Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Design and *De Novo* Synthesis of 6-Aza-artemisinins

Karunakar Reddy Bonepally,[†] Takahisa Hiruma,[‡] Haruki Mizoguchi,[‡] Kyohei Ochiai,[‡] Shun Suzuki,[‡] Hideaki Oikawa,[‡] Aki Ishiyama,[§] Rei Hokari,[§] Masato Iwatsuki,[§] Kazuhiko Otoguro,[§] Satoshi Ōmura,[§] and Hiroki Oguri*[,†]

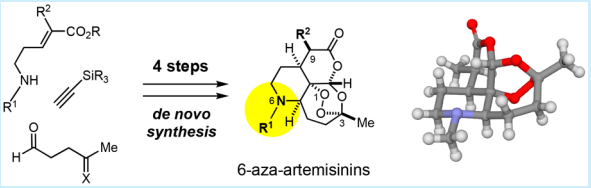
[†]Division of Applied Chemistry, Graduate School of Engineering, Tokyo University of Agriculture and Technology, 2-24-16 Nakacho, Koganei, Tokyo 184-8588, Japan

[‡]Division of Chemistry, Graduate School of Science, Hokkaido University, North 10 West 8, Kita-ku, Sapporo 060-0810, Japan

[§]Research Center for Tropical Diseases, Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan

Supporting Information

ABSTRACT: Development of designer natural product variants, 6-aza-artemisinins, enabled us to achieve structural modification of the hitherto unexplored cyclohexane moiety of artemisinin and concise *de novo* synthesis of the tetracyclic scaffold in just four steps from the modular assembly of three simple building blocks. This expeditious catalytic asymmetric synthetic approach generated lead candidates exhibiting superior *in vivo* antimalarial activities to artemisinin.



Artemisinin-based combination therapies (ACTs) have been consistently successful in reducing the malaria burden in tropical and subtropical regions. Artemisinin (**1**), a sesquiterpene lactone bearing an unusual peroxide bridge, is found in *Artemisia annua* (Figure 1).[1] The therapeutic

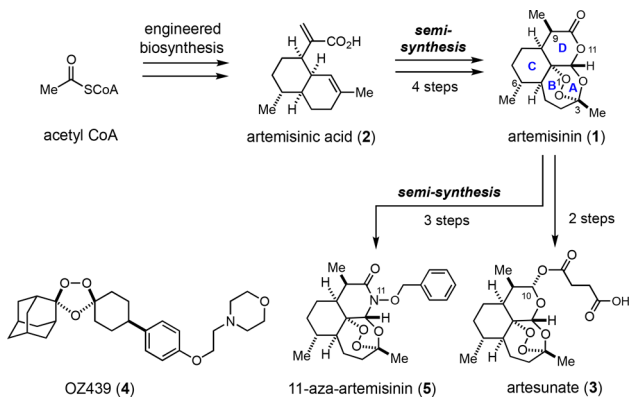


Figure 1. Artificial synthesis of artemisinins and structure of a fully synthetic analogue.

efficacies of **1**, coupled with its unusual structure, have prompted chemists to accomplish pioneering total syntheses.[2] Avery developed a flexible synthetic approach and conducted structure−activity relationship studies,[3] and Cook reported a highly concise synthesis of **1**.[4] Recently, the engineered biosynthesis of artemisinic acid (**2**) and subsequent chemical conversions allowed artificial synthesis of **1**.[5,6] In addition, fully synthetic antimalarial peroxides represented by OZ439 (**4**)[7] have been developed for designing more accessible analogues with simplified structures.[8]

Semisynthetic approaches for generating artemisinin derivatives mostly relies on the chemical modification of the lactone moiety (D-ring) of **1** to produce artesunate (**3**) and other variants,[9] including 11-aza-analogues[10] exemplified as **5** (Figure 1). Due to the absence of functional groups except for the lactone, structural diversification of the other regions, especially for the cyclohexane ring (C-ring), remains largely untouched through exploitation of natural products and fermentation-derived substances.[11] In order to achieve the structural modification of the hitherto unexplored region as well as concise access to the antimalarial tetracyclic scaffold, herein, we report the design and concise *de novo* synthesis of 6-aza-artemisinins (Figure 2). Installation of nitrogen into the cyclohexane ring could make a drastic change in the retrosynthetic disconnections for the concise asymmetric synthesis. This approach could gain rapid access to a series of 6-aza-artemisinins with generation of substitutional variations on the nitrogen.

