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Concise and Stereocontrolled Synthesis of the Tetracyclic Core of Daphniglaucin C

Stephen Hanessian,* Stéphane Dorich, and Helge Menz

Department of Chemistry, Université de Montréal, P.O. Box 6128, Station Centre-ville, Montreal, QC, H3C 3J7, Canada

stephen.hanessian@umontreal.ca

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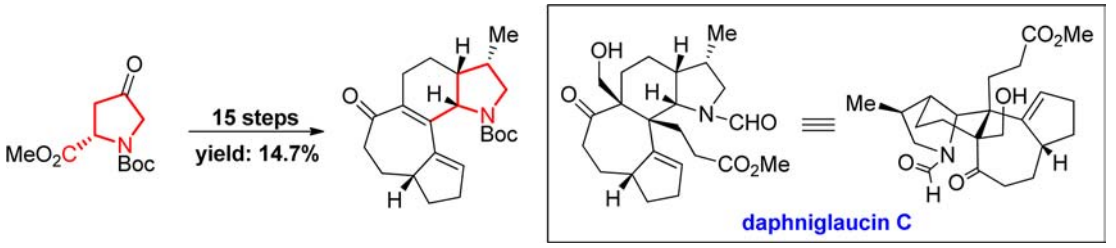
ABSTRACT



The tetracyclic core of daphniglaucin C was prepared from the known 4-keto-*N*-Boc methyl-L-prolinate in 15 steps with a cumulative yield of 14.7%. The key steps toward this core motif feature a reductive double bond transposition from an unactivated tertiary allylic alcohol, a Pd-catalyzed Stille coupling, and Dieckmann cyclizations.

An architecturally complex and structurally novel family of alkaloids has been isolated from the leaves of *daphnyphyllum* species over the past decade.[1] Among these, the daphniglaucins A−K consist of a highly conserved polycyclic core featuring octahydroindole and hexahydroazulene fused ring systems (Figure 1). In 2003, Kobayashi and co-workers[2] isolated daphniglaucin C (**3**), in which the octahydroindole subunit (red contours, Figure 1) was part of a tetracyclic core encompassing the hexahydroazulene ketone core. Daphniglaucin C was reported to have significant antitumor activity (IC_{50} = 0.1 μg/mL against murine lymphoma) as well as inhibitory effects toward tubulin polymerization (IC_{50} = 2.5 μM).[2]

Although the absolute configuration of the daphniglaucins is not known, it is highly probable that they are derived from (3*R*)-mevalonic acid[3] as a biogenetic precursor to the octahydroindole subunit containing the methyl group, which establishes the stereochemistry as indicated. Analysis of the structure of daphniglaucin C reveals two vicinal quaternary carbon centers bisecting the highly convex tetracyclic core motif.

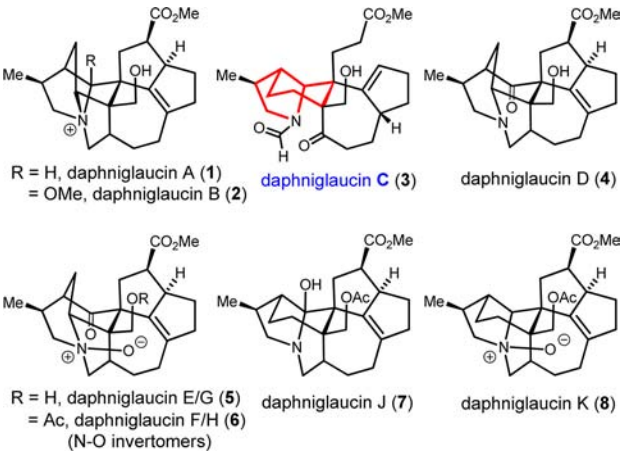


Figure 1. Selected members of the Daphniglaucin family.

It was envisaged that the stereocontrolled total synthesis of a high value advanced intermediate tetracyclic enone such as **9** could establish a general strategy toward further elaboration to some of the individual members of this

(1) (a) Kobayashi, J.; Takatsu, Y.; Shen, Y. C.; Morita, H. *Org. Lett.* **2003**, *5*, 1733–1736. (b) Takatsu, Y.; Shen, Y. C.; Morita, H.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 6279–6284. (c) For a review, see: Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936–962.

(2) Morita, H.; Takatsu, H.; Shen, Y.-C.; Kobayashi, J. *Tetrahedron Lett.* **2004**, *45*, 901–904.

