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Skeletal and Stereochemical Diversification of Tricyclic Frameworks Inspired by Ca^{2+}-ATPase Inhibitors, Artemisinin and Transtaganolide D

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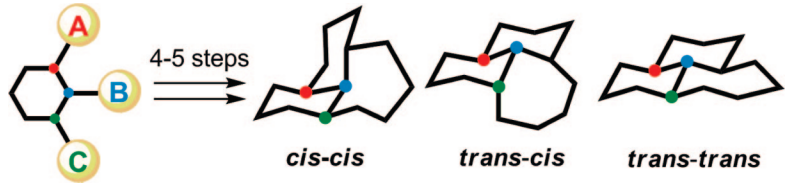
ABSTRACT



Inspired by the common skeletal motifs of Ca^{2+}-ATPases inhibitors involving artemisinin and transtaganolide D, small molecule collections with the three-dimensional structural diversity of tricyclic systems were designed and expeditiously synthesized (4−5 steps). A synthetic strategy featuring stereochemical diversification of ring-junctions and control of cyclization modes was devised to access varied molecular architectures in a systematic fashion.

Artemisinin (**1**), a naturally occurring sesquiterpene endoperoxide, and its derivatives have been clinically used to treat drug-resistant malaria.[1,2] The widely accepted mechanism of their action involves iron (II)-dependent cleavage of the endoperoxide bridge to generate cytotoxic radical intermediates. It has been proposed that artemisinins act by inhibiting PfATP6, the ortholog of the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) of the parasite *Plasmodium falciparum*.[3] In 2005, structurally related sesquiterpene lactones without peroxide bridges, designated as transtaganolides (basiliolides), were also reported to inhibit SERCA.[4,5] As highlighted in Figure 1, we focused our attention on the tricyclic system as a common structural motif of the naturally occurring SERCA modulators despite the differences in the stereochemical relationships of the ring junctions and oxygenated functionalities incorporated into the cyclic skeletons. Inspired by the common structural features of these biologically intriguing sesquiterpenes, we sought to develop expeditious and systematic synthetic processes to the related tricyclic skeletons as a privileged structural motif for designing natural product-inspired small molecules.[6] Herein,

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(1) For recent reviews on artemisinin and its analogues, see: (a) O'Neill, P. M.; Posner, G. H. *J. Med. Chem.* **2004**, *47*, 2945–2964. (b) Tang, Y. Q.; Dong, Y. X.; Vennerstrom, J. L. *Med. Res. Rev.* **2004**, *24*, 425–448. (c) Jefford, C. W. *Drug Discovery Today* **2007**, *12*, 487–495. (d) White, N. J. *Science* **2008**, *320*, 330–334.

(2) For selected examples of the total synthesis of artemisinin, see: (a) Schimid, G.; Hofheinz, W. *J. Am. Chem. Soc.* **1983**, *105*, 624–625. (b) Xu, X. X.; Zhu, J.; Huang, D. Z.; Zhou, W. S. *Tetrahedron* **1986**, *42*, 819–828. (c) Ravindranathan, T.; Kumar, M. A.; Menon, R. B.; Hiremath, S. V. *Tetrahedron Lett.* **1990**, *31*, 755–758. (d) Avery, M. A.; Chong, W. K. M.; White, C. J. *J. Am. Chem. Soc.* **1992**, *114*, 974–979. (e) Liu, H. J.; Yeh, W. L.; Chew, S. Y. *Tetrahedron Lett.* **1993**, *34*, 4435–4438. (f) Yadav, J. S.; Satheesh Babu, R.; Sabitha, G. *Tetrahedron Lett.* **2003**, *44*, 387–389.

(3) Eckstein-Ludwig, U.; Webb, R. J.; van Goethem, I. D. A.; East, J. M.; Lee, A. G.; Kimura, M.; O'Neill, P. M.; Bray, P. G.; Ward, S. A.; Krishna, S. *Nature* **2003**, *424*, 957–961.