We designed 6-aza-artemisinins by replacing a stereogenic sp^3 carbon center at the C6 position of **1** with a nitrogen (Figure 2). Installation of the nitrogen could not only allow deep-seated structural modifications of the cyclohexane ring but also pave a new path for the modular synthesis. By exploiting the versatile reactivities of the nitrogen, we conceived a disconnection into three simple building blocks, amine, aldehyde, and alkyne. Catalytic asymmetric assembly of the three components could gain direct access to the chiral

Received: June 25, 2018

DOI: 10.1021/acs.orglett.8b01987
Org. Lett. XXXX, XXX, XXX−XXX

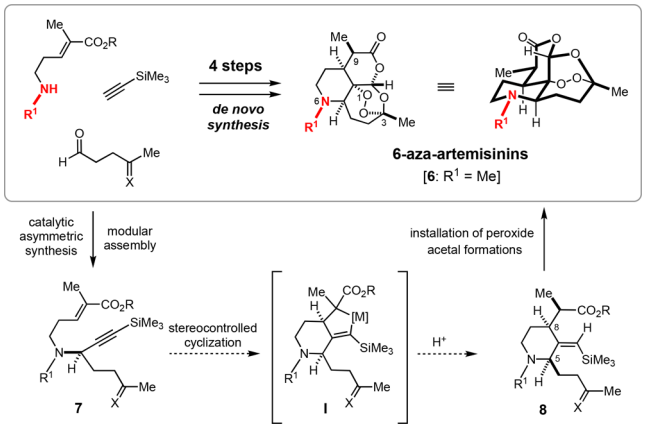
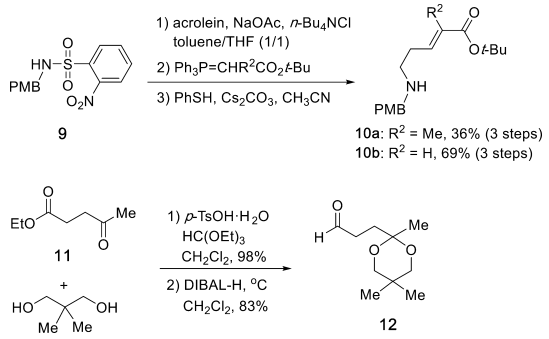


Figure 2. Outline for catalytic asymmetric synthesis of 6-aza-artemisinins.

ene-yne **7**, which possesses all of the framework carbon and nitrogen atoms of the 6-aza-artemisinins. Next, the precursor **8**, composed of a piperidine ring with a (*Z*)-vinyl silane moiety and two contiguous stereogenic centers, would be forged through diastereo-controlled cyclization of **7** via the metallacyclic intermediate **I**, followed by protonation. Protecting group manipulations of **8**, installation of peroxide, and cyclic acetal formations could assemble the tetracyclic scaffold of 6-aza-artemisinins.

The amine building blocks **10a**/**10b** and the aldehyde **12** were synthesized from the known sulfonamide **9**[12] and commercially available ethyl levulinate (**11**), respectively (Scheme 1).