(3) Niwa, H.; Hirata, Y.; Suzuki, K. T.; Yamamura, S. *Tetrahedron Lett.* **1973**, *14*, 2129–2132.

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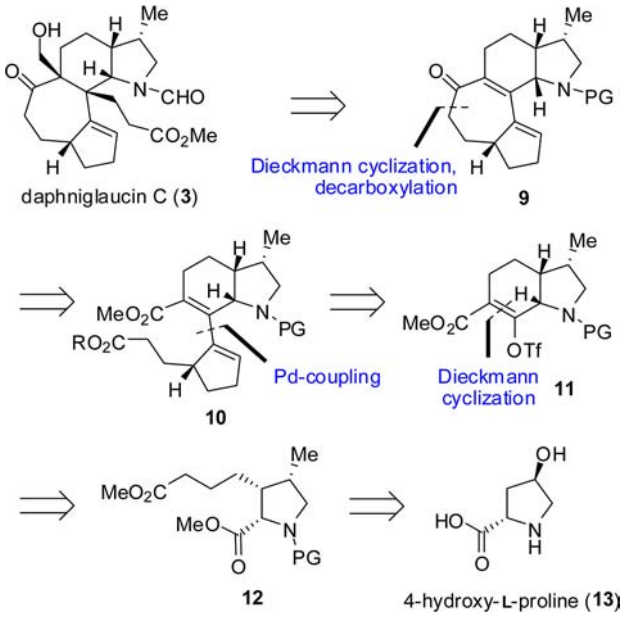
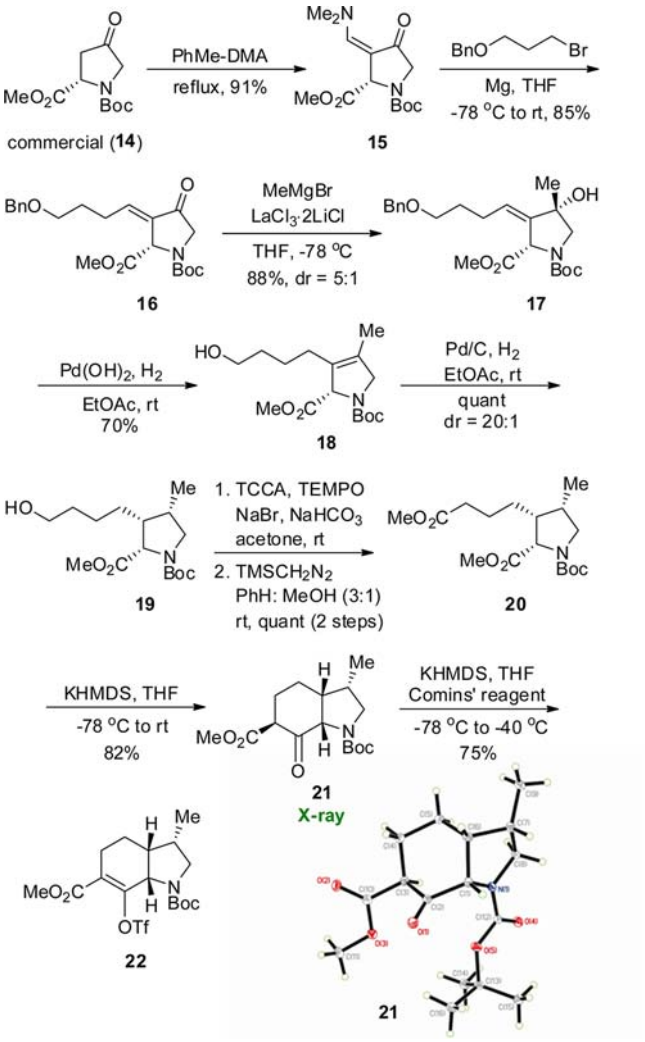
fascinating family of alkaloids (Scheme 1). To the best of our knowledge, synthetic approaches toward the tetracyclic core structure of daphniglaucin C harboring four stereogenic centers are yet to be reported.[4,5] Intermediate **9** could originate from the tricyclic intermediate **10** by means of a Dieckmann cyclization. Pd-mediated Stille coupling of a hexahydroindole motif **11** with an appropriately substituted cyclopentene moiety would lead to **10**. Access to **11** would envisage a Dieckmann cyclization of an all-*syn* substituted proline derivative **12**, prepared in a stereocontrolled manner from the readily available 4-hydroxy-L-proline as a partially hidden chiron.[6]

Scheme 1. Key Disconnections toward Daphniglaucin C



The synthesis commenced with **14**,[7] which was transformed into the enaminone **15** with 1,1-dimethoxy-*N*,*N*-dimethylmethanamine (DMA)[8] in 91% yield (Scheme 2). A three-carbon appendage was then introduced in 85% yield by taking advantage of the reactivity of the enaminone **15** as a versatile Michael acceptor.[9] Thus, an addition–elimination reaction with 3-benzyloxypropyl magnesium bromide[10] led to the enone **16**, which, upon treatment with MeMgBr and $LaCl_3 \cdot LiCl$,[11] led to the tertiary allylic alcohol **17** in a 5:1 dr and 88% yield.