(4) (a) Saouf, A.; Guerra, F. M.; Rubal, J. J.; Moreno-Dorado, F. J.; Akssira, M.; Mellouki, F.; López Matias, M.; Pujadas, A. J.; Jorge, Z. D.; Massanet, G. M. *Org. Lett.* **2005**, *7*, 881–884. (b) Appendino, G.; Prosperini, S.; Valdivia, C.; Ballero, M.; Colombano, G.; Billington, R. A.; Genazzani, A. A.; Sterner, O. *J. Nat. Prod.* **2005**, *68*, 1213–1217.

(5) Nelson, H. M.; Stoltz, B. M. *Org. Lett.* **2008**, *10*, 25–28.

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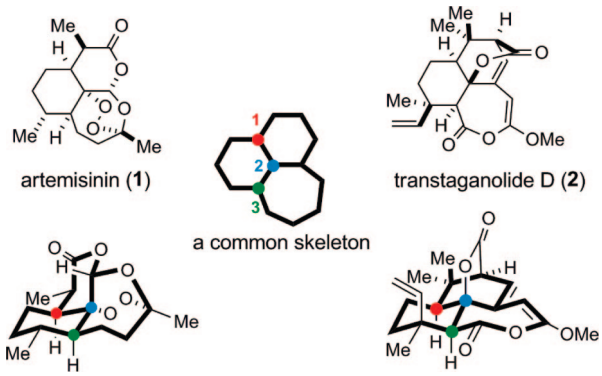


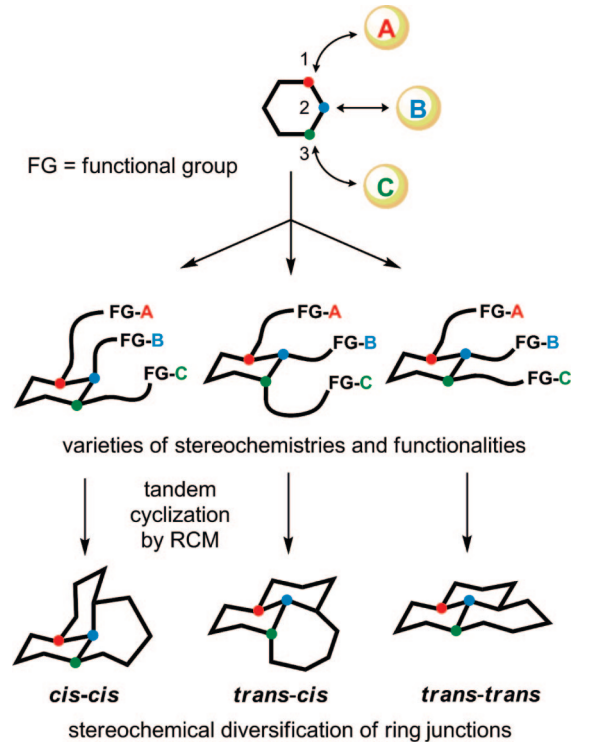
Figure 1. Naturally occurring sesquiterpenes, artemisinin (**1**) and transtaganolide D (**2**). The common skeleton is highlighted in bold.

we describe the development of a synthetic process entailing generation of skeletal and stereochemical diversity[7] of the tricyclic systems.

To access varied molecular architectures in a systematic fashion, we envisioned stereochemical diversification of ring-junctions of the tricyclic system into three types involving cis−cis, trans−cis, and trans−trans fused skeletons (Scheme 1). The collections of precursors having distinct functional groups at three sites (A−C) with requisite stereochemical variations (syn−syn, anti−syn, and anti−anti) would be synthesized by assembly of three building blocks into consecutive carbon centers of a six-membered ring. Reliable and robust cyclization reactions must be employed for the paring of the functionalities at the three sites to override the stereochemical bias of the substrates. To this end, we planned tandem ring-closing olefin metathesis reactions of dienynes[8] leading to tricyclic systems with concomitant incorporation of diene functionalities into the skeletons. The collection of the resultant tricycles would be a useful platform for incorporation of heteroatom functionalities leading to small molecule collections reminiscent of naturally occurring sesquiterpenes with high oxidation levels.

