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Synthesis of (+)-Dihydro-*epi*-deoxyarteannuin B

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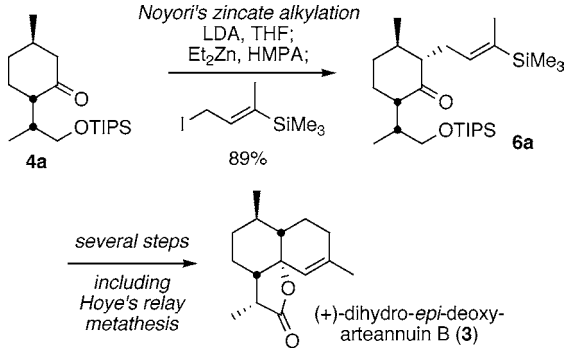
ABSTRACT



The synthesis of (+)-dihydro-*epi*-deoxyarteannuin B (3) from (−)-isopulegol is described. Difficulties in the alkylation of menthone derivatives (e.g., 4a → 6a) were overcome by using Noyori's zincate enolate method. Related problems with nucleophilic addition to the hindered menthone core of 6a were resolved by using either organocerium or acetylide nucleophiles. Finally, two alternative olefin metathesis approaches are reported for the final cyclization. This study provides insight into the reactivity and synthetic processing of the artemisinin sesquiterpenes.

Artemisinin[1] (qinghaosu, **1**) is an important weapon in the battle against malaria,[2] one of the world's most devastating infectious diseases.[3] The malaria pandemic has even been implicated in the economic struggles of tropical Third World nations.[3] Artemisinin is the active ingredient of herbal treatments that have been in use in China for millenia.[4] Western medicine has embraced artemisinin over the past few decades; unfortunately, resistant strains of P. *falciparum* are now beginning to emerge.[5]

Synthetic studies on artemisinin[6,7] and related compounds[8] may improve our ability to stay ahead of the resistance curve

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(1) Klayman, D. L. *Science* **1985**, *228*, 1049−1055.

(2) The WHO advocates artemisinin-combination therapy (ACT) as the preferred treatment for malaria: *Guidelines for the treatment of malaria*; World Health Organization: Geneva, Switzerland, 2006.

(3) See: Weiss, U. Nature Insight: Malaria. *Nature* **2002**, *415*, 669; also see the associated articles and references cited.

(4) Recent reviews on the artemisinin family of antimalarial endoperoxides: (a) Haynes, R. K. *Curr. Top. Med. Chem.* **2006**, *6*, 509−537. (b) Begue, J. P.; Bonnet-Delpon, D. *Drugs Future* **2005**, *30*, 509−518. (c) Li, Y.; Wu, Y. L. *Curr. Med. Chem.* **2003**, *10*, 2197−2230. (d) For an interesting anthropological perspective on artemisinin, see: Hsu, E. *Br. J. Clin. Pharmacol.* **2006**, *61*, 666−670.

(5) (a) Towie, N. *Nature* **2006**, *440*, 852−853. (b) Duffy, P. E.; Sibley, H. *Lancet* **2005**, *366*, 1908−1909.

(6) Kim, B. J.; Sasaki, T. *Org. Prep. Proced. Int.* **2006**, *38*, 1−80.

(7) Previous chemical syntheses of artemisinin: (a) Schmid, 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) Roth, R. J.; Acton, N. *J. Nat. Prod.* **1989**, *52*, 1183−1185. (d) Ravindranathan, T.; Anil Kumar, M.; Menon, R. B.; Hiremath, S. V. *Tetrahedron Lett.* **1990**, *31*, 755−758. (e) Avery, M. A.; Chong, W. K. M.; Jennings-White, C. *J. Am. Chem. Soc.* **1992**, *114*, 974−979. (f) Liu, H. J.; Yeh, W. L.; Chew, S. Y. *Tetrahedron Lett.* **1993**, *34*, 4435−4438. (g) Bhonsle, J. B.; Pandey, B.; Deshpande, V. H.; Ravindranathan, T. *Tetrahedron Lett.* **1994**, *35*, 5489−5492. (h) Constantino, M. G.; Beltrame, M., Jr.; da Silva, G. V. J. *Synth. Commun.* **1996**, *26*, 321−329. (i) Nowak, D. M.; Lansbury, P. T. *Tetrahedron* **1998**, *54*, 319−336. (j) Yadav, J. S.; Satheesh Babu, R.; Sabitha, G. *Tetrahedron Lett.* **2003**, *44*, 387−389. (k) Related synthetic work: Avery, M. A.; Fan, P.; Karle, J. M.; Bonk, J. D.; Miller, R.; Goins, D. K. *J. Med. Chem.* **1996**, *39*, 1885−1897.

