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Synthesis of a Potent Antimalarial Amphilectene

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Supporting Information

ABSTRACT: 7-Isocyano-11(20),14-epiamphilectadiene, the most potent of antimalarial amphilectenes, is synthesized in seven steps from readily available materials. The synthesis is enabled by a new dendrimeric triene (Danishefsky [3]-dendralene) and a new method for stereo- and chemoselective isocyanation. This chemistry provides a useful entry into an underexplored yet promising family of antimalarial terpenoids.

In 2009, clinicians working along the Thai−Cambodia border confirmed reports of malaria infections that showed decreased susceptibility to artemisinin-combination therapies (ACT), which are the standard of care for treating malignant malaria (*P. falciparum*).[1] The incidence of artemisinin resistance is on the rise,[2] with some communities reporting reduced ACT-sensitivity in 50% of the patient population.[3b] Consequently, there is an urgent need to identify, produce, and analyze promising new drugs for the treatment of malaria.[3] The isocyanoamphilectenes (e.g., **1**−**3**, Figure 1) are marine

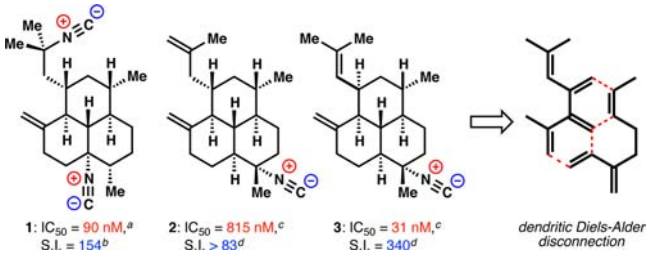


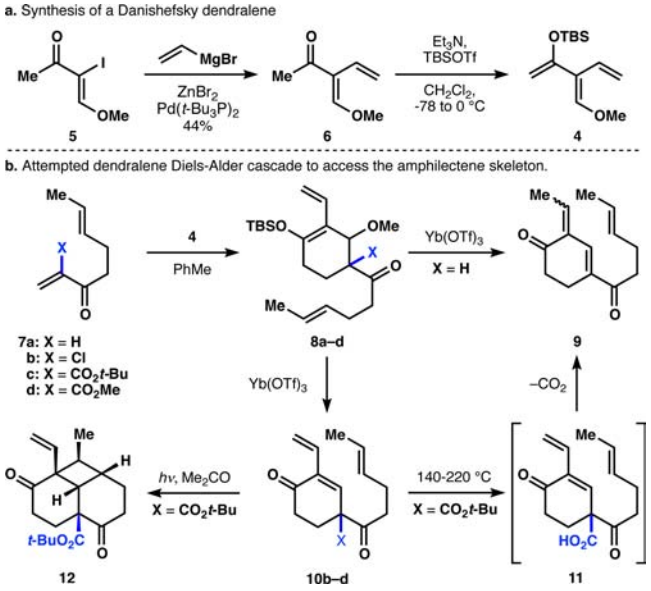
Figure 1. Antimalarial amphilectenes. [a]IC_{50} (*P. falciparum* K1); [b]S.I. = IC_{50} (human fibroblast)/*a*; [c]IC_{50} (*P. falciparum* W2); [d]S.I. = IC_{50} (human fibroblast)/*c*.

diterpenes[4] which have demonstrated antimalarial activity and selectivity comparable to the broadly prescribed medicines chloroquine and mefloquine.[5] Notably, **3** is highly active (IC_{50} = 31 nM) toward chloroquine-resistant (W2) *P. falciparum*. Unfortunately, isolation from tropical sponges over the course of three decades has not proved a viable means of procuring the mono- or diisocyanoamphilectenes in large quantity,[6] and chemical synthesis routes have been lengthy (**1** in 27 and 25 steps; and **2** in 34 steps).[7] Here we demonstrate a concise entry into this isocyanoterpene (ICT) family, the total synthesis of **3**, and an unusual stereoinversion of a tertiary alcohol.

Our lab is developing syntheses of medicinally important small molecules from linear polyunsaturated oligomers using controlled polycyclizations.[8] The global strategy of converting small monomers to linear polyunsaturated oligomers, followed by selective polycyclization, is a common strategy in secondary metabolite biosynthesis[9] and benefits from both synthetic efficiency and divergency. We realized that the amphilectene skeleton might be reasonably disconnected by scission into two polyunsaturated chains (Figure 1), one of which resembled a dendrimeric isoprene dimer.

Dendrimeric polyenes, or dendralenes, are attractive Diels−Alder cycloaddition reactants because their initial reaction with a dienophile generates a new diene, which can undergo further cycloaddition to yield multiple rings in one step.[10] This process of cycloaddition and diene transmission can proceed in $n + 1$ iterations, if n is equal to the number of conjugated trienes in the initial dendralene. Unfortunately, dendralenes have seen only limited use in natural product synthesis[10] since substituted variants can exhibit poor chemo-, regio-, and stereoselectivity upon cycloaddition.[10,11] In contrast, highly polarized, non-dendrimeric dienes, especially the Danishefsky diene and its derivatives, undergo facile and highly regioselective cycloadditions with electron-deficient dienophiles.[12] We reasoned that providing Danishefsky-diene character to a dendralene might expand the utility of these polyenes and provide rapid access to the amphilectene skeleton.