Scheme 2. Synthesis of the Key Intermediate **22** and ORTEP Diagram for **21** (ellipsoids drawn at 30% probability level)



When treated with $Pd(OH)_2/C$ (Pearlman's catalyst)[12] under 1 atm of hydrogen, **17** was reductively transposed to give the tetrasubstituted alkene **18** in 70% yield with concommitent hydrogenolysis of the benzyl ether group. Surprisingly, the epimeric tertiary alcohol (not shown) reacted sluggishly under the hydrogenolysis conditions to afford low yields (20–25%) of **18**. To the best of our

(4) For seminal work on the biomimetic synthesis of related alkaloids, see: (a) Heathcock, C. H.; Stafford, J. A. *J. Org. Chem.* **1992**, *57*, 2566–2574 and references cited therein.

(5) For selected examples of synthetic approaches to related alkaloids, see: (a) Coldham, I.; Burrell, A. J. M.; Guerrand, H. D. S.; Oram, N. *Org. Lett.* **2011**, *13*, 1267–1269. (b) Bélanger, G.; Boudreault, J.; Lévesque, F. *Org. Lett.* **2011**, *13*, 6204–6207. (c) Denmark, S. E.; Baiazitov, R. Y. *J. Org. Chem.* **2006**, *71*, 593–605. (d) Solé, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2005**, *7*, 5461–5464.

(6) For a review, see: Remuzon, P. *Tetrahedron* **1996**, *52*, 13803–13835.

(7) Del Valle, J. R.; Goodman, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1600–1602 and references cited therein.

(8) (a) Barraclough, P.; Hudhomme, P.; Spray, C. A.; Young, D. W. *Tetrahedron* **1995**, *51*, 4195–4212. (b) Chabaud, P.; Pèpe, G.; Courcambeck, J.; Camplo, M. *Tetrahedron* **2005**, *61*, 3725–3731. When Bredereck's reagent was used instead, lower yields were obtained.

(9) Selection of articles using this strategy: (a) Shawe, T. T.; Hansen, D. B.; Peet, K. A.; Prokopowicz, A. S.; Robinson, P. M.; Cannon, A.; Dougherty, K. E.; Ross, A. A.; Landino, L. M. *Tetrahedron* **1997**, *53*, 1547–1556. (b) Coudert, E.; Acher, F.; Azerad, R. *Synthesis* **1997**, 863–865. (c) Fontenas, C.; Aït-Haddou, H.; Bejan, E.; Balavoine, G. G. A. *Synth. Commun.* **1998**, *28*, 1743–1753. (d) Andrew, R. J.; Mellor, J. M. *Tetrahedron* **2000**, *56*, 7261–7266.

(10) (a) Thies, H.; Wolfschütz, R.; Frenking, G.; Schmidt, J.; Schwarz, H. *Tetrahedron* **1982**, *38*, 1647–1656. (b) Frankowski, J. K.; Golden, J. E.; Zeng, Y.; Lei, Y.; Aubé, J. *J. Am. Chem. Soc.* **2008**, *130*, 6018–6024.

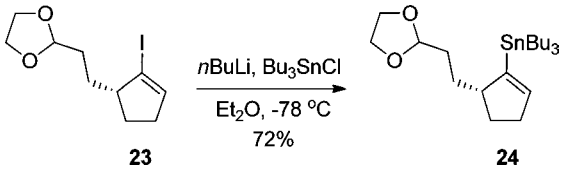
(11) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 497–500. When the Grignard reagent was used alone, substantial amounts of the 1,4-addition product were observed.