With our goal toward the rapid and stereocontrolled assembly of building blocks, six-membered oxonitrile **3** was designed as a versatile scaffold for installing the dienynes on the three sites (A−C)[9] (Scheme 2). Addition of a R_1 group to the carbonyl group would produce a hydroxylalkenenitrile that allows chelation-controlled conjugate additions of acetylides as the R_2

Scheme 1. Schematic Illustration of Synthetic Strategies for Sesquiterpene-Like Small Molecules[a]



[a] Systematic stereochemical alterations of ring-junctions were devised to generate three-dimensional structural diversity.

group by adapting Fleming's protocol.[10] Subsequent alkylation of the resulting *C*-magnesiated nitrile would proceed with retention of configuration to afford a product having R_1−R_3 groups installed with high levels of stereoselectivities. Either alkylation of the secondary alcohol or introduction of a R_1 group having a terminal olefin as a Grignard reagent at site A would construct syn or anti stereochemical relationships with the acetylene group at site B. Likewise, introduction of an olefin group as the R_3 group or manipulation of the nitrile group would establish requisite stereochemical relationships between sites B and C. In addition to stereochemical diversification, we planned to generate skeletal diversity by controlling the modes of dienyne cyclizations leading to products with distinct cyclic arrays. Since olefin substitution can alter the site of initial ruthenium carbene complex formation,[11] the tandem ring-closure of dienyne with sterically differentiated olefins would proceed via cyclization from sites A to B followed by B to C leading to a tricyclic diene, whereas a reversed substitution

(6) (a) Boldi, A. M. *Curr. Opin. Chem. Biol.* **2004**, *8*, 281–286. (b) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40–49. (c) Hübel, K.; Lebmann, T.; Waldmann, H. *Chem. Soc. Rev.* **2008**, *37*, 1361–1374.

(7) Recent reviews for diversity-oriented synthesis, see: (a) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46–58. (b) Arya, P.; Joseph, R.; Gan, Z.; Rakic, B. *Chem. Biol.* **2005**, *12*, 163–180. (c) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74–84. (d) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48–56. (e) Spandl, R. J.; Bender, A.; Spring, D. R. *Org. Biomol. Chem.* **2008**, *6*, 1149–1158.

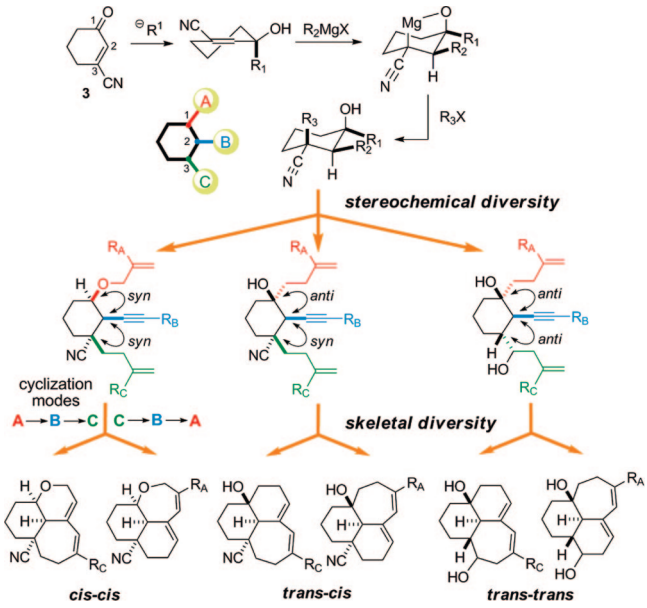
(8) For recent reviews, see: (a) Mori, M. *Adv. Synth. Catal.* **2007**, *349*, 121–135. (b) Hansen, E. C.; Lee, D. *Acc. Chem. Res.* **2006**, *39*, 509–519. (c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382.

(9) Generation of skeletal diversity employing a scaffold with three reactive sites, see: Oguri, H.; Schreiber, S. L. *Org. Lett.* **2005**, *7*, 47–50.