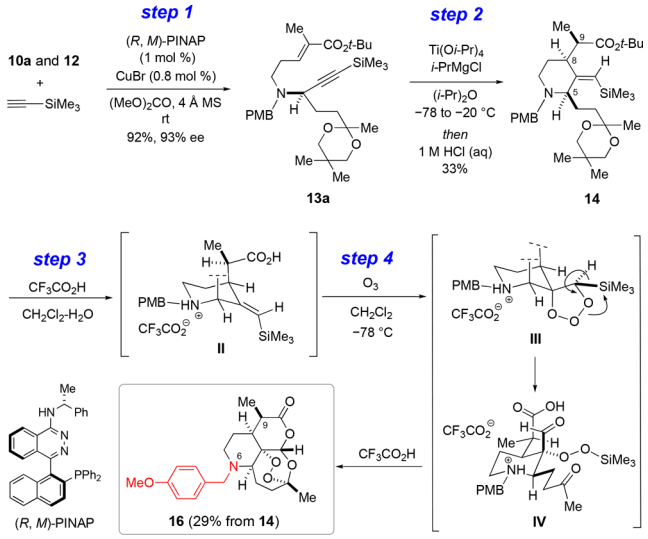
Scheme 1. Synthesis of Building Blocks



A four-step synthesis of the tetracyclic scaffold of 6-aza-artemisinins commenced with Cu-catalyzed condensation of the three building blocks, **10a**, **12**, and trimethylsilylacetylene (Scheme 2). To establish a catalytic asymmetric synthetic route, we adopted Carreira's chiral catalyst CuBr/(*R*,*M*)-PINAP for Cu(I)-mediated assembly.[13] Under the optimized conditions employing only 1 mol % of the chiral catalyst, the three-component condensation proceeded smoothly at room temperature to give the ene-yne **13a** in 92% yield with excellent enantioselectivity (93% ee). The use of dimethyl carbonate as a solvent in the presence of 4 Å molecular sieves was critical for smooth catalytic conversion to furnish **13a**.[14]

Next, we explored diastereo-controlled formation of the piperidine **14**, with a *syn*-stereochemical relationship between C5 and C8, as well as a 9*R*-methyl group (Scheme 2). Low-valent titanium(II)-mediated cyclization of the ene-yne

Scheme 2. Catalytic Asymmetric Synthesis of Tetracyclic Scaffold 16 in Four Steps from Three Building Blocks



provided optimal results.[15] Treatment of **13a** with "Ti(O*i*-Pr)$_2$", generated *in situ* at low temperature in diisopropyl ether, effected the intended cyclization, presumably via metallacyclic intermediate **I** (Figure 2) as the temperature was gradually increased (−78 °C → −20 °C). Subsequent protonation of the intermediate furnished the desired **14** in 33% yield as the major product. The relative configurations of crystalline **14** were unambiguously elucidated based on X-ray analysis (Supporting Information (SI), Figure S2). Thus, Ti(II)-mediated cyclization of **13a** leading to **14** allowed direct installation of consecutive stereogenic centers (C8 and C9) in a highly diastereo-controlled manner, despite the modest yield.

The tetracyclic scaffold **16** composed of the trioxane moiety was then constructed employing a sequential one-pot protocol (Scheme 2). First, treatment of **14** with trifluoroacetic acid effected removal of the protecting groups and formation of an ammonium salt (**II**). Since temporary protection of the amine was assumed to be required for the subsequent oxidative conditions, the resulting **II** was directly subjected to ozonolysis using conditions modified from Avery's protocol.[3a] To minimize the allylic strain of the vinyl silane **14**, the substrate may adopt the conformation (**II**), and [3 + 2] dipolar cycloaddition of ozone occurred predominantly at the less-hindered α-face to generate molozonide (**III**). Spontaneous migration of the silyl group allowed simultaneous installation of aldehyde and trimethylsilyl peroxide (**IV**). Upon additional treatment with trifluoroacetic acid, tandem formation of two cyclic acetals furnished the trioxane **16** in 29% yield from **14**. Accordingly, this approach allowed streamlined access to the tetracyclic array of 6-aza-artemisinins in a sequence of just four steps starting from modular assembly of the three building blocks.

