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Concise Synthesis of the Antiplasmodial Isocyanoterpene 7,20-Diisocyanoadociane

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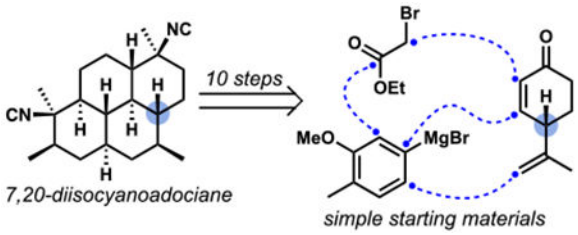
Abstract

The flagship member of the antiplasmodial isocyanoterpenes, 7,20-diisocyanoadociane (DICA), was synthesized from dehydrocryptone in 10 steps, and 13 from commercially available material. Our previous formal synthesis was reengineered, leveraging only productive transformations to deliver DICA in fewer than half the number of steps of our original effort. Important contributions, in addition to the particularly concise strategy, include a solution to the problem of axial nucleophilic methylation of a late-stage cyclohexanone, and the first selective synthesis and antiplasmodial evaluation of the DICA stereoisomer with both isonitriles equatorial.

Graphical Abstract

The flagship antimalarial isocyanoterpene, diisocyanoadociane, was constructed in ten steps from simple starting materials.



Keywords

terpenoids; antimalarial; Birch reduction; total synthesis; stereocontrol

Sponge-derived isocyanoterpene (ICT) secondary metabolites are striking for their isonitrile functional groups—rarely found in natural products—and their potent antiplasmodial

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activity, which appear correlated.[1] This family includes a range of complex polycyclic architectures (Figure 1a) that has inspired our group to develop a unified strategy toward seemingly topologically disparate ICT diterpenes. Among them, 7,20-diisocyanoadociane (DICA, **1**) stands out as arguably the most stereochemically complex.[1] DICA was described in 1976,[2] but it wasn't until studies by König and colleagues two decades later[3] that DICA's potent antiplasmodial activity was revealed. The compelling combination of its structure and activity originated our interest in DICA and, by extension, the rest of the ICT family.[4–7]

Upon initiation of our efforts in this area, we identified 2-isocyanodecalin fragment **6** (Figure 1b) as a common motif in many potent ICT diterpenes and developed a general strategy around retron **5**.[8] An intermolecular conjugate addition/enolate trapping strategy was devised with the goal of maximizing convergency and overall efficiency; this approach appeared to offer the flexibility to be generalizable to many ICTs.[9] Indeed, this strategy was central to our synthesis of kalihinol B (**2**),[4] many simplified yet active kalihinol analogues,[5] and our previous formal synthesis of DICA (**1**).[6a]

In 1987, Corey and Magriotis described the first synthesis of DICA via a logical, Diels–Alder based strategy that generated tetracyclic diketone (Corey dione) **7** in about two dozen steps (Scheme 1).[10] Double equatorial nucleophilic methylation, activation by trifluoroacetylation and treatment with TMSCN and $TiCl_4$ led to stereochemically uncontrolled formation of **1** and its three stereoisomers. Several subsequent formal syntheses were based on the formation of the Corey dione, and thus inherited its troublesome endgame. These achievements include a Diels–Alder approach strategically similar to Corey's from the Miyaoka group,[11] an oxidative enolate coupling/ring-closing metathesis approach from Robinson and Thomson[12] and our own conjugate addition/enolate trapping strategy.[6a] Two total syntheses sought to solve the stereocontrol conundrum at the C7 and C20 isonitrile-bearing carbons: Fairweather and Mander's approach used stereospecific Curtius rearrangements to install tertiary carbinolamines as isonitrile precursors,[13] and the Shenvi group's synthesis[14] featured their method for invertive displacement of tertiary trifluoroacetates (TMSCN, $Sc(OTf)_3$) on the bis-trifluoroacetate derived from **8**, which provided a stereoselective counterpoint to the endgame from **7**.[15]

Our previous formal synthesis was problematic because it required over two dozen steps to arrive at the Corey dione, from which no satisfactory stereocontrolled endgame could be envisaged. Improving on this earlier work required addressing its critical problems: (1) underfunctionalized early intermediate **9** required late-stage introduction of the C17 and C19 methyl groups; (2) the THF ring in **9**, introduced as a protecting group for the corresponding 1,4-diol, proved challenging to open, and required a half dozen steps to appropriately elaborate; and (3) the end-game from the Corey dione to DICA would be unselective. The reconciliation of these problems has led to the total synthesis of DICA itself described herein, which was completed in fewer than half the number of operations and captures the spirit of our general ICT strategy.