(12) Pearlman, W. M. *Tetrahedron Lett.* **1967**, *8*, 1663–1664.

knowledge, such examples of reductive allylic transposition of tertiary allylic alcohols are sparse.[13] The alkene **18** was then hydrogenated with Pd/C under 1 atm of hydrogen to afford the all-*syn* pyrrolidine **19** as a single diastereomer in quantitative yield. One-pot oxidation of the primary alcohol to the carboxylic acid using trichloroisocyanuric acid (TCCA),[14] then esterification, led to the diester **20** in a quantitative yield. A study of the conditions for the Dieckmann cyclization[15] of **20** showed that a concentration of 0.4 M in THF using KHMDS was optimal to obtain the crystalline β-ketoester **21** in 82% yield (X-ray). Conversion to the enol triflate **22** was best achieved using Comins' reagent[16] with KHMDS as the base. With LiHMDS, NaHMDS, or KHMDS and Tf_2O in THF at −78 °C, the yield of **22** was 60%. Attempts to prepare **22** in a one-pot process by trapping the potassium enolate of **21** with Comins' reagent led to lower yields (40%).

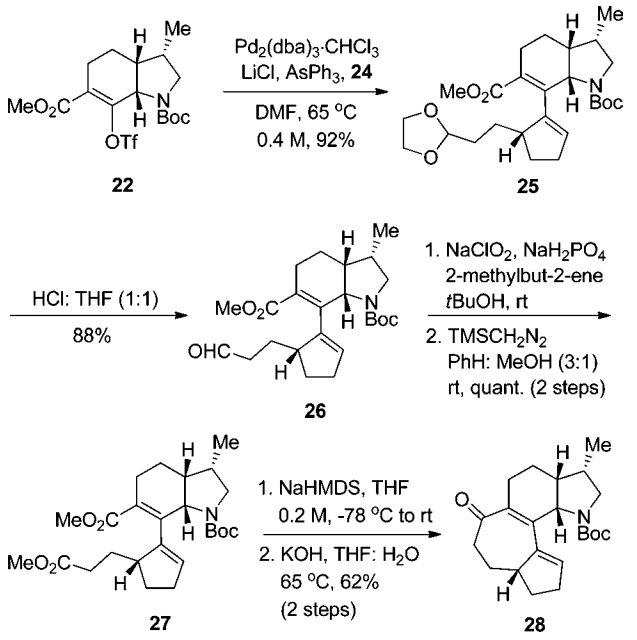
With **22** in hand, our efforts were then turned toward synthesizing a properly substituted cyclopentenyl Stille-coupling partner. To this end, an efficient method developed by Knochel[17] was utilized to prepare the vinyl iodide **23** (Scheme 3). Treatment of this vinyl iodide with *n*BuLi in Et_2O, followed by quenching with Bu_3SnCl, cleanly yielded the vinyl stannane **24** in 72% yield.[18] Using other solvents such as THF, hexanes, and THF/HMPA led to lower yields.

Scheme 3. Synthesis of the Cyclopentenyl Stannane **24**



The Stille coupling between **22** and **24** was then investigated (Scheme 4). It was found that the concentration of the reactants had an important influence on the conversion.[19] Under optimized conditions, the intended coupling product **25** was obtained in 92% yield on gram scale.

Scheme 4. Synthesis of the Tetracyclic Core **28**



Initially, attempted cleavage of the acetal group in **25** under conditions that would not affect the *N*-Boc group ($In(OTf)_3$,[20] TESOTf,[21] $TrBF_4$,[22] etc.) led to lower yields or decomposition. We were pleased to find that selective cleavage took place simply with aq. HCl in THF to give the corresponding aldehyde **26** in 88% yield. Pinnick oxidation,[23] followed by esterification, afforded the diester **27** in quantitative yield over two steps. After some experimentation, we found that, unlike the case of **20**, the Dieckmann cyclization[24] of **27** was best achieved in the presence of NaHMDS to afford a tautomeric mixture of tetracyclic intermediates which, upon saponification with KOH in THF/H_2O for 16 h, was decarboxylated to the tetracyclic dienone **28** in 62% yield over two steps.

Upon treatment of **28** with bromine in $CHCl_3$, a bromocarbamoylation reaction was smoothly achieved to afford the pentacyclic bromocarbamate **29** in 88% yield (Scheme 5). We assumed that the topology of the precursor **28** would actually control the formation of the epibromonium ion from the convex face of the tetracyclic system,

(13) Shafikov, R. V.; Afon'kina, S. R.; Savchenko, R. G.; Galyautdinov, I. V.; Odinokov, V. N. *Russ. J. Org. Chem.* **2007**, *43*, 305–306. Also see ref 5b.

(14) De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999–5001.

(15) Schaefer, J. P.; Bloomfield, J. J. *Organic Reactions*, Vol. 15; John Wiley and Sons: New York, 1967; pp 1–203.

(16) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299–6302.