To improve the yield of Ti(II)-mediated cyclization, we employed the less sterically demanding substrate **13b** without the C9 methyl group to form **17** (Scheme 3). Cu(I)-catalyzed three-component assembly employing **10b** in place of **10a** afforded **13b** (94% ee) in 85% yield. Subsequent Ti(II)-mediated cyclization of **13b** proceeded smoothly to produce the desired **17** in 61% yield along with the C8 epimer (7% yield). We thus substantially improved the cyclization process to form **17**, relative to the corresponding conversion of the C9-

DOI: 10.1021/acs.orglett.8b01987
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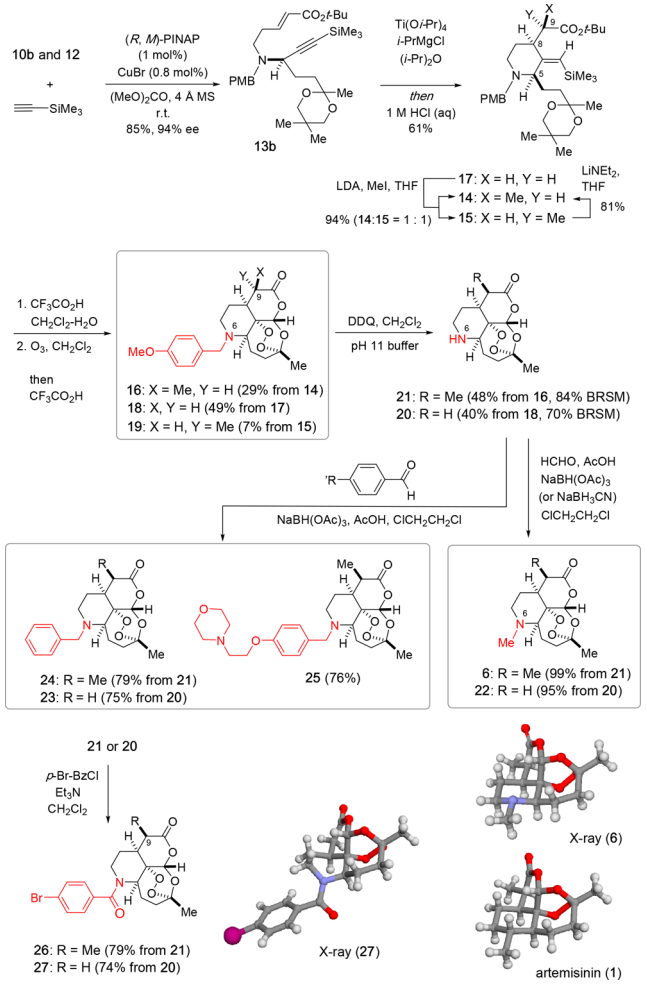
Scheme 3. Synthesis and Installation of a Substituent of 6-Aza-artemisinins



methylated **13a** into **14** (33% yield). Alkylation of **17** with methyl iodide afforded an easily separable 1:1 mixture of diastereomers **14** and **15** in 94% yield. C9 epimerization of **15** was feasible to give **14** in 81% yield with the recovery of **15** (17%). This protocol provides a high-yielding alternative route to the precursor **14** and also enables us to access the C9 epimeric precursor. The resulting precursors **17** and **15** were subjected to the one-pot conversions to generate 6-aza-artemisinins: **18** without the C9 methyl group and **19** having the 9*S*-methyl group, respectively. The C9 methyl substituent and its stereochemistry had considerable impacts on the yields of the trioxane formation. Conversion of the C9-desmethylated **17** led to a significant improvement, providing **18** in 49% yield, compared to the transformation of **14** into **16** (29% yield). Meanwhile, the corresponding conversion with the C9 epimer **15** produced **19** in 7% yield.

With the tetracyclic scaffold **16** in hand, we then modified the substituent on the nitrogen (Scheme 3). Removal of the *p*-methoxy benzyl group in **16** with DDQ liberated the secondary amine **21**. Reductive amination of **21** with formaldehyde gave rise to 6-aza-artemisinin (**6**). X-ray analysis of crystalline **6** confirmed the relative configuration of the 6-aza-artemisinins (Scheme 3). Notably, the three-dimensional structure of **6**, in which the N6 methyl group adopts a pseudoequatorial conformation, is essentially identical to that of **1**. Thus, this approach is capable of accurate emulation of the methyl substituent at the stereogenic C6 position of **1**. Similar reductive amination of **20**/**21** with aldehydes provided three derivatives (**23**−**25**) in good yields (>75%). The absolute configurations of the 6-aza-artemisinins were elucidated based on X-ray analysis of **27** prepared via acylation with *p*-bromobenzoyl chloride (Scheme 3). Thus, several substituents were installed on the nitrogen at the latest stage of the synthesis.

