# Enantioselective Synthesis of the 5–6–7 Carbocyclic Core of the Gagunin Diterpenoids

LETTERS XXXX Vol. XX, No. XX 000–000

ORGANIC

# Grant M. Shibuya, John A. Enquist Jr., and Brian M. Stoltz\*

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 East California Boulevard, MC 101-20, Pasadena, California 91125, United States

stoltz@caltech.edu

### Received May 29, 2013



A catalytic enantioselective double allylic alkylation reaction has been employed in the synthesis of the core of the gagunin diterpenoids. Enantioenriched material was advanced in 11 steps to afford the core of the highly oxygenated target, which includes two all-carbon quaternary stereocenters.

The gagunin family of diterpenoids (1-7, Figure 1) were isolated from the sponge *Phorbas* sp. off the coast of South Korea by Shin and co-workers.<sup>1</sup> A wide range of cytotoxicity (LC<sub>50</sub> =  $0.03-50 \,\mu \text{g/mL}$ ) was reported for gagunins A-G against the human leukemia cell line K562. The cytotoxicity of the gagunins is modulated by the differential hydroxylation or esterification level present in a specific gagunin, as Shin and co-workers found gagunins A (1) and B(2) to be less active than other family members, likely due to the presence of a butyrate group at C(11) of these molecules.<sup>1</sup> Additionally, a perhydroxylated derivative of gagunin A (8) exhibited no cytotoxicity, further suggesting the importance of substitution patterns. Gagunin E (5) displayed an LC<sub>50</sub> value of 0.03  $\mu$ g/mL (50 nM), the most potent cytotoxicity within this family of natural products. In the course of a reisolation of the gagunins from *Phorbas* sp., gagunin E was not found despite the reisolation of all other known gagunins and the discovery of 10 new gagunins.<sup>1b</sup> Given the scarcity of gagunin E in nature and broad range of biological activity displayed by the gagunin family, we sought to pursue a general synthetic route toward the gagunins to allow for additional biological profiling and structure–activity relationship studies. Herein we report our progress toward a synthesis of the carbocyclic core of the gagunin family.

The carbon skeleton of the gagunins resembles the carbon skeleton of the cyathane family of diterpenoids.<sup>2</sup> A general route toward the cyathanes was previously reported by our laboratory using our enantioselective Tsuji

<sup>(1) (</sup>a) Rho, J.-R.; Lee, H.-S.; Sim, C. J.; Shin, J. *Tetrahedron* **2002**, *58*, 9585–9591. (b) Jang, K. H.; Jeon, J.; Ryu, S.; Lee, H.-S.; Oh, K.-B.; Shin, J. J. Nat. Prod. **2008**, *71*, 1701–1707.

<sup>(2) (</sup>a) Green, D.; Goldberg, I.; Stein, Z.; Ilan, M.; Kashman, Y. *Nat. Prod. Lett.* **1992**, *1*, 193–199. (b) Peng, J.; Walsh, K.; Weedman, V.; Bergthold, J. D.; Lynch, J.; Lieu, K. L.; Braude, I. A.; Kelly, M.; Hamann, M. T. *Tetrahedron* **2002**, *58*, 7809–7819. (c) Peng, J.; Avery, M. A.; Hamann, M. T. *Org. Lett.* **2003**, *5*, 4575–4578. (d) Peng, J.; Kasanah, N.; Stanley, C. E.; Chadwick, J.; Fronczek, F. R.; Hamann, M. T. *J. Nat. Prod.* **2006**, *69*, 727–730. (e) Enquist, J. A., Jr.; Stoltz, B. M. *Nat. Prod.* **2009**, *26*, 661–680.



**Figure 1.** Gagunins A-G(1-7) and perhydroxylated gagunin A (8) and their reported biological activities.

allylation methodology.<sup>3</sup> Bis- $\beta$ -ketoester 9, comprised of a mixture of racemic and *meso* diastereomers, was treated with a catalytic amount of Pd<sub>2</sub>(pmdba)<sub>3</sub> and the ligand (*S*)-*t*-Bu-PHOX (10)<sup>4</sup> to forge two all-carbon quaternary stereocenters in a single operation, affording diketone 11 in 99% ee as a 4.4:1 mixture of (*R*,*R*) to *meso*-diastereomers (Scheme 1). Diketone 11 was converted to enol triflate 12, a common intermediate used in the syntheses of cyanthiwigins F (13),<sup>5</sup> B (14),<sup>5b</sup> and G (15).<sup>5b</sup>

Our retrosynthetic analysis of gagunin E(5) is shown in Scheme 2. We planned to employ a similar overall strategy in our approach to the gagunins, as was used in the cyanthiwigins. Retrosynthetically, we envisionsed a Scheme 1. Enantioselective Tsuji Allylic Alkylation Applied to the Synthesis of Cyanthiwigins F (13), B (14), and G (15)



Scheme 2. Retrosynthesis of Gagunin E (5)



late-stage installation of the five-membered ring, preceded by establishing the seven-membered ring through a ringclosing methathesis (RCM) reaction. Such an approach would again allow for the early and essentially simultaneous introduction of both quaternary stereocenters.

