Isocyanoterpenes

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A Formal Enantiospecific Synthesis of 7,20-Diisocyanoadociane

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Abstract: *7,20-Diisocyanoadociane (DICA) is a potent antimalarial isocyanoterpene endowed with a fascinating tetracyclic structure composed of fused chair cyclohexanes. We report a highly stereocontrolled synthesis of a late-stage intermediate, the "Corey dione", from which DICA has been made previously. This formal synthesis features a rapid buildup of much of the complexity of the target through a sequence of enone tandem vicinal difunctionalization, Friedel–Crafts cyclodehydration, and sequential stereocontrolled reductions. Most importantly, this success establishes the broader feasibility of our previously developed general synthesis approach to the isocyanoterpene family and provides a blueprint for a very direct synthesis of DICA and related natural products.*

Potent antimalarial activity among a fascinating array of polycyclic structures, unexplained structure–activity relationships, and poorly understood mechanism(s) of action combine to elevate the importance of the isocyanoterpenes (ICTs, **1**–**4**, Figure 1) for detailed study.[1] A synthesis design that is applicable to the broad range of structures in this family would serve admirably in the development of the potential of these natural products. In that context, we report a formal enantiospecific synthesis of 7,20-diisocyanoadociane (DICA, **1**) that builds on a general approach to many ICTs that was first showcased in our recent synthesis of kalihinol B (**2**).[2]

The ICTs have been known to science since the mid-1970s;[3] however, the first indication of antimalarial activity in this family of natural products came from studies by the Angerhofer and the König groups in the 1990s[4] and, since that time, many studies on the synthesis, antimalarial activity, and mechanism of action of the ICTs have accumulated.[1] The focus of this report is synthesis, and in that respect, several prior accomplishments are particularly relevant. Corey and Magriotis reported a first synthesis of DICA in 1987 with a route of about 27 steps, with asymmetry arising from an auxiliary-controlled enolate Michael addition; however, stereocontrol in the introduction of the two isonitrile substituents was not accomplished in this inaugural synthesis.[5] Rather, tetracyclic dione **5** ("Corey dione") was subjected to double nucleophilic methylation and activation of the corresponding tertiary carbinols as trifluoroacetate esters, the displacement of which under the conditions shown was, unsurprisingly, not selective. Nearly two decades later, Fairweather and Mander reported a longer synthesis that

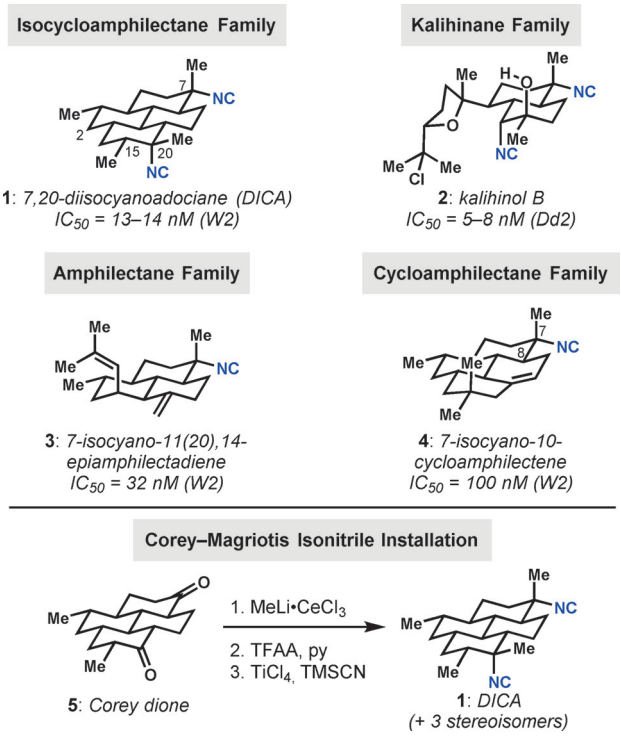

Figure 1. Potent antimalarial isocyanoterpenes and the Corey dione, a late-stage intermediate in the Corey–Magriotis synthesis of DICA. W2 and Dd2 are drug-resistant strains of *Plasmodium falciparum*, a malaria-causing parasite.

featured completely stereocontrolled introduction of the tertiary carbinolamine precursors to the C7 and C20 isonitriles by using Curtius degradation of carboxylic acid precursors.[6] In 2011, Miyaoka and co-workers disclosed a formal synthesis of DICA, reaching the Corey dione through a sequence that is strategically aligned with the Corey and Magriotis accomplishment but somewhat lengthier.[7] Piers and co-workers completed syntheses of amphilectane and cycloamphilectane ICTs with isonitriles located at ring junctions,[8] and Miyaoka and Okubo made an amphilectane natural product related to **3**.[9] Finally, the stunning 2014 synthesis of (±)-amphilectene **3** by Pronin and Shenvi in approximately 10 steps raised the bar for synthesis in this area;[10] moreover, they introduced an important tool for stereocontrolled introduction of the tertiary isonitriles, namely a largely invertive displacement of tertiary trifluoroacetates.[11]

