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Enantioselective Synthesis of the 5−6−7 Carbocyclic Core of the Gagunin Diterpenoids

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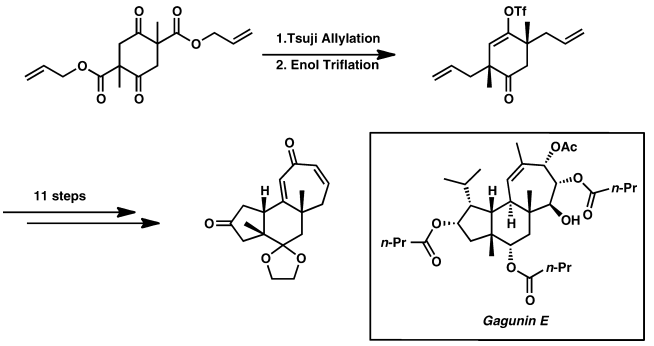
ABSTRACT



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.[1] A wide range of cytotoxicity (LC_{50} = 0.03−50 μg/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.[1] Additionally, a perhydroxylated derivative of gagunin A (**8**) exhibited no cytotoxicity, further suggesting the importance of substitution patterns. Gagunin E (**5**) displayed an LC_{50} value of 0.03 μg/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.[1b] 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.[2] A general route toward the cyathanes was previously reported by our laboratory using our enantioselective Tsuji

(1) (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.

(2) (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. Rep.* **2009**, *26*, 661–680.

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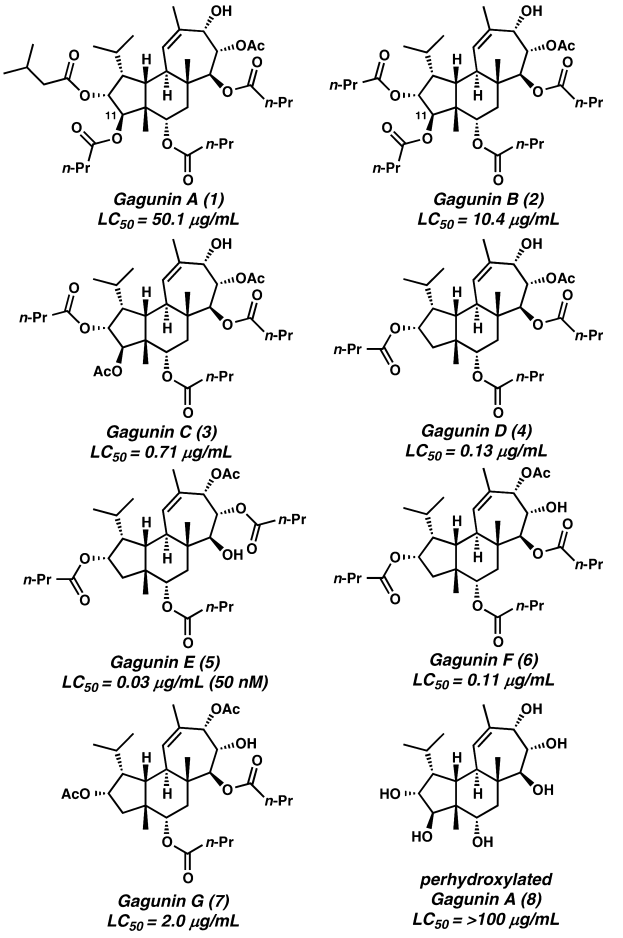
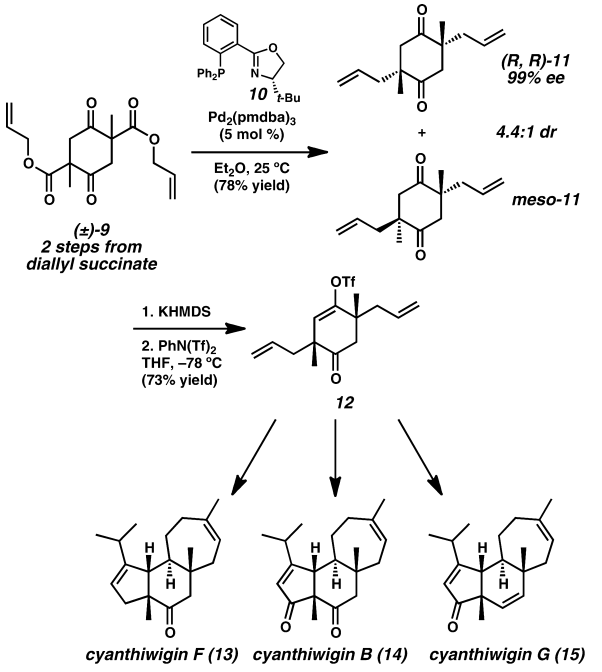


Figure 1. Gagunins A–G (**1**–**7**) and perhydroxylated gagunin A (**8**) and their reported biological activities.