Scheme 1. Synthesis of 4 and Attempted Diels−Alder Cascade



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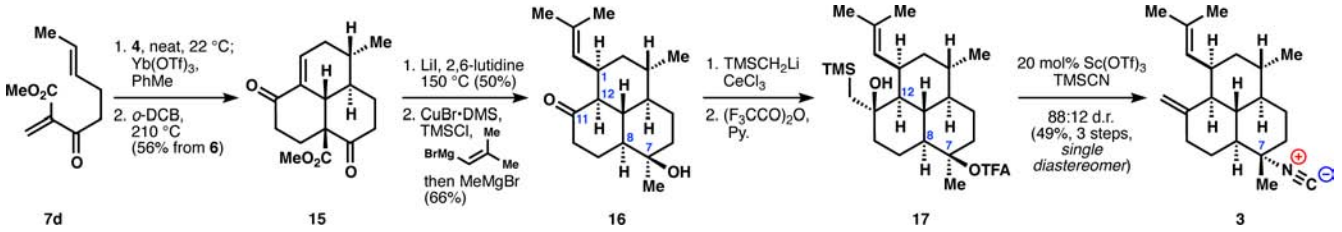
Scheme 2. Synthesis of (±)-7-Isocyano-11(20),14-epiamphilectadiene (3)



Danishefsky dendralene **4** (Scheme 1a) can be synthesized from commercially available *trans*-4-methoxy-3-buten-2-one by (1) iodination to yield **5**;[13] (2) Negishi coupling of **5** with vinylzinc bromide to yield **6**; and (3) silylation of **6** using *tert*-butyldimethylsilyl triflate (TBSOTf) and triethylamine. This process is scalable and reproducible; however organoiodide **5** colors at ambient temperature, which corresponds to a drop in the conversion of Negishi coupling, so **5** must be used fresh.

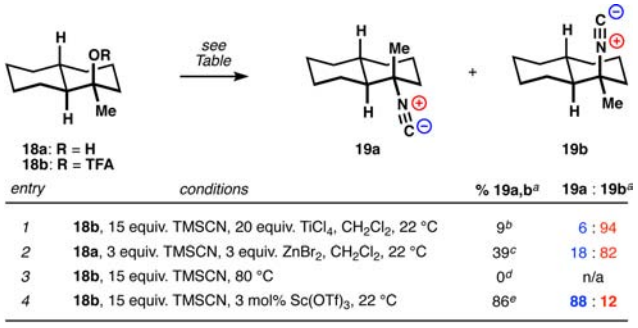
Initial attempts to apply dendralene **4** to the synthesis of the amphilectene skeleton were frustrated on several fronts (Scheme 1b). First, although unsaturated ketone **7a** (X = H) underwent facile and regioselective cycloaddition with **4**, treatment of cycloadduct **8a** with $Yb(OTf)_3$ caused rapid and irreversible isomerization to **9**. To circumvent this isomerization, we synthesized α-chloro ketone **7b** (X = Cl), which also underwent clean cycloaddition, but **10b** was too unstable to undergo a second Diels–Alder reaction and rapidly decomposed, even upon storage at −20 °C. The third tactic involved use of the corresponding *tert*-butyl ester **7c** (X = CO_2t-Bu), which underwent smooth cycloaddition to **8c**. Unfortunately, the energy of activation for subsequent cycloaddition exceeded that of thermal hetero-retro-ene (loss of isobutylene, **10c**→**11**), and only **9** was observed after prolonged heating. Photochemical cycloadditions were attempted using **10c**, but only strained cyclobutane **12** was formed, which resisted subsequent vinyl cyclobutane rearrangement to our target tricycle.

Eventually, we found that methyl ester **7d** serves as a competent dienophile (Scheme 2), but this highly reactive compound lacks the steric bulk of **7c** and is subject to decomposition, presumably through oligomerization. Therefore **7d** is generated under dilute conditions and then concentrated in the presence of dendralene **4**. The utility of this reaction for the total synthesis of **3** is shown in Scheme 2. Cycloaddition between **4** and **7d** occurs at ambient temperature, and addition of 5 mol % $Yb(OTf)_3$ generates the intermediate cross-conjugated enone[14] (see Scheme 1b, **10d**), which undergoes a second Diels–Alder cycloaddition upon heating in *o*-dichlorobenzene in a microwave reactor. Tricycle **15** can be isolated in 56% yield (calculated from vinylketone **6**), and its diastereomer (probably the *endo*-cycloadduct) is detected in only small quantities (d.r. > 10: 1). The reaction **7d** + **4** → **15** can also be conducted in one pot, but the yield is lower (31%) due to the presence of $Yb(OTf)_3$, which causes competitive decomposition.