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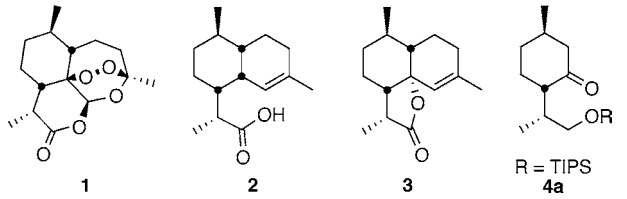


Figure 1. (−)-Artemisinin (**1**), (−)-dihydroartemisinic acid (**2**), (+)-dihydro-*epi*-deoxyarteannuin B (**3**), and building block **4a**.

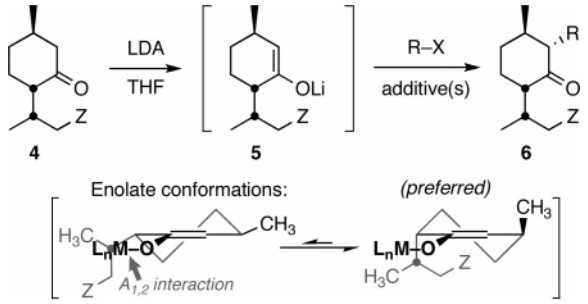
and further develop this potent weapon in the fight against malaria.[9] The most daunting challenge associated with the synthesis of artemisinin is the endoperoxide bridge, a feature that challenges our assumptions regarding the stability of such species. Artemisinin has stimulated considerable research in the synthesis of endoperoxides, several of which show promise as potential malaria treatments.[10] Artemisinin shows selective cytotoxicity against iron-rich cancer cells, and it is now emerging as a lead compound for cancer research.[11]

(+)-Dihydro-*epi*-deoxyarteannuin B (**3**), also a natural isolate of *Artemisia annua*,[12] plays a central role in our long-term efforts to develop efficient synthetic approaches to artemisinin. Barriault and Deon prepared *ent*-(**3**) through an elegant application of the tandem oxy-Cope/transannular ene reaction en route to *ent*-(+)-arteannuin M.[13] Both artemisinin and **3** arise from nonenzymatic autoxidation of dihydroartemisinic acid (**2**), a related sesquiterpene isolated from *Artemisia annua*[14] that has emerged as a key chemical precursor to artemisinin (**1**).[7,9] Natural **3** has also been converted chemically into semisynthetic **1**.[7i]

With the broader aim of identifying new methods for accessing artemisinin-derived antimalarial compounds, we targeted the chemical synthesis of (+)-dihydro-*epi*-deoxyarteannuin B (**3**). We initiated our studies with silyloxymenthone **4a**, prepared from (−)-isopulegol in three steps: diastereoselective hydroboration,[15] selective monosilylation, and Swern oxidation.[7k]

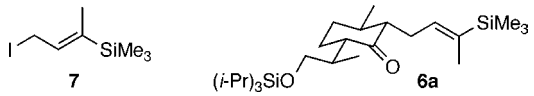
Coupling of silyloxymenthone **4a** with allyl iodide **7** (the Stork−Jung reagent)[16] was more challenging than may be apparent at first glance (Table 1). An attempt at alkylation

Table 1. Allylation of Menthone and Silyloxymethone **4a**[18]



entry	Z	R−X	additive(s)	yield (%)
1	H	allyl bromide	none	17[17a]
2	OBn	**7**	none	53[17b]
3	H	allyl iodide	HMPA	53
4	H	allyl iodide	HMPA, Et_2Zn	~80[a]
5	OTIPS	allyl iodide	HMPA, Et_2Zn	80
6	OTIPS	**7**	HMPA	45
7	**OTIPS**	**7**	**HMPA, Et_2Zn**	**89**

[a] Estimated by ^1H NMR spectroscopy.



of **4a** (Z = OTIPS) under standard conditions yielded **6a** in only 45% yield (entry 6). Similar alkylations of menthone (**4**, Z = H) are also problematic (entries 1 and 3).[17]