A key element of our recent synthesis of kalihinol B (**2**) was the stereocontrolled tandem vicinal difunctionalization of cyclohexenone intermediate **6** (Figure 2), which we accessed in a direct way. The challenge of the C7-C6-C1 stereotriad was thus succinctly met through substrate-controlled selectivity. In a retrospective analysis, we recognized the potential power

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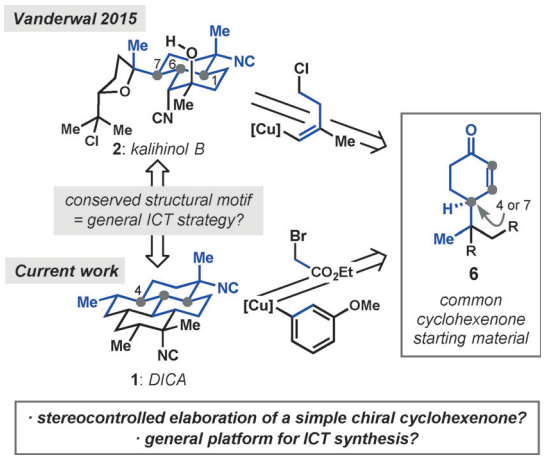
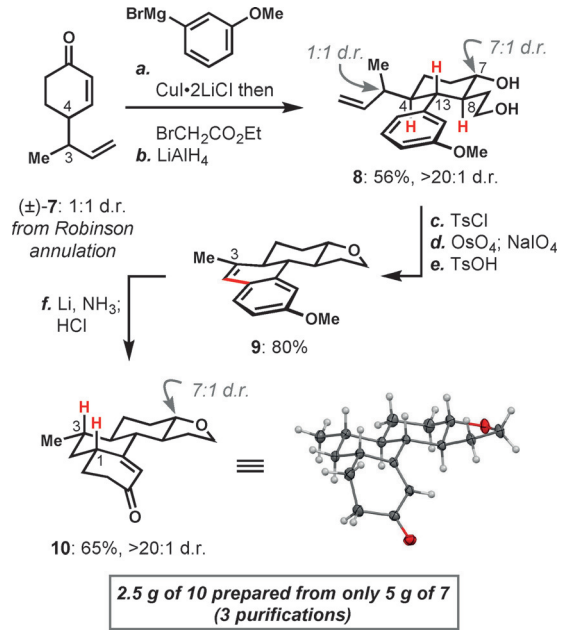


Figure 2. A potentially general synthesis plan for ICTs.

of this strategy to address a conserved structural motif among many of the ICTs. Herein, we describe our first successful foray along these lines, which led to a formal synthesis of DICA by intersection with the Corey dione (**5**, Figure 1). This accomplishment serves as a proof-of-principle for the generality of our synthesis, and it is noteworthy for the high levels of stereocontrol in accessing the all-*trans*-perhydropyrene of **5**, for the enabling use of carbonyl-based reactivity, and for the ability to telescope multiple reaction sequences. Ultimately, a highly stereoselective synthesis of the Corey dione was achieved via only ten purified intermediates from commercially available materials.

Our synthesis of the Corey dione begins with cyclohexenone (±)-**7** and is shown in Schemes 1 and 2, in which only the structures of chromatographically purified intermediates are provided; all other intermediates were used in crude form. We accessed racemic enone **7** on multigram scale from known (±)-3-methyl-4-pentenal[12] and methyl vinyl ketone, surmising that application of a chiral organocatalyst to the Michael addition step,[13] as in our kalihinol B synthesis, would render the route highly enantioselective (see below). Key to this strategy is the use of the single C4 asymmetric center (DICA numbering) in **7** to control all others in the target molecule; the center at C3 will be removed and stereoselectively reinstalled at a later stage.

The synthesis began with the vicinal difunctionalization of (±)-**7** (Scheme 1).[14] Conjugate arylation/enolate alkylation was efficient and highly diastereoselective, setting the three required stereocenters of C4, C13 and C8 as all-*trans*. Facile epimerization α to the ketone necessitated a quick reduction to diol **8** (d.r. 7:1 at the new carbinol center at C7, which is not relevant to the target). Our observations of the propensity of the diol to cyclize led us to purposefully generate the tetrahydrofuran ring as a means of internally protecting both groups; two-stage oxidative alkene cleavage and acid-mediated Friedel–Crafts-type cyclodehydration afforded dihydronaphthalene **9**, thereby erasing the configuration at C3. Birch reduction of the styrenyl system followed by acidic hydrolysis/conjugation efficiently provided enone **10** with exquisite stereocontrol at both C1 and C3, as confirmed by X-ray crystallographic analysis. Notably, this efficient and readily executed sequence provides reliable access to grams