In vivo antimalarial activities of 6-aza-artemisinins were evaluated by Peter's four-day suppressive test employing a mouse model infected with rodent malaria *P. berghei N* strain (Figure 3 and SI, Table S2). Although the highly potent *in vitro*

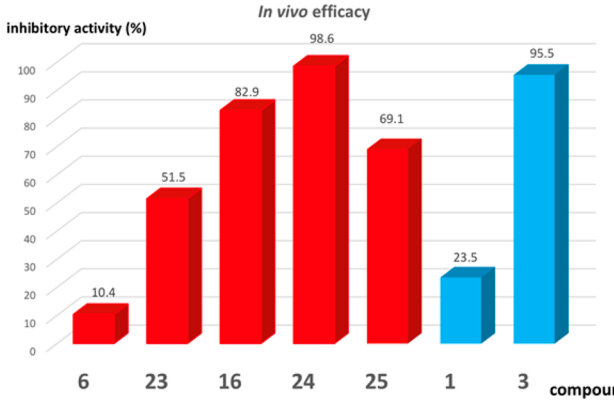


Figure 3. *In vivo* antimalarial therapeutic effects of 6-aza-artemisinins using the *P. berghei* rodent malaria model. Activities resulting in average parasitemia reduction were evaluated upon intraperitoneal administration [dosage 15 mg/kg, once a day for 4 days].

activities made it difficult to prioritize the lead candidates among the 6-aza-artemisinins (SI, Table S1), the results of preliminary *in vivo* experiments produced discernible differences between selected compounds. Intraperitoneal administration of **6** bearing *N*-methyl and C9-methyl groups (dosage 15 mg/kg, once a day for 4 days) exhibited limited efficacy in parasite clearance under the assay conditions, despite the high activity *in vitro* (IC_{50} = 32 nM for *P. falciparum* K1 strain, SI, Table S1). *N*-Benzylated **23** without the C9 methyl group showed potent activity (51.5%) greater than that of artemisinin (**1**) (23.5%), confirming the significance of the N6 arylalkyl substituents. More importantly, **24** bearing the *N*-benzyl and the C9 methyl group exhibited almost identical or even superior *in vivo* therapeutic activity (98.6%) to that of the first-line drug artesunate (**3**, 95.5%). The analogues **16** and **25** having either a methoxy or 2-morpholinoethoxy substituent on the para-position of the benzene ring also exerted potent inhibitory activities, 82.9% and 69.1%, respectively.

We further performed oral administration of the optimum 6-aza-artemisinin **24** (SI, Table S3 and Figure S1). Oral treatment of **24** (dosage 30 mg/kg, once a day for 4 days) exhibited a potent therapeutic efficacy (95.6%), which is superior to artemisinin (**1**, 74.5%) and comparable to artesunate (**3**, 97.7%).[16] Thus, we have generated 6-aza-artemisinins as lead candidates for next-generation artemisinin-based malaria chemotherapy. Modifications at the C6 position were demonstrated to have drastic impacts on the antimalarial activities.

In summary, we have designed 6-aza-artemisinins and developed a catalytic asymmetric synthetic process in just four steps initiated by the modular assembly of three simple

DOI: 10.1021/acs.orglett.8b01987
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building blocks. This *de novo* synthetic approach led to the discovery of a novel scaffold bearing the *N*-arylalkyl group generated by the element substitution at the cyclohexane moiety of **1**. We demonstrated that installation of a relatively large substituent at N6 is acceptable and sometimes intensifies the activities, which allowed generation of lead candidates exerting the very potent *in vivo* antimalarial efficacy greater than artemisinin (**1**) and comparable to the first-line semisynthetic drug artesunate (**3**). These results underlie the promising, but still untapped, potential of 6-aza-artemisinins with manipulatable physical and pharmacological properties. The next challenge will be the generation of chemical probes for chemical proteomics studies[17] and hybrid molecules to cope with emerging artemisinin-resistant parasites.[18] The simple molecular design strategy featuring element substitution of a skeletal carbon center is expected to be generally applicable to other intricate scaffolds,[19] which could facilitate the development of streamlined and versatile chemical platforms generating natural-product-inspired molecules without substantial structural simplification.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01987.