Efficient conversion of **15** to amphilectene **3** requires an exact choreography of steps, initiated by immediate excision of the methyl carboxylate.[15] Due to the sensitivity of **15** toward conjugate nucleophilic additions, we utilize a modified Krapcho decarboxylation[16] to remove the superfluous methyl ester, which provides the diketone with high stereoselectivity. A tandem conjugate addition/1,2 addition succeeds due to the intermediacy of a silylenol ether which prevents addition of methylmagnesium bromide to the C11 ketone. As predicted, the product of this sequence, **16**, possesses the required configurations at C1, C7, C8, and C12 for conversion to **3**.

Transformation of **16** into **3** involves C11 ketone methylenation and a challenging stereoselective displacement of the C7 tertiary alcohol via *N*-alkylation of cyanide. Activation of both functions in **16** is achieved by addition of trimethylsilylmethyl cerium chloride to the C11 ketone,[17] followed by selective trifluoroacetylation of the C7 tertiary alcohol to yield **17**. However, final installation of the equatorial isonitrile pharmacophore required extensive exploration since existing methods were not suited to substrates bearing additional sites of unsaturation. For example, application of tertiary alcohol isocyanation reported by Tada[18] and Kitano[19] led first to alkene formation and then to the slow and indiscriminate addition of isocyanide to alkenes mediated by a Brønsted acid. The conditions of Corey and Magriotis for isocyanation were reported to exhibit low stereoselectivity,[20] and we also observed competitive formation of tertiary chlorides and cyanides. Therefore we developed our own method for isocyanation[21] using model decalin **18** (Table 1).

Table 1. Comparison of Isocyanation Methods



entry	conditions	% 19a,b[a]	19a : 19b[a]
1	**18b**, 15 equiv. TMSCN, 20 equiv. $TiCl_4$, CH_2Cl_2, 22 °C	9[b]	6 : 94
2	**18a**, 3 equiv. TMSCN, 3 equiv. $ZnBr_2$, CH_2Cl_2, 22 °C	39[c]	18 : 82
3	**18b**, 15 equiv. TMSCN, 80 °C	0[d]	n/a
4	**18b**, 15 equiv. TMSCN, 3 mol% $Sc(OTf)_3$, 22 °C	86[e]	88 : 12

[a]According to GC. [b]Major byproducts were alkyl chlorides. [c]Major byproducts were alternative isomeric isonitriles [d]Products were alkenes. [e]Isolated yield of **19a**,**b** from entry 4 is 66%; isolated yield of **19a** is 51%.

As shown in entries 1 and 2, the conditions of Corey and Tada, respectively, produce *axial isonitrile* **19b** from **18a** or **18b**, in preference to equatorial isonitrile **19a**.[22] We interpret these results to indicate the intermediacy of a solvent separated carbocation, which is expected to undergo facile axial attack.[23] Since inversion of configuration at the C7 tertiary trifluoroacetate was desired, we explored displacement conditions[24] that would instead induce reaction at a contact ion pair.[25]

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Unfortunately, attempts at thermal solvolysis[24a] of **18b** provide alkenes exclusively (entry 3). However, ionization of **18b** with a weak, oxophilic Lewis acid,[26] $Sc(OTf)_3$, in the presence of 15 equiv of TMSCN and in the absence of any other solvent provides **19a** with high stereoselectivity and little elimination (entry 4). Notably, the major diastereomer derives from inversion of configuration and suggests either (1) attack of a contact ion pair or (2) departure of the trifluoroacetate coincident with attack by the TMSCN nucleophile (structure **20**). It should be noted that addition of TMSCN to a 4-*tert*-butyl-1-methylcyclohexyl carbocation in dichloromethane is reported to proceed with primarily the opposite selectivity to yield an axial isonitrile.[19] Application of this new method to penultimate intermediate **17** also effects elimination of the C11 alcohol and provides **3** in good yield and high diastereoselectivity.

In conclusion, we have disclosed a short synthesis of **3**, which is a low nanomolar antimalarial agent and the most potent of the amphilectene isocyanoterpenes. The synthesis of **3** relies on a new dendrimeric variant of the Danishefsky diene which allows rapid assembly of polycycles from linear unsaturated polyenes. Furthermore, we have uncovered a potentially useful, chemoselective inversion of tertiary alcohols with TMSCN; this reactivity is currently being explored. We anticipate that the approach reported herein will be applicable to the asymmetric synthesis of the entire amphilectene family,[27] related isocyanoterpenes, and easily derived analogs which could constitute a new arsenal of medicines in the fight against malaria.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

This paper was published ASAP on November 15, 2012. The title of Scheme 2 has been corrected. The revised version was posted on November 20, 2012.