We suspect that, upon treatment with strong base, $A_{1,2}$-strain favors a conformation for enolate **5** in which the flanking alkyl substitutents adopt pseudoaxial orientations, shielding the top and bottom faces (Table 1). Noyori's

(8) (a) Posner, G. H.; Paik, I.-H.; Chang, W.; Borstnik, K.; Sinishtaj, S.; Rosenthal, A. S.; Shapiro, T. A. *J. Med. Chem.* **2007**, *50*, 2516−2519. Reviews on artemisinin and related compounds: (b) Dhingra, K. V.; Rao, V.; Narasu, M. L. *Life Sci.* **2000**, *66*, 279−300. (c) Haynes, R. K.; Vonwiller, S. C. *Acc. Chem. Res.* **1997**, *30*, 73−79. (d) Vroman, J. A.; Alvim-Gaston, M.; Avery, M. A. *Curr. Pharm. Des.* **1999**, *5*, 101−138. (e) Posner, G. H.; O'Neill, P. M. *Acc. Chem. Res.* **2004**, *37*, 397−404.

(9) For example, a combination of biosynthetic engineering and chemical synthesis is at the heart of the combined venture between the Gates Foundation and One World Health for lowering the cost of artemisinin. See: Ro, D. K.; Paradise, E. M.; Ouellet, M.; Fisher, K. J.; Newman, K. L.; Ndungu, J. M.; Ho, K. A.; Eachus, R. A.; Ham, T. S.; Kirby, J.; Chang, M. C. Y.; Withers, S. T.; Shiba, Y.; Sarpong, R.; Keasling, J. D. *Nature* **2006**, *440*, 940−943 and references cited therein.

(10) (a) Posner, G. H.; Jeon, H. B.; Parker, M. H.; Krasavin, M.; Paik, I.-H.; Shapiro, T. A. *J. Med. Chem.* **2001**, *44*, 3054−3058. (b) Posner, G. H.; Cumming, J. N.; Krasavin, M. Carbon-Centered Radicals and Rational Design of New Antimalarial Peroxide Drugs. In *Biomedical Chemistry*: *Applying Chemical Principles to the Understanding and Treatment of Disease*; Torrence, P. F., Ed.; Wiley-Interscience: New York, 2000; pp 289−309. (c) Vennerstrom, J. L.; Arbe-Barnes, S.; Brun, R.; Charman, S. A.; Chiu, F. C. K.; Chollet, J.; Dong, Y.; Dorn, A.; Hunziker, D.; Matile, H.; McIntosh, K.; Padmanilayam, M.; Tomas, J. S.; Scheurer, C.; Scorneaux, B.; Tang, Y.; Urwyler, H.; Wittlin, S.; Charman, W. N. *Nature* **2004**, *430*, 900−904. (d) Tang, Y.; Dong, Y.; Vennerstrom, J. L. *Med. Res. Rev.* **2004**, *24*, 425−448.

(11) Singh, N. P.; Lai, H. C. *Anticancer Res.* **2004**, *24*, 2277−2280.

(12) (a) Brown, G. D. *J. Nat. Prod.* **1992**, *55*, 1756−1760. (b) Sy, L.-K.; Brown, G. D.; Haynes, R. *Tetrahedron* **1998**, *54*, 4345−4356. (c) Sy, L.-K.; Cheung, K.-K.; Zhu, N.-Y.; Brown, G. D. *Tetrahedron* **2001**, *57*, 8481−8493. (d) Sy, L.-K.; Brown, G. D. *Phytochemistry* **2001**, *58*, 1159−1166. (e) Brown, G. D.; Liang, G. Y.; Sy, L.-K. *Phytochemistry* **2003**, *64*, 303−323.

(13) Barriault, L.; Deon, D. H. *Org. Lett.* **2001**, *3*, 1925−1927.

(14) (a) Wallaart, T. E.; Pras, N.; Quax, W. J. *J. Nat. Prod.* **1999**, *62*, 1160−1162. (b) Sy, L.-K.; Brown, G. D. *Tetrahedron*, **2002**, *58*, 897−908.