In the forward direction, enol triflate **12** was subjected to conditions reported by Mulzer and co-workers to effect an intermolecular Heck reaction at the hindered neopentyl enol triflate.<sup>6</sup> The addition of silyl ketene acetal **17**,<sup>7</sup> Pd(PPh<sub>3</sub>)<sub>4</sub>, and LiOAc afforded methyl ester **18** in 77% yield

<sup>(3) (</sup>a) Behenna, D. C.; Stoltz, B. M. J. Am. Chem. Soc. **2004**, *126*, 15044–15045. (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. Angew. Chem., Int. Ed. **2005**, *44*, 6924–6927. (c) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A., Jr.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. Chem.—Eur. J. **2011**, *17*, 14199–14223.

<sup>(4)</sup> Helmchen, G.; Pfaltz, A. Acc. Chem. Res. 2000, 33, 336-345.

<sup>(5) (</sup>a) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* 2008, 453, 1228–1231.
(b) Enquist, J. A., Jr.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* 2011, 17, 9957–9969.

<sup>(6)</sup> Magauer, T.; Mulzer, J.; Tiefenbacher, K. Org. Lett. 2009, 11, 5306–5309.

<sup>(7)</sup> Oisaki, K.; Suto, Y.; Kanai, M.; Shibasaki, M. J. Am. Chem. Soc. 2003, 125, 5644–5645.

(Scheme 3).<sup>8</sup> Next, ketone **18** was converted to the corresponding ketal (**19**) in 47% yield by treatment with ethylene glycol and catalytic *p*-toluenesulfonic acid in benzene at reflux. Methyl ester **19** was then exposed to *N*,*O*-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride to afford Weinreb amide **20** in 93% yield. The addition of vinylmagnesium bromide to amide **20** at -20 °C furnished enone **21** in 74% yield.

## Scheme 3. Synthesis of Enone 21



Enone 21 was treated with Hoveyda–Grubbs generation 2 catalyst 22<sup>9</sup> in benzene at 40 °C to afford RCM adduct 23 in 85% yield (Scheme 4). The enone of 23 was next functionalized to the corresponding enol carbonate (24) in 93% yield after treatment with LHMDS followed by the addition of methyl chloroformate. A selective Wacker oxidation was performed on the terminal allyl group of tetraene 24, giving methyl ketone 25 in 61% yield.<sup>10</sup> Further purification by HPLC allowed 25 to be isolated as a single diastereomer. Previously, the separation of such diastereomers was accomplished only after closure of the

(8) Our initial investigations centered on a direct RCM approach to a cycloheptadiene via pentaene ii, available by cross-coupling of i with enol triflate **12**. Unfortunately, RCM of **ii** produced a mixture of **iii** and **iv** when employing a range of ruthenium catalysts. Therefore, the approach outlined above was pursued.



(9) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. J. Am. Chem. Soc. 2000, 122, 8168–8179. (b) Gessler, S.; Randl, S.; Blechert, S. Tetrahedron Lett. 2000, 41, 9973–9976.

(10) Using a Parr shaker was necessary to obtain product in good yield.

final ring.<sup>5</sup> Ketone **25** was next diazotized using Danheiser's diazo transfer conditions<sup>11</sup> to afford **26** in 47% yield over two steps.

### Scheme 4. Synthesis of Diazoketone 26



With diazoketone **26** in hand, we proceeded to form the final carbocycle of **5**. Treatment of **26** with catalytic  $Rh_2(OAc)_4$  afforded cyclopropane product **27** in 71% yield (Scheme 5).<sup>12,13</sup> The structure of **27** was confirmed by single crystal X-ray analysis (Figure 2).<sup>14</sup> Finally, enol carbonate cleavage and cyclopropane opening was accomplished by exposing ketone **27** to K<sub>2</sub>CO<sub>3</sub> in methanol at 0 °C, giving the desired ring-opening product **28** and an unexpected rearranged product (**29**) in a 1:1.8 ratio as determined by crude <sup>1</sup>H NMR analysis. The structure of **29** was again unambiguously confirmed by single crystal X-ray diffraction following chromatographic purification

<sup>(13)</sup> Concurrent to the preparation of diazo ketone **26**, we prepared diazodiketone v using a similar approach. Treatment of v with  $Rh_2(OAc)_4$  did not yield a cyclopropanation, but instead a C–O insertion product tentatively assigned as vi was isolated in 38% yield.