Scheme 1. Synthesis of tetracyclic enone **10** through a Birch reduction strategy. Reagents and conditions: a) ArMgBr, cat. CuI·2LiCl, THF (−78 °C→RT) then HMPA, $BrCH_2CO_2Et$; b) $LiAlH_4$, Et_2O (0 °C→RT), 56% yield over 2 steps; c) TsCl, pyridine (40 °C); d) cat. OsO_4, NMO, aq. acetone; $NaIO_4$, aq. THF; e) cat. TsOH, Dean–Stark, toluene (reflux), 80% over 3 steps; e) Li, MeOH, NH_3, THF (−40 °C); HCl, aq. MeOH, 65%. The diastereoselectivity for each reaction is shown in the scheme. THF = tetrahydrofuran, HMPA = hexamethylphosphoramide, Ts = *para*-toluenesulfonyl.

of tetracyclic enone **10**. Cyclohexenone **10** can also be prepared as a single diastereomer through purification at separate stages;[15] however, the irrelevance of the C7 stereocenter to the target did not justify the extra effort.

Cyclohexenone **10** has features reminiscent of the A/B ring system of many steroidal systems which, when treated under dissolving-metal reduction conditions, typically afford excellent selectivity for the *trans* ring junction.[16] Likely owing to the *syn*-pentane interaction present in key reduction intermediates (Figure 3), selecting for the *trans* ring fusion proved challenging in this case (Table 1). When enone **10** was treated with Li/NH_3, the major product was *cis*- protonated **12** with 2:1 selectivity (entry 1). A screen of alkali-metal reductants and the use of *t*BuOH as a bulky proton source had little impact on the selectivity (entries 2–4). Homogeneous hydride reagents such as Karstedt's catalyst[17] and *t*BuCu/DIBAl[18] only enhanced the *cis*-selectivity (entries 5–6). Fortunately, hetereogenous reducing agents provided mixtures significantly enriched in the *trans* product (entries 7–9). A small screen of hydrogenation catalysts led

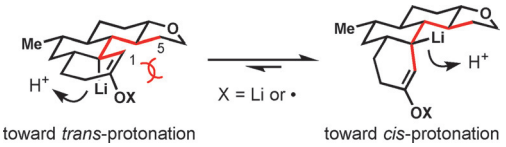
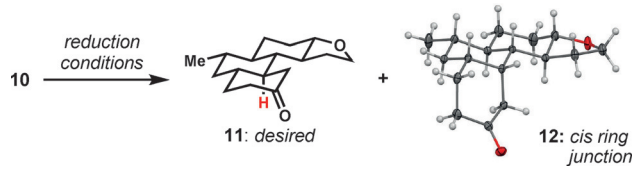


Figure 3. Comparison of protonation events to explain the preference for *cis*-reduced **12** over *trans*-reduced **11** with dissolving metals.

Table 1: Selectivity in the reduction of enone **10**.

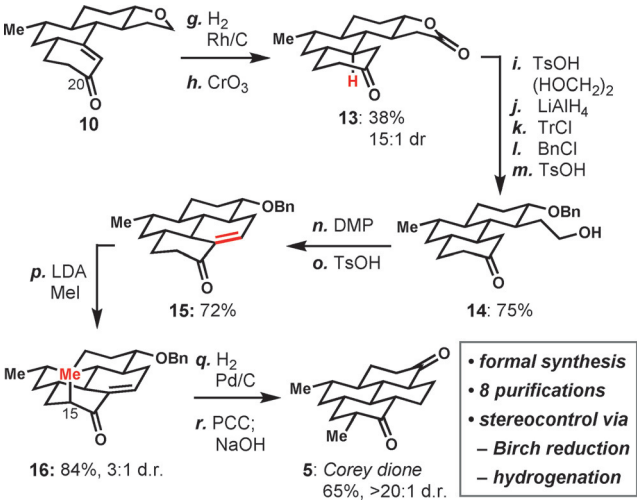


Entry	Reduction Conditions	Yield [%][a]	11/12
1	Li, NH_3, THF (−40 °C)	64	1:2
2	Na, NH_3, THF (−78 °C)	85	1:1
3	K, NH_3, THF (−78 °C)	82	1:1
4	K, *t*-BuOH, NH_3, THF (−78 °C)	80	1:3
5	Karstedt, Et_3SiH (70 °C)[b]	92	1:5
6	*t*-BuCu, DIBAl, HMPA, THF (−50 °C)	86	<1:20
7	H_2, Pd/C, EtOAc	94	6:1
8	H_2, Rh/alumina, EtOAc[c]	93	8:1
9	H_2, Rh/C, EtOAc[c]	93	15:1

[a] Yields of isolated product after column chromatography. [b] Followed by TBAF, THF. [c] i. 400–500 psi H_2 ii. PCC, Celite, CH_2Cl_2 (to reoxidize any undesired alcohol formed). Karstedt = platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex, DIBAl = diisobutylaluminum hydride, TBAF = tetrabutylammonium fluoride, PCC = pyridinium chlorochromate.