(10) Fleming, F. F.; Zhang, Z.; Wei, G.; Steward, O. W. *J. Org. Chem.* **2006**, *71*, 1430–1435.

(11) For selected examples of synthesis of polycyclic systems by tandem metathesis of dienynes, see: (a) Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073–1081. (b) Codesido, E. M.; Castedo, L.; Granja, J. R. *Org. Lett.* **2001**, *3*, 1483–1486. (c) Shimizu, K.; Takimoto, M.; Mori, M. *Org. Lett.* **2003**, *5*, 2323–2325. (d) Honda, T.; Namiki, H.; Kaneda, K.; Mizutani, H. *Org. Lett.* **2004**, *6*, 87–89. (e) Boyer, F.-D.; Hanna, I.; Ricard, L. *Org. Lett.* **2004**, *6*, 1817–1820. (f) Garcia-Fandino, R.; Codesido, E. M.; Sobarzo-Sanchez, E.; Castedo, L.; Granja, J. R. *Org. Lett.* **2004**, *6*, 193–196. (g) Gonzalez, A.; Dominguez, G.; Castells, J. P. *Tetrahedron Lett.* **2005**, *46*, 7267–7270.

Scheme 2. Synthetic Strategy for Six Distinct Tricyclic Dienes: Generation of Stereochemical Diversity Based on Chelation-Controlled Conjugate Addition-Alkylations Leading to Dienynes and Functional Group Manipulations at Sites A and C



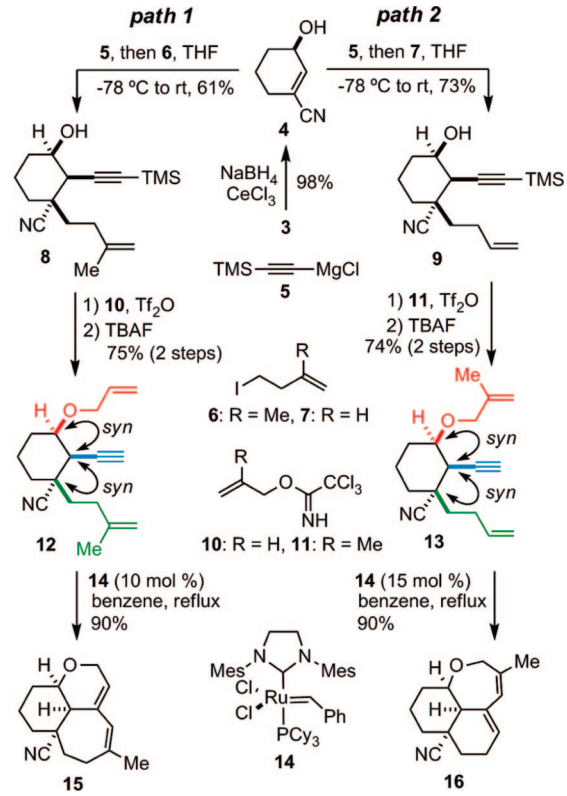
pattern of olefins at sites A and C could invert the cyclization mode to produce a distinct tricycle.

With this strategic plan in mind, we commenced synthesis of the six distinct tricycles incorporating internal dienes starting from the common scaffold **3** (Scheme 2). First, we developed synthetic pathways 1 and 2 to produce cis−cis fused tricyclic dienes **15** and **16** (Scheme 3). The C1 position of the scaffold **3** was reduced with $NaBH_4$−$CeCl_3$ to provide hydroxylalkenenitrile **4**. The chelation-controlled conjugate addition of acetylide **5** and subsequent steteroselective alkylation of the resulting anion with **6** produced **8** in 61% yield. Since allylation of the alcohol **8** under basic conditions caused isomerization of the acetylene into an allene, we applied acid-catalyzed conditions using trichloroacetimidate **10**. Subsequent removal of the trimethylsilyl group furnished the dienyne **12** in 75% yield (2 steps). Similarly, the precursor **13** with a 2-methylallyl ether at site A and a 3-butenyl group at site C was synthesized. Upon treatment of **12** with 10 mol % Grubbs second generation catalyst **14** in benzene under reflux for 3.5 h, tandem ring-closing metathesis (RCM) of the dienyne system proceeded smoothly to afford the desired tricyclic diene **15** in 90% yield.[12,13] Accordingly, ring-closure of **13** produced tricyclic diene **16** in excellent yield (90%). Thus, pathways 1 and 2 generated skeletal diversity in tricyclic dienes having cis−cis fused ring-junctions, in which the modes of ring closure were