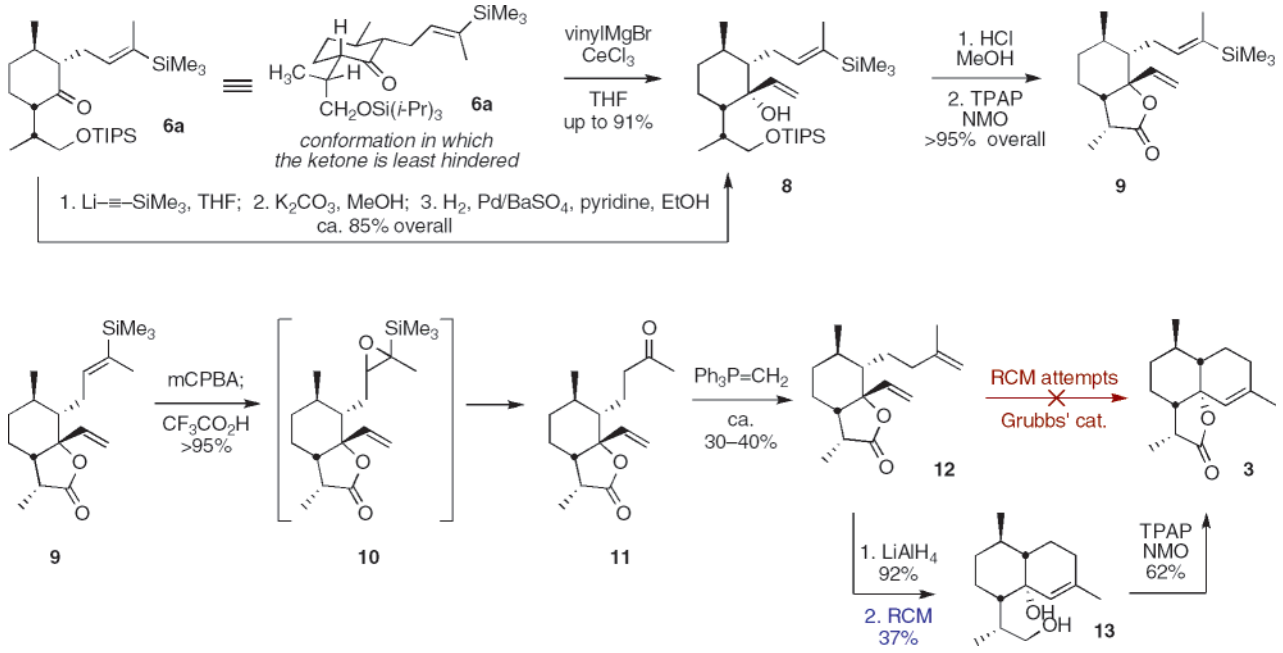
(15) Schulte-Elte, K. H.; Ohloff, G. *Helv. Chim. Acta* **1967**, *50*, 153.

(16) (a) Stork, G.; Jung, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 3682−3684. (b) Stork, G.; Jung, M. E.; Colvin, E.; Noel, Y. *J. Am. Chem. Soc.* **1974**, *96*, 3684−3686. (c) Singletary, J. A.; Lam, H.; Dudley, G. B. *J. Org. Chem.* **2005**, *70*, 739−741.

(17) (a) Nakashima, K.; Imoto, M.; Sono, M.; Tori, M.; Nagashima, F.; Asakawa, Y. *Molecules* **2002**, *7*, 517−527. For other representative alkylations of menthone and its derivatives, see: (b) Reference 7a: 62%, 6:1 dr. (c) Halterman, R. L.; Crow, L. D. *Tetrahedron Lett.* **2003**, *44*, 2907−2909. (d) Avery, M. A.; Gao, F.; Chong, W. K. M.; Hendrickson, T. F.; Inman, W. D.; Crews, P. *Tetrahedron* **1994**, *50*, 957−972.

(18) See the Supporting Information for experimental procedures and data.

Scheme 1. Elaboration to First Metathesis Precursor (**6a** → **12**)[18]



report[19] on the use of diethylzinc as an additive for enolate alkylations provided for dramatic improvements (cf. entries 3 and 4; 6 and 7). Although the conformational dynamics may remain problematic, the better behaved zincate enolate of **5** reacted cleanly with allyl iodide (entry 5) and with **7** to afford **6a** in 89% yield. This powerful and convenient procedure should be considered immediately in cases where the efficiency of an enolate alkylation is low.

Despite the steric congestion of **6a**—treatment with simple Grignard reagents failed to provide the corresponding tertiary alcohols—the organocerium reagent[20] derived from freshly prepared vinylmagnesium bromide and freshly activated $CeCl_3$ added cleanly to afford **8** (Scheme 1). Alternatively, a three-step sequence starting with the addition of lithium trimethylsilylacetylide provided **8** in reduced yield (85% overall). Considering the need to prepare the Grignard and cerium reagents for the one-step procedure, the three-step sequence could be completed in less time and with less technical effort.