Scheme 2 reveals how dehydrocryptone (**11**) is converted to DICA in 10 steps (13 steps from its chiral pool precursor perillaldehyde[16]). Conjugate arylation and *in situ* enolate trapping with ethyl bromoacetate provides the three-component coupling product in high yield with

complete stereochemical control. Selective nucleophilic methylation of the ketone leads to lactone **12**.[17] Equatorial methyl addition to the C7 ketone delivers an axial C–O bond that will later—upon displacement with TMSCN—result in the C7 equatorial isonitrile found in the natural product. Notably, the conversion of **11** to **12** introduces all of the skeletal carbon atoms of DICA except for the C16 methyl group. Sequential epoxidation and Lewis-acid-induced Meinwald rearrangement/Friedel–Crafts cyclodehydration affords tetracyclic styrene **13**.[18]

Although dihydronapthalene **13** appears to be only moderately related to DICA, it is readily elaborated to the target's perhydropyrene core in only four carefully orchestrated transformations, with which five stereogenic centers are installed by reduction, each with greater than 10:1 diastereoselectivity. Birch reduction of **13** proceeds with the addition of six molar equivalents of electrons, reducing the styrene, the electron-rich aromatic ring, and—critically—the lactone. After hydrolysis of the initial reduction product, **14** is obtained with high control at C1 and C3 (C15 is easily epimerizable in a subsequent step, and the acetal center is irrelevant). Heterogeneous hydrogenation of the enone is completely selective for the *trans*-ring juncture, and provides the ketone that serves as the pronucleophile for an aldol condensation with the acetal carbon. Controlling the reduction to deliver a lactol ensured the correct oxidation state for the subsequent proline-mediated aldol condensation, which directly provided **15**. A second heterogeneous enone hydrogenation—performed in basic methanol—introduces the C11 stereogenic center with high efficiency and selectivity, and equilibrates the C15 center such that the methyl group resides equatorially, delivering **16** as a single diastereomer.

Given our focus on brevity to this point, we were compelled to find a way to directly introduce the C16 methyl group in an axial orientation. The Shenvi group reported that their efforts to do so were unsuccessful, opting instead for a multi-step but highly diastereoselective sequence of Peterson olefination and oxymercuration/reduction.[14] Presented with this opportunity for discovery, we embarked upon a screen of combinations of different methyl organometallic reagents, Lewis acids additives, solvents, and co-solvents, while simultaneously studying classical literature on carbonyl additions. In this way, and with guidance from the critical studies of Ashby and co-workers,[20] we found that an excess of trimethylaluminum in solvents of low polarity tended to favor the generation of the desired axially methylated adduct **8**.

To date, we have managed selectivities of 2–2.5:1, but the trivial separation of the resulting diastereomers, the avoidance of stoichiometric mercury reagents, and the identical yield to Shenvi's multi-step solution makes this an attractive alternative. Conversion of **8** to **1** by application of Shenvi's invertive isocyanation protocol afforded the natural product exactly as described.[14,15] At this stage, we have made over 30 mg of DICA via this sequence, without any particular efforts to scale up the chemistry; indeed, all indications to date suggest that significant quantities of the natural product should be available when needed.

While DICA itself has been tested many times, the activities of its isonitrile-bearing-carbon stereoisomers have not been reported. The general preference for equatorial methylation of cyclohexanones renders **16** particularly well suited to making the unnatural epimer of DICA

with both isonitriles equatorial (C20-*epi*-DICA, **17**, Figure 2). Treatment of **16** with methylmagnesium chloride was diastereoselective for equatorial methylation, and further processing afforded **17**.[20] The potent activity of DICA is largely retained in its stereoisomer **17**, with only a five-fold decrease in potency toward a drug-resistant (Dd2) strain of *Plasmodium falciparum* and a 25-fold decrease against a drug-sensitive (3D7) strain. This outcome is consistent with the model put forth by Wright, Tilley and co-workers pertaining to the antiplasmodial activity of many polycyclic ICTs;[21] their modeling analysis suggests that the C7 equatorial isonitrile correlates with significant antiplasmodial activity, and that C20 axial substitution provides a supportive role in slightly improving potency. The model appears to embrace either electron-poor or alkyl groups axial at C20, which is further supported by **17**'s only modest loss in activity. Given this outcome, evaluation of the antiplasmodial activity of the other C7/C20 diastereomers of DICA is warranted—especially given the pseudo-symmetry of these compounds—and will be reported in due course.