(12) The stereochemistry of **15** with cis−cis fused ring junction was unambiguously determined based on X-ray analysis of a crystalline derivative (see, the Supporting Infromation and ref 13).

(13) CCDC-699155 (derivative of **15**), CCDC-699152 (**24**), CCDC-699153 (silylated derivative of **27**), and CCDC-699151 (mono *p*-bromobenzoate of **34**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 3. Synthesis of Tricyclic Dienes with Cis−Cis Ring-Junctions in 5 Steps



successfully controlled by exploiting the group-selective ruthenium carbene complex formation of monosubstituted olefins in the presence of disubstituted olefins.

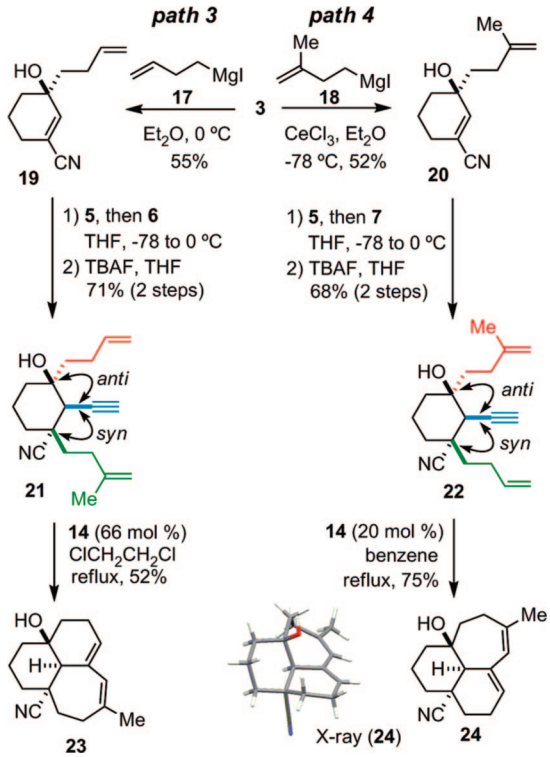
We then investigated pathways 3 and 4 affording trans−cis fused tricyclic dienes **23** and **24** (Scheme 4). Addition of Grignard reagent **17** to **3** gave alcohol **19** in 55% yield.[14] Chelation-controlled conjugate addition-alkylation and subsequent removal of the silyl group produced **21** in 71% yield (2 steps) as the major product.[15] Similar stepwise transformations produced **22**, in which the substitution pattern of terminal olefins at sites A and C was exchanged compared to that of **21** by the use of Grignard reagent **18** and alkyliodide **7** in place of **17** and **6**, respectively. Tandem cyclization of **21** required a high catalyst loading (**14**: 66 mol %) and resulted in a modest yield (52%) of the desired **23** with trans−cis ring junctions. On the other hand, ring closure of **22** with 20 mol % catalyst produced **24** in satisfactory yield (75%). The structure of **24** was confirmed based on X-ray analysis.[13]

Next, tricyclic dienes, **31**−**34**, with trans−trans ring-junctions were synthesized via pathways 5 and 6 (Scheme 5). Three-component assembly of **3**, **17**, and **5** followed by protonation of the resulting carbanion in one pot stereoselectively produced **25** in 46% yield. Reduction of the nitrile **25** gave an aldehyde in 88% yield, which was treated with 2-methylallyl Grignard

