954**, 822. (b) Watt, D. S.; Selikson, S. J. *J. Org. Chem.* **1975**, *40*, 267. (c) Wasserman, H. H.; E. H. Lipshutz, E. H. *Tetrahedron Lett.* **1975**, 1731. (d) Ma, S.; Wu, B.; Shi, Z. *J. Org. Chem.* **2004**, *69*, 1429. (e) Bagal, S. K.; Adlington, R. M.; Rohan, A. B.; Brown, R. A. B.; Baldwin, J. E. *Tetrahedron Lett.* **2005**, *46*, 4633. (f) Bagal, S. K.; Adlington, R. M.; Baldwin, J. E.; Marquez, R. *J. Org. Chem.* **2004**, *69*, 9100. (g) Bagal, S. K.; Adlington, R. M.; Rohan, A. B.; Brown, R. A. B.; Baldwin, J. E. *Tetrahedron Lett.* **2005**, *46*, 4633. (h) Kim, K. H.; Lee, H. S.; Kim, S. H.; Lee, K. Y.; Lee, J.-E.; Kim, J. N. *Bull. Korean Chem. Soc.* **2009**, *30*, 1012.
(13) Corey, E.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

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