Full experimental procedures, NMR spectra, chiral HPLC analysis, and ORTEP diagrams (PDF)

Accession Codes

CCDC 1510941, 1511018, and 1511023 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: h_oguri@cc.tuat.ac.jp.

ORCID

Hideaki Oikawa: 0000-0002-6947-3397

Hiroki Oguri: 0000-0001-8007-1631

Notes

The authors declare the following competing financial interest(s): A patent application on antimalarial 6-aza-artemisinins has been filed by Tokyo University of Agriculture & Technology and Kitasato University.

■ ACKNOWLEDGMENTS

The authors thank Drs. Timothy N. C. Wells, Jeremy Burrows, and Didier Leroy of Medicines for Malaria Venture (MMV) for their invaluable advice and continuous support. The authors thank Mr. Takashi Matsumoto (Rigaku) and Mr. Ryo Watanabe (Hokkaido Univ.) for X-ray analysis. This work was supported in part by the GHIT fund HTLP RFP (2014-001), JSPS KAKENHI Grant Numbers JP23310156, JP26102702, and JP16H01135, the Naito Foundation, and the Uehara Memorial Foundation. This work was inspired by the international and interdisciplinary environments of the JSPS Asian CORE Program, "Asian Chemical Biology Initiative", and JSPS A3 Foresight Program.

■ REFERENCES

(1) (a) Enserink, M. *Science* **2005**, *307*, 33. (b) White, N. J. *Science* **2008**, *320*, 330.

(2) (a) Schmid, G.; Hofheinz, W. *J. Am. Chem. Soc.* **1983**, *105*, 624. (b) Ravindranathan, T.; Kumar, M. A.; Menon, R. B.; Hiremath, S. V. *Tetrahedron Lett.* **1990**, *31*, 755. (c) Liu, H. J.; Yeh, W. L.; Chew, S. Y. *Tetrahedron Lett.* **1993**, *34*, 4435. (d) Zhou, W.-S.; Xu, X.-X. *Acc. Chem. Res.* **1994**, *27*, 211. (e) Constantino, M. G.; Beltrame, M., Jr; da Silva, G. V. J.; Zukerman-Schpector, J. *Synth. Commun.* **1996**, *26*, 321. (f) Yadav, J. S.; Thirupathaiah, B.; Srihari, P. *Tetrahedron* **2010**, *66*, 2005.

(3) (a) Avery, M. A.; Chong, W. K. M.; Jennings-White, C. *J. Am. Chem. Soc.* **1992**, *114*, 974. (b) Avery, M. A.; Gao, F.; Chong, W. K. M.; Mehrotra, S.; Milhous, W. K. *J. Med. Chem.* **1993**, *36*, 4264. (c) Avery, M. A.; Muraleedharan, K. M.; Desai, P. V.; Bandyopadhyaya, A. K.; Furtado, M. M.; Tekwani, B. L. *J. Med. Chem.* **2003**, *46*, 4244 and references cited therein.

(4) Zhu, C.; Cook, S. P. *J. Am. Chem. Soc.* **2012**, *134*, 13577.

(5) Paddon, C. J.; Westfall, P. J.; Pitera, D. J.; Benjamin, K.; Fisher, K.; McPhee, D.; Leavell, M. D.; Tai, A.; Main, A.; Eng, D.; Polichuk, D. R.; Teoh, K. H.; Reed, D. W.; Treynor, T.; Lenihan, J.; Jiang, H.; Fleck, M.; Bajad, S.; Dang, G.; Dengrove, D.; Diola, D.; Dorin, G.; Ellens, K. W.; Fickes, S.; Galazzo, J.; Gaucher, S. P.; Geistlinger, T.; Henry, R.; Hepp, M.; Horning, T.; Iqbal, T.; Kizer, L.; Lieu, B.; Melis, D.; Moss, N.; Regentin, R.; Secrest, S.; Tsuruta, H.; Vazquez, R.; Westblade, L. F.; Xu, L.; Yu, M.; Zhang, Y.; Zhao, L.; Lievense, J.; Covello, P. S.; Keasling, J. D.; Reiling, K. K.; Renninger, N. S.; Newman, J. D. *Nature* **2013**, *496*, 528.