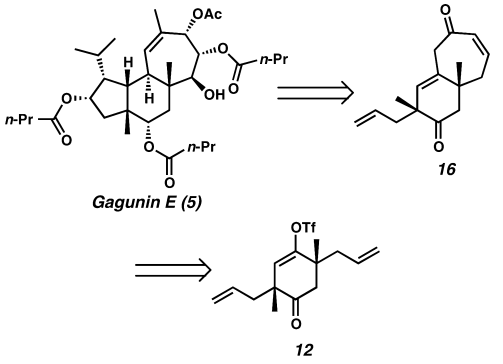
allylation methodology.[3] Bis-β-ketoester **9**, comprised of a mixture of racemic and *meso* diastereomers, was treated with a catalytic amount of $Pd_2(pmdba)_3$ and the ligand (*S*)-*t*-Bu-PHOX (**10**)[4] to forge two all-carbon quaternary stereocenters in a single operation, affording diketone **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**),[5] B (**14**),[5b] and G (**15**).[5b]

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

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**)



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.[6] The addition of silyl ketene acetal **17**,[7] $Pd(PPh_3)_4$, and LiOAc afforded methyl ester **18** in 77% yield

(3) (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.

(4) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345.

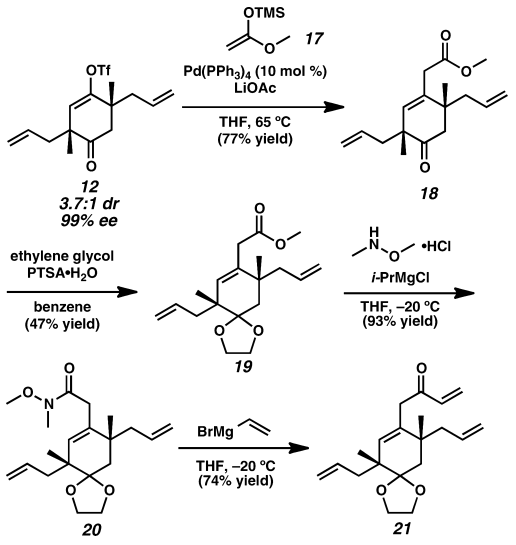
(5) (a) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231. (b) Enquist, J. A., Jr.; Virgil, S. C.; Stoltz, B. M. *Chem.—Eur. J.* **2011**, *17*, 9957–9969.

(6) Magauer, T.; Mulzer, J.; Tiefenbacher, K. *Org. Lett.* **2009**, *11*, 5306–5309.

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

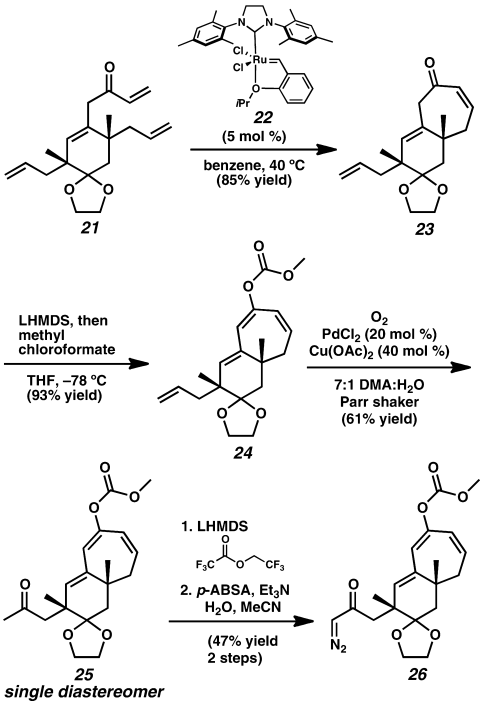
(Scheme 3).[8] Next, ketone **18** was converted to the corresponding ketal (**19**) in 47% yield by treatment with ethylene glycol and catalytic *p*-toluenesulfonic acid in benzene at reflux. Methyl ester **19** was then exposed to *N*,*O*-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride 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**