(17) (a) Demay, S.; Harms, K. H.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 4981–4984. (b) Calaza, M. I.; Hupe, E.; Knochel, P. *Org. Lett.* **2003**, *5*, 1059–1061.

(18) For relevant examples, see: (a) Helliwell, M.; Thomas, E. J.; Townsend, L. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1286–1296. (b) Webster, R.; Gaspar, B.; Mayer, P.; Trauner, D. *Org. Lett.* **2013**, *15*, 1866–1869. See also: (c) Scott, T. L.; Söderberg, B. C. G. *Tetrahedron* **2003**, *59*, 6323–6332. (d) Sünnemann, H. W.; Banwell, M. G.; de Meijere, A. *J. Chem. Eur.* **2008**, *14*, 7236–7249.

(19) See Supporting Information.

(20) Gregg, B. T.; Golden, K. C.; Quinn, J. F. *J. Org. Chem.* **2007**, *72*, 5890–5893.

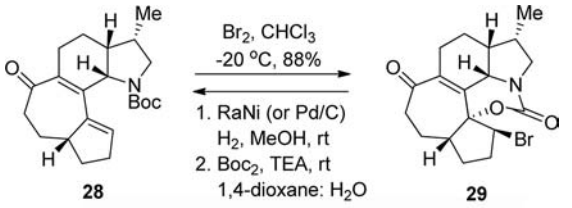
(21) Fujioka, H.; Okitsu, T.; Sawama, Y.; Murata, N.; Li, R.; Kita, Y. *J. Am. Chem. Soc.* **2006**, *128*, 5930–5938.

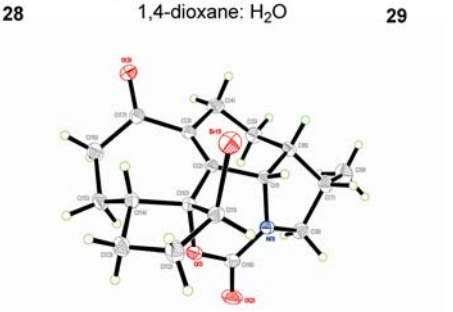
(22) (a) Barton, D. H. R.; Magnus, P. D.; Smith, G.; Zurr, D. *Chem. Commun.* **1971**, 861–863. (b) Barton, D. H. R.; Magnus, P. D.; Smith, G.; Streckert, G.; Zurr, D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 542–552. (c) Hanessian, S.; Staub, A. P. A. *Tetrahedron Lett.* **1973**, *14*, 3551–3554. (d) Uemura, M.; Minami, T.; Hayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 6271–6274. (e) See Supporting Information.

(23) (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888–890. (b) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.

(24) For examples of Dieckmann cyclizations to seven-membered rings, see: (a) Ponticello, G. S.; Baldwin, J. J.; Lumma, P. K.; McClure, D. E. *J. Org. Chem.* **1980**, *45*, 4236–4238. (b) Bao, G.; Liu, C.; Burnell, D. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2657–2668. (c) Denmark, S. E.; Matsuhashi, H. *J. Org. Chem.* **2002**, *67*, 3479–3486. (d) Muto, S.; Bando, M.; Mori, K. *Eur. J. Org. Chem.* **2004**, 1946–1952. (e) Hopf, H.; Abhilash, K. G. *Synlett* **2009**, *20*, 3349–3351.

Scheme 5. Formation of the Bromocarbamate **29** and Its ORTEP Diagram (ellipsoids drawn at 30% probability level)





allowing the *N*-Boc group to attack in an *anti*-fashion. Indeed, a single crystal X-ray structure of the resulting pentacyclic bromocarbamate **29** confirmed the proposed structure and the relative and absolute configuration of the original **28**. The double bond could be restored by treatment of **29** with Raney nickel or Pd/C under 1 atm of hydrogen, giving back **28** after *N*-Boc reprotection.

In conclusion, the tetracyclic core unit (**28**) of daphniglaucin C was synthesized in a highly stereocontrolled and convergent manner, in a cumulative yield of 14.7% over 15 steps from the known and commercially available 4-keto-*N*-Boc methyl-L-prolinate. The structure and stereochemistry were ascertained by conversion to a pentacyclic bromocarbamate derivative (**29**) and X-ray analysis. Studies toward the challenging functionalization of the tricyclic and tetracyclic intermediates **27** and **28** respectively toward daphniglaucin C and related members of the same family are in progress and will be reported in due course.

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Supporting Information Available. Experimental procedures, copies of ^{1}H and ^{13}C spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.