Cleavage of the silyl ether of **8** in the presence of the vinylsilane by using methanolic HCl was followed by oxidation of the resulting diol to lactone **9**. The lactone moiety served to shield the newly installed vinyl group from epoxidation during the ensuing oxidative conversion of the vinylsilane functionality. Sequential treatment of vinylsilane **9** with *m*-CPBA and trifluoroacetic acid afforded methyl ketone **11**; deferring oxidation of the vinylsilane until this stage in the sequence enabled us to minimize undesirable protective group manipulations.

Wittig methylenation of ketone **11** provided **12** in modest yield, but attempts to effect a ring-closing alkene metathesis[21] (**12** → **3**) were unsuccessful. In addition to steric congestion, one must consider that the spiro-tricyclic product (**3**) might be sufficiently more strained than the fused bicyclic substrate (**12**) so as to inhibit an already challenging cyclization. Indeed, reductive opening of the lactone with lithium aluminum hydride allowed the RCM reaction to proceed, albeit in relatively low yield (**12** → **13**, 37%). TPAP oxidation restored the lactone to provide (+)-dihydro-*epi*-deoxyarteannuin B (**3**).

Note that the formation of spiro-fused lactone **3** was less efficient than the earlier installation of the *cis*-fused lactone (**8** → **9**), presumably due to mild ring strain introduced during the spiro-lactonization step (**13** → **3**).

Cross-metathesis byproducts isolated from our initial experiments aimed at the RCM cyclization of **12** suggested that the ruthenium catalysts were accessing the monosubstituted alkene (immediately adjacent to the fused lactone) but failing to cyclize. We were therefore intrigued by the potential application of Hoye's relay metathesis strategy[22] for delivering the catalyst selectively onto the disubstituted alkene (Scheme 2). Wittig olefination of ketone **11** again proceeded in modest yield, this time to provide **15**; efforts to improve or circumvent this "weak link" in the synthetic chain are ongoing. Nevertheless, tethered triene **15** proved to be a vastly improved substrate for the RCM reaction (**15** → **3**). We plan to incorporate Hoye's relay RCM strategy in our future synthetic efforts in this arena.

Complete and unambiguous NMR spectral assignments for **3** are provided in the Supporting Information.[18] Spectroscopic data for our synthetic material (^1H, ^{13}C, IR, HRMS, DQCOSY, HMBC, HMQC, NOESY) support the indicated

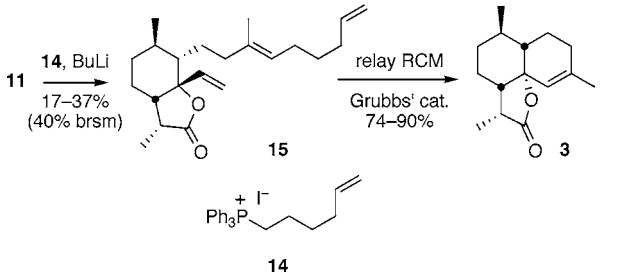
(19) Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785−1787.

(20) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392−4398.

(21) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: New York, 2003.

(22) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210−10211.

Scheme 2. Relay Metathesis Cyclization Reaction[18]



structure (**3**) and match the data reported for natural (+)-dihydro-*epi*-deoxyarteannuin B.[12]

In summary, we report the chemical synthesis of (+)-dihydro-*epi*-deoxyarteannuin B (**3**) from silyloxymenthone **4a**. Tactical advances enabled the synthesis of allylated menthone derivatives (e.g., **6a**) that can serve as valuable building blocks for synthetic artemisinin and related compounds. Two solutions were developed to overcome initial difficulties in the late-stage ring-closing metathesis reaction. Despite modest yields in the late-stage Wittig olefination of **11** (consistently around 40% of **15** based on recovered **11**), spiro-lactone **3** is now available from **4a** in ca. 20−25% yield for the overall process. These studies lay the groundwork for continued research on the chemical synthesis of key members of the artemisinin family of antimalarial compounds.

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Supporting Information Available: Detailed experimental procedures, characterization data, and NMR spectra for all compounds in the synthetic sequence, including complete NMR analysis of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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