(14) Two conformations of the ketal of **27** were observed in the X-ray structure. Only one has been shown here.

<sup>(11)</sup> Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. J. Org. Chem. 1990, 55, 1959–1964.

<sup>(12) (</sup>a) Fernández-Mateos, A.; Pérez Alonso, J. J.; Rubio González,
R. *Tetrahedron* 1999, 55, 847–860. (b) Srikrishna, A.; Jagadreswar Reddy, T. J. Chem. Soc., Perkin Trans. 1 2001, 2040–2046.

Scheme 5. Completion of the Tricyclic Core of 5 via Cyclopropanation and Ring Opening



of **28** and **29**.<sup>15</sup> Ultimately, desired dienone **28** was isolated in 31% yield, and cyclopropane **29**, in 27% yield; the change in ratio between the crude analysis and isolated yields suggest cyclopropane **29** may be unstable to chromatography conditions. Cyclopropane **29** is presumably formed from desired product **28** by a retro-norcaradiene rearrangement after formation of an enolate following deprotonation at C(6).<sup>16</sup>

In summary, an expediant route toward the tricyclic core of the gagunins has been established, giving 16 of 20 carbons present in the core of these diterpenoids and the full tricyclic skeleton. The seven-membered ring was synthesized via an intermolecular Heck reaction at a hindered neopentyl carbon followed by a ruthenium-catalyzed RCM reaction of an enone and an allyl group. The five-membered ring was prepared from an allyl group via a Wacker oxidation and ring-forming cyclopropanation from a diazoketone. Efforts to optimize this sequence and carry **28** and **29** forward to the gagunins and their analogs are ongoing.



Figure 2. Single-crystal X-ray structures of 27 and 29.

Acknowledgment. The authors wish to thank NIH-NIGMS (R01GM080269-01), Amgen, Abbott, Boehringer Ingelheim, and Caltech for financial support. Mr. Austin Moehle (Caltech) is thanked for the preparation of early compounds. Dr. David Vander Velde (Caltech) is gratefully acknowledged for assistance with the characterization of compounds by NMR spectroscopy. Mr. Lawrence Henling (Caltech) is gratefully acknowledged for X-ray crystallographic structural determination and Dr. Alexander Goldberg (Caltech) is acknowledged for assisting in the preparation of crystallographic images for publication. Ms. Kelly Kim (Caltech) is acknowledged for assistance with the IR data of a late-stage compound. Materia, Inc. and Dr. Keith Keitz (Caltech) are thanked for the generous donation of ruthenium catalysts. The Bruker KAPPA APEXII X-ray diffractometer was purchased via an NSF CRIF:MU award to the California Institute of Technology, CHE-0639094. We also wish to acknowledge helpful discussions with Christina White (UIUC), Huw Davies (Emory), and other members of the CCI Center for Selective C-H Functionalization supported by NSF (CHE-1205646).

**Supporting Information Available.** Experimental details and NMR spectra of all intermediates. These materials are available free of charge via the Internet at http://pubs.acs.org.

<sup>(15)</sup> For similar structures containing cyclopropane rings, please see:
(a) Nani, R. R.; Reisman, S. E. J. Am. Chem. Soc. 2013, 135, 7304–7311. (b) Levin, S.; Nani, R. R.; Reisman, S. E. J. Am. Chem. Soc. 2011, 133, 774–776.
(c) Tseng, C.-C.; Ding, H.; Li, A.; Guan, Y.; Chen, D. Y.-K. Org. Lett. 2011, 13, 4410–4413. (d) Ng, W.; Wege, D. Tetrahedron Lett. 1996, 37, 6797–6798.
(e) Ruppert, J. F.; White, J. D. J. Am. Chem. Soc. 1981, 103, 1808–1813.

<sup>(16)</sup> Alternatively, enol carbonate cleavage of 27 without cyclopropane fragmentation would give an enone that could be deprotonated at the C(6) position and allow for the formation of 29 directly from 27 after cyclopropane opening.

The authors declare no competing financial interest.