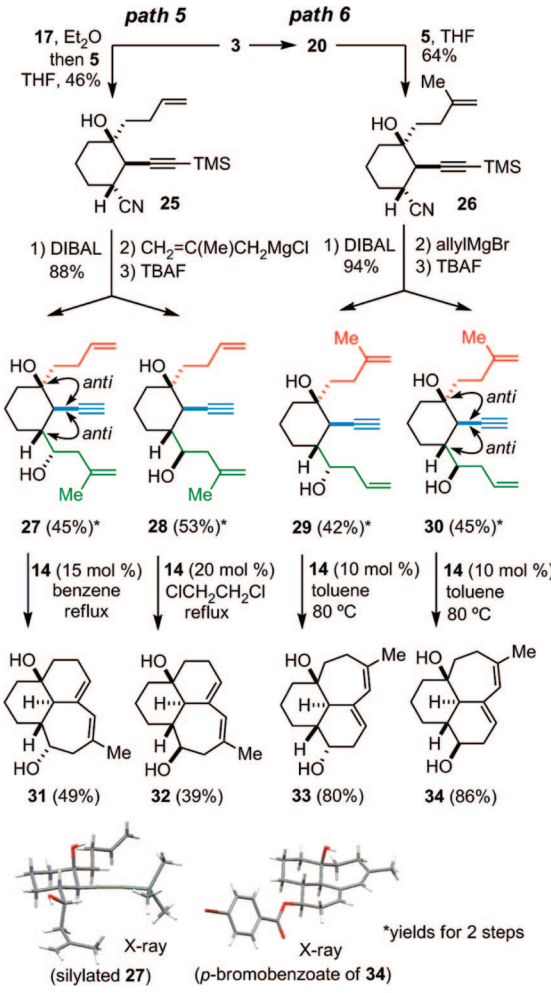
(14) The four-component assembly of **3**, **5**, **6**, and **17** in one pot turned out to be impracticable (**21** <15% yield).

(15) The undesired diastereomer (7% yield) formed by the alkylation was separated by silica gel chromatography.

Scheme 4. Synthesis of Tricyclic Dienes with Trans−Cis Ring-Junctions in 4 Steps



Scheme 5. Synthesis of Tricyclic Dienes with Trans−Trans Ring-Junctions in 5 Steps



reagent to yield a diastereomeric mixture of diols in an approximately 1:1 ratio. Separation of the diastereomers and removal of the silyl group produced the dieneynes **27** and **28**. The dieneynes **29** and **30** with the substitution patterns of terminal olefins at sites A and C exchanged were synthesized in a similar fashion except for stepwise additions of the Grignard reagents (**3** → **20** → **26**). While tandem ring-closures of **27** and **28** to afford the tricyclic dienes **31** and **32** resulted in moderate yields (39−49%), cyclizations of **29** and **30** proceeded smoothly to produce **33** and **34** in good yields (80−86%). Structures of **27** and **34** were unambiguously determined based on X-ray analysis of their derivatives.[13] Thus, we have successfully constructed the six types of tricyclic systems incorporating internal dienes in a systemic fashion.

In conclusion, we have developed an expeditious and programmable synthetic process that controls not only the stereochemical relationships of ring-junctions but also the modes of cyclization, and entails the formation of six types of sesquiterpene-like skeletons in 4−5 steps from **3**. In this synthetic process, functional groups including conjugated dienes, hydroxyl groups and nitrile were incorporated in the skeletons to allow further manipulations to produce natural product-inspired small molecule collections. In addition, since this synthetic process employs eneynes as precursors for cyclizations, a variety of metal-catalyzed or radical-initiated transformations would be readily applicable for the synthesis of terpenoid-like fused skeletons. Further synthetic investigations and preliminary screenings of biological activities are currently underway and will be reported in due course.

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Supporting Information Available: Exprimental procedures and ^{1}H and ^{13}C NMR sprctra of compounds **8**, **9**, **12**, **13**, **15**, **16**, **19**−**34**, as well as CIF files for **24**, and crystalline derivatives of **15**, **27** and **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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