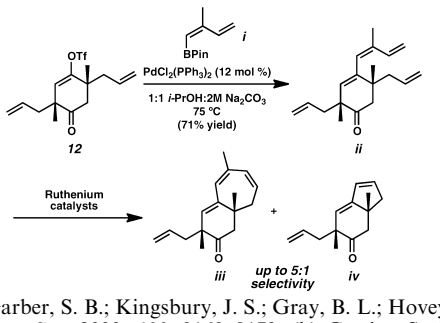
Enone **21** was treated with Hoveyda−Grubbs generation 2 catalyst **22**[9] in benzene at 40 °C to afford RCM adduct **23** in 85% yield (Scheme 4). The enone of **23** was next functionalized to the corresponding enol carbonate (**24**) in 93% yield after treatment with LHMDS followed by the addition of methyl chloroformate. A selective Wacker oxidation was performed on the terminal allyl group of tetraene **24**, giving methyl ketone **25** in 61% yield.[10] 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 final ring.[5] Ketone **25** was next diazotized using Danheiser's diazo transfer conditions[11] 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).[12,13] The structure of **27** was confirmed by single crystal X-ray analysis (Figure 2).[14] Finally, enol carbonate cleavage and cyclopropane opening was accomplished by exposing ketone **27** to K_2CO_3 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 ^{1}H NMR analysis. The structure of **29** was again unambiguously confirmed by single crystal X-ray diffraction following chromatographic purification

(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.



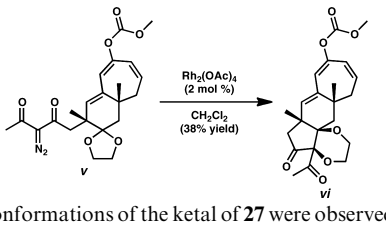
(9) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179. (b) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973–9976.

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

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

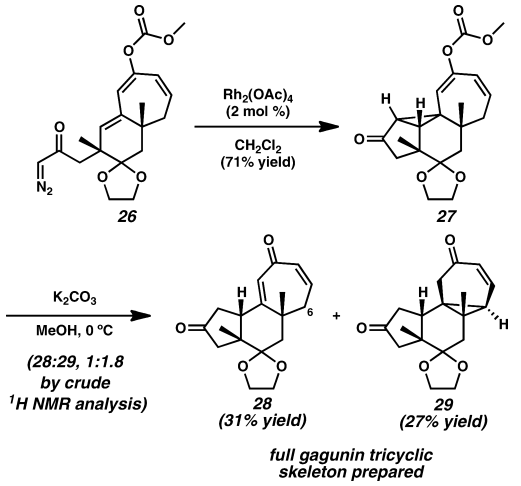
(12) (a) Fernández-Mateos, A.; Pérez Alonso, J. J.; Rubio González, R. *Tetrahedron* **1999**, *55*, 847–860. (b) Srikrishna, A.; Jagadreswar Reddy, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2040–2046.

(13) 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.

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



of **28** and **29**.[15] 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).[16]

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.

(15) 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.

(16) 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.

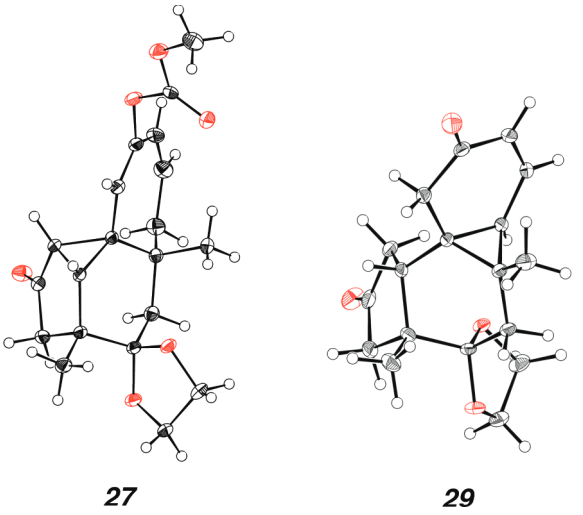


Figure 2. Single-crystal X-ray structures of **27** and **29**.

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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.

The authors declare no competing financial interest.