(6) (a) Acton, N.; Roth, R. J. *J. Org. Chem.* **1992**, *57*, 3610. (b) Lévesque, F.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1706. (c) Kopetzki, D.; Lévesque, F.; Seeberger, P. H. *Chem. - Eur. J.* **2013**, *19*, 5450. (d) Turconi, J.; Griolet, F.; Guevel, R.; Oddon, G.; Villa, R.; Geatti, A.; Hvala, M.; Rossen, K.; Göller, R.; Burgard, A. *Org. Process Res. Dev.* **2014**, *18*, 417. (e) Amara, Z.; Bellamy, J. F. B.; Horvath, R.; Miller, S. J.; Beeby, A.; Burgard, A.; Rossen, K.; Poliakoff, M.; George, M. W. *Nat. Chem.* **2015**, *7*, 489.

(7) Charman, S. A.; Arbe-Barnes, S.; Bathurst, I. C.; Brun, R.; Campbell, M.; Charman, W.; Chiu, F. C. K.; Chollet, J.; Craft, J. C.; Creek, D. J.; Dong, Y.; Matile, H.; Maurer, M.; Morizzi, J.; Nguyen, T.; Papastogiannidis, P.; Scheurer, C.; Shackleford, D. M.; Sriraghavan, K.; Stingelin, L.; Tang, Y.; Urwyler, H.; Wang, X.; White, K. L.; Wittlin, S.; Zhou, L.; Vennerstrom, J. L. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 4400.

(8) (a) 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.; Santo, T. J.; Scheurer, C.; Scorneaux, B.; Tang, Y.; Urwyler, H.; Wittlin, S.; Charman, W. N. *Nature* **2004**, *430*, 900. (b) O'Neill, P. M.; Amewu, R. K.; Nixon, G. L.; Bousejra ElGarah, F.; Mungthin, M.; Chadwick, J.; Shone, A. E.; Vivas, L.; Lander, H.; Barton, V.; Muangnoicharoen, S.; Bray, P. G.; Davies, J.; Park, B. K.; Wittlin, S.; Brun, R.; Preschel, M.; Zhang, K.; Ward, S. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 5693. (c) Oguri, H.; Hiruma, T.; Yamagishi, Y.; Oikawa, H.; Ishiyama, A.; Otoguro, K.; Yamada, H.; Omura, S. J. *J. Am. Chem. Soc.* **2011**, *133*, 7096.

(9) For selected reviews, see: (a) O'Neill, P. M.; Posner, G. H. *J. Med. Chem.* **2004**, *47*, 2945. (b) Chaturvedi, D.; Goswami, A.; Pratim Saikia, P.; Barua, N. C.; Rao, P. G. *Chem. Soc. Rev.* **2010**, *39*, 435. (c) Slack, R. D.; Jacobine, A. M.; Posner, G. H. *MedChemComm* **2012**, *3*, 281.

(10) (a) Avery, M. A.; Bonk, J. D.; Chong, W. K. M.; Mehrotra, S.; Miller, R.; Milhous, W.; Goins, D. K.; Venkatesan, S.; Wyandt, C. *J. Med. Chem.* **1995**, *38*, 5038. (b) Torok, D. S.; Ziffer, H.; Meshnick, S. R.; Pan, X.-Q.; Ager, A. *J. Med. Chem.* **1995**, *38*, 5045. (c) Mekonnen, B.; Weiss, E.; Katz, E.; Ma, J.; Ziffer, H.; Kyle, D. E. *Bioorg. Med. Chem.* **2000**, *8*, 1111. (d) Al-Oqail, M. M.; Galal, A. M.; Ahmad, M. S.; Al-Fishawi, A. M.; El-Feraly, F. S. *Molecules* **2003**, *8*, 901.