In conclusion, we have developed a particularly concise synthesis of DICA—based on our general strategy—that features a rapid buildup of much of its carbon scaffold, followed by efficient introduction of key stereogenic centers by reduction. We have thereby reduced the problem posed by DICA to a sequence of ten chemical steps from simple, known starting materials, obviating all of the unproductive steps that plagued our previous effort. This synthesis further showcases the power of the conjugate addition/enolate trapping strategy as a valuable means of accessing ICT natural products. We have capitalized on this short, stereoselective synthesis to produce C20-*epi*-DICA, which was tested for antiplasmodial activity for the first time, the results of which support the current working hypothesis on the activity of polycyclic ICTs.

Our achievement provides a reminder that efficient syntheses need not necessarily rely on the development of new chemical methods. Indeed, with the wealth of chemical tools currently at our disposal, strategic advances will continue to be major contributors to efficiency.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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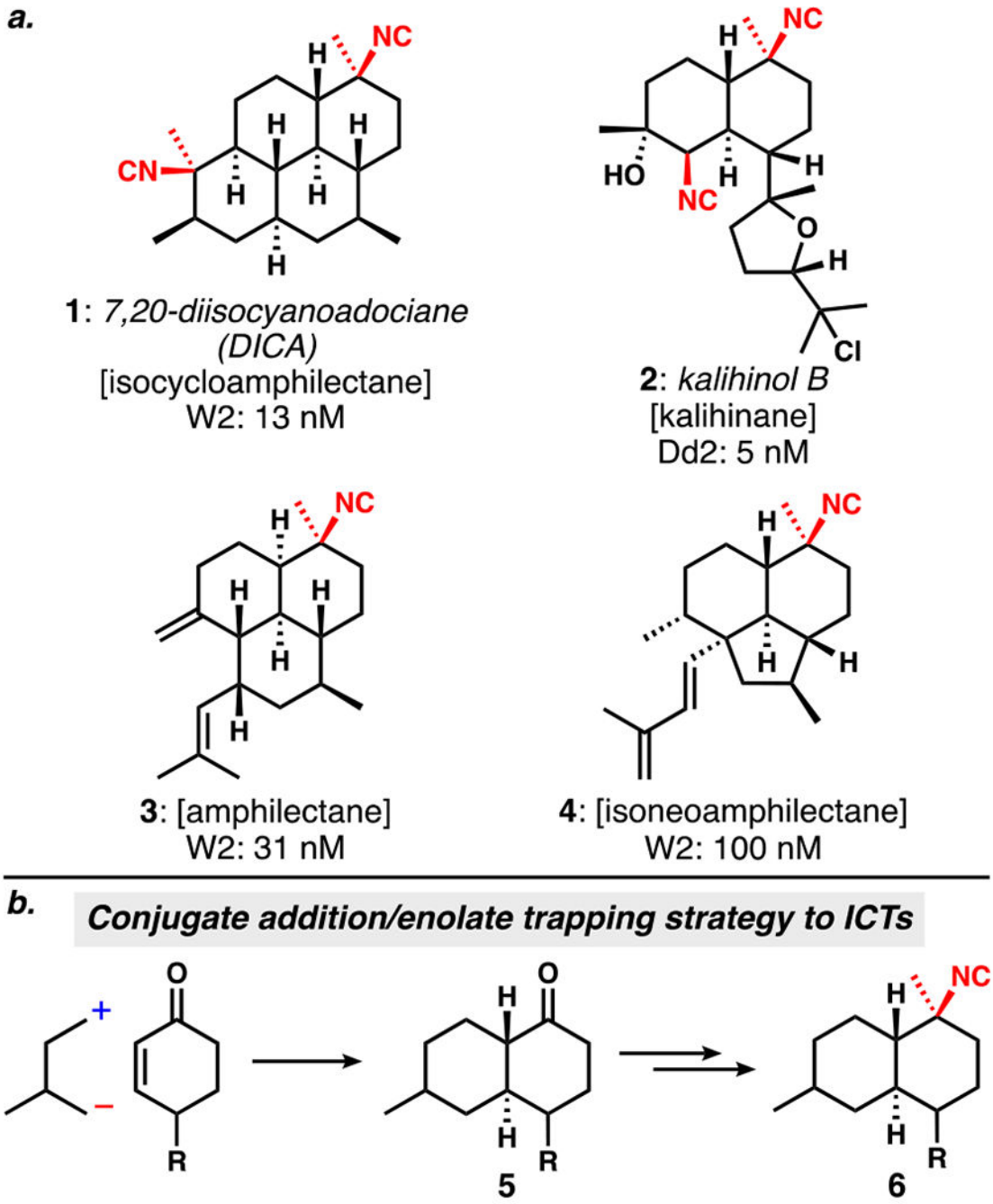


Figure 1.

a. Select ICTs including 7,20-diisocyanoadociane and their antiplasmodial activities. W2 and Dd2 are drug-resistant strains of the malaria-causing parasite *Plasmodium falciparum*; the concentrations given are IC_{50} values. These data are taken from refs 3c and 4. **b.** A general strategy to access various ICT architectures.

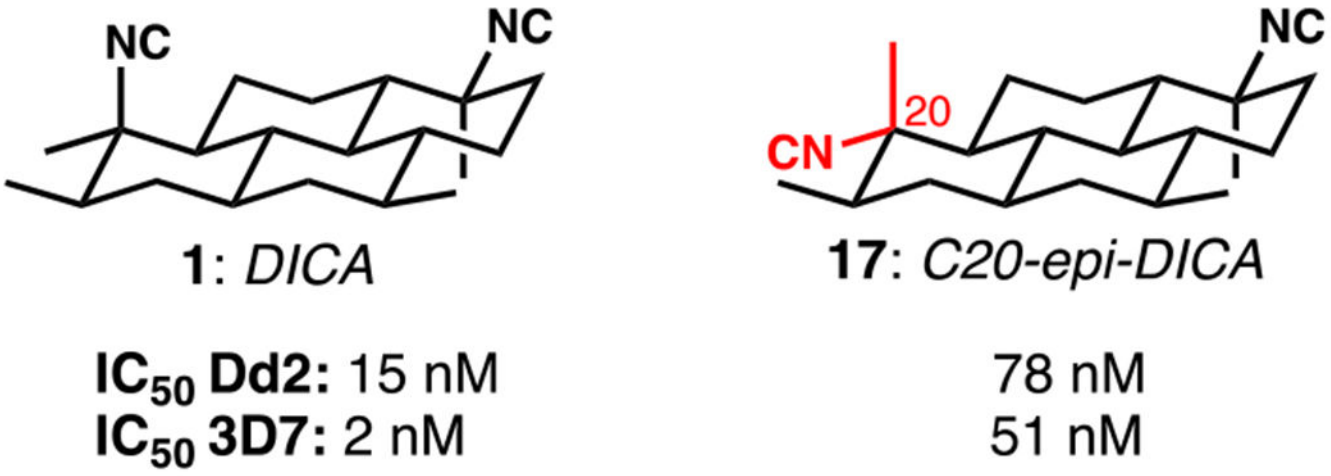
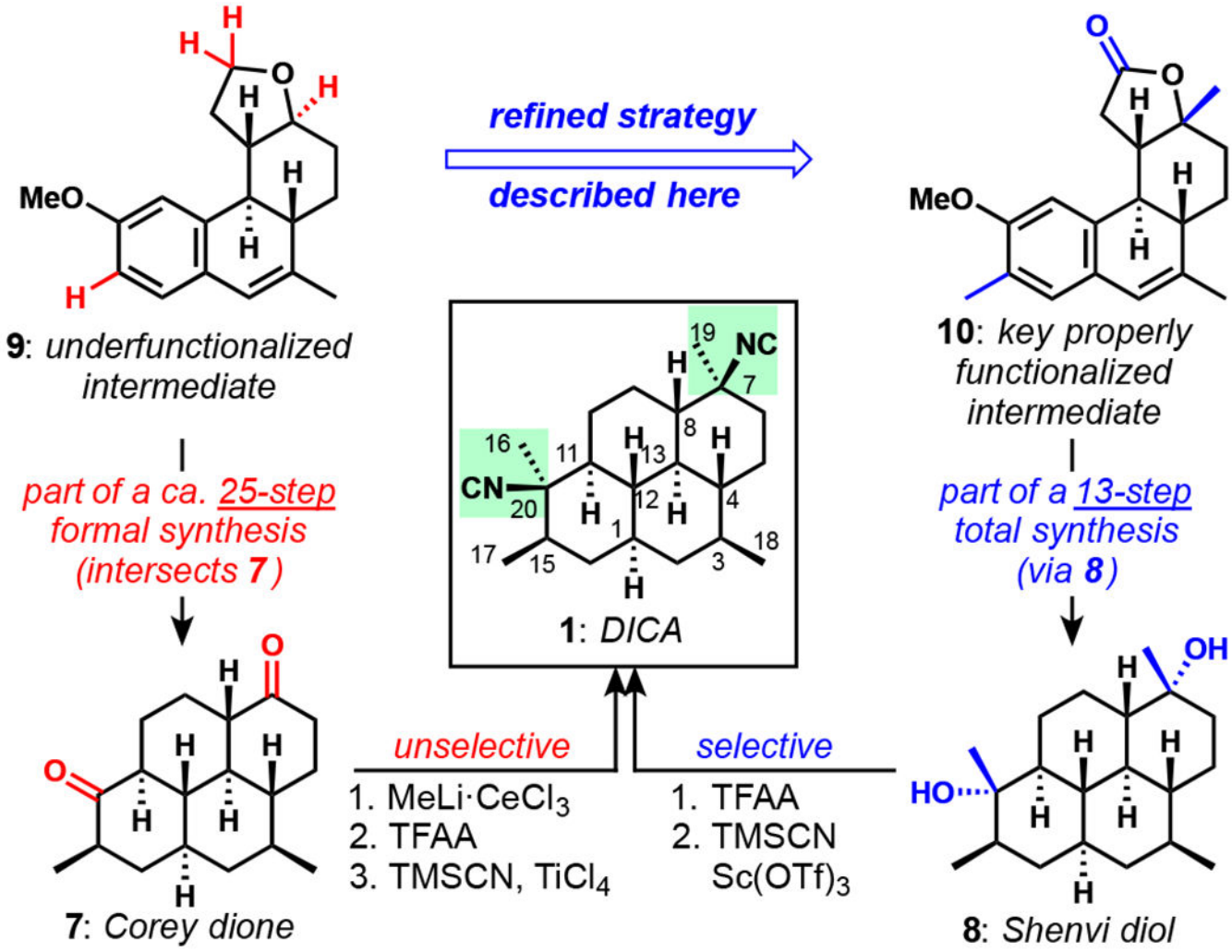
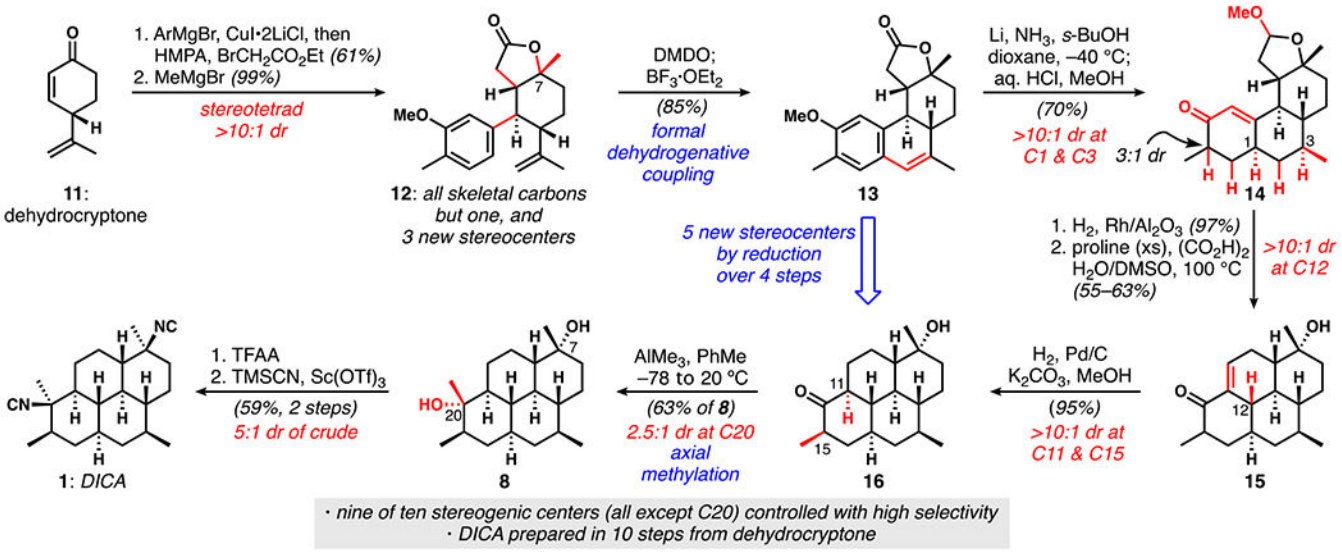


Figure 2.
The antiplasmodial activity of DICA and C20-*epi*-DICA



Scheme 1.

Our previous synthesis via intermediate **9** enabled a lengthy formal synthesis by producing the Corey dione (**7**), for which stereocontrolled conversion to DICA is not straightforward. Our improved synthesis proceeds via **10**, permitting a concise and stereocontrolled synthesis. TFAA: trifluoroacetic anhydride.



Scheme 2.

A short synthesis of DICA from dehydrocryptone. HMPA: hexamethylphosphoramide; DMDO: dimethyldioxirane; DMSO: dimethyl sulfoxide.