DOI: 10.1021/acs.orglett.8b01987
Org. Lett. XXXX, XXX, XXX−XXX

(e) Haynes, R. K.; Wong, H.-N.; Lee, K.-W.; Lung, C.-M.; Shek, L. Y.; Williams, I. D.; Croft, S. L.; Vivas, L.; Rattray, L.; Stewart, L.; Wong, V. K. W.; Ko, B. C. B. *ChemMedChem* **2007**, *2*, 1464. (f) Singh, A. S.; Verma, V. P.; Hassam, M.; Krishna, N. N.; Puri, S. K.; Singh, C. *Org. Lett.* **2008**, *10*, 5461. (g) Nguyen Le, T.; De Borggraeve, W. M.; Grellier, P.; Pham, V. C.; Dehaen, W.; Nguyen, V. H. *Tetrahedron Lett.* **2014**, *55*, 4892. (h) Singh, C.; Verma, V. P.; Hassam, M.; Singh, A. S.; Naikade, N. K.; Puri, S. K. *J. Med. Chem.* **2014**, *57*, 2489. (i) Harmse, R.; Wong, H. N.; Smit, F.; Haynes, R. K.; N'Da, D. D. *Curr. Med. Chem.* **2015**, *22*, 3607.

(11) (a) Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 14052. (b) Zhang, X.; Yang, H.; Tang, P. *Org. Lett.* **2015**, *17*, 5828.

(12) Kurosawa, W.; Kan, T.; Fukuyama, T. *Org. Synth.* **2002**, *79*, 186.

(13) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971.

(14) The catalytic asymmetric condensation employing toluene as solvent resulted in sluggish reaction.[13] Solvents such as dichloromethane or 1,2-dimethoxyethane were suitable for this condensation attaining high enantioselectivities (>90% ee) but provided **13** with slightly lower yields compared to the optimum solvent, dimethyl carbonate.

(15) Urabe, H.; Suzuki, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 10014.

(16) Based on comparison of the *P* values for the oral administration between artemisinin (**1**) and 6-aza-artemisinin (**24**), **24** exhibited potent therapeutic efficacies greater than that of 1 ($P = 0.0245$) on day 4. Comparison between **24** and artesunate (**3**) showed no significant difference.

(17) (a) 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. (b) Wang, J.; Zhang, C. J.; Chia, W. N.; Loh, C. C. Y.; Li, Z. J.; Lee, Y. M.; He, Y. K.; Yuan, L. X.; Lim, M. T. K.; Liu, C.; Liew, X.; Lee, Y. Q.; Zhang, J. B.; Lu, N. C.; Lim, C. T.; Hua, Z. C.; Liu, B.; Shen, H. M.; Tan, K. S. W.; Lin, Q. S. *Nat. Commun.* **2015**, *6*, 10111.

(18) (a) Straimer, J.; Gnädig, N. F.; Witkowski, B.; Amaratunga, C.; Duru, V.; Ramadani, A. P.; Dacheux, M.; Khim, N.; Zhang, L.; Lam, S.; Gregory, P. D.; Urnov, F. D.; Mercereau-Puijalon, O.; Benoit-Vical, F.; Fairhurst, R. M.; Ménard, D.; Fidock, D. A. *Science* **2015**, *347*, 428. (b) Mbengue, A.; Bhattacharjee, S.; Pandharkar, T.; Liu, H.; Estiu, G.; Stahelin, R. V.; Rizk, S. S.; Njimoh, D. L.; Ryan, Y.; Chotivanich, K.; Nguon, C.; Ghorbal, M.; Lopez-Rubio, J.-J.; Pfrender, M.; Emrich, S.; Mohandas, N.; Dondorp, A. M.; Wiest, O.; Haldar, K. *Nature* **2015**, *520*, 683.

(19) Bebbington, M. W. P. *Chem. Soc. Rev.* **2017**, *46*, 5059.

DOI: 10.1021/acs.orglett.8b01987
Org. Lett. XXXX, XXX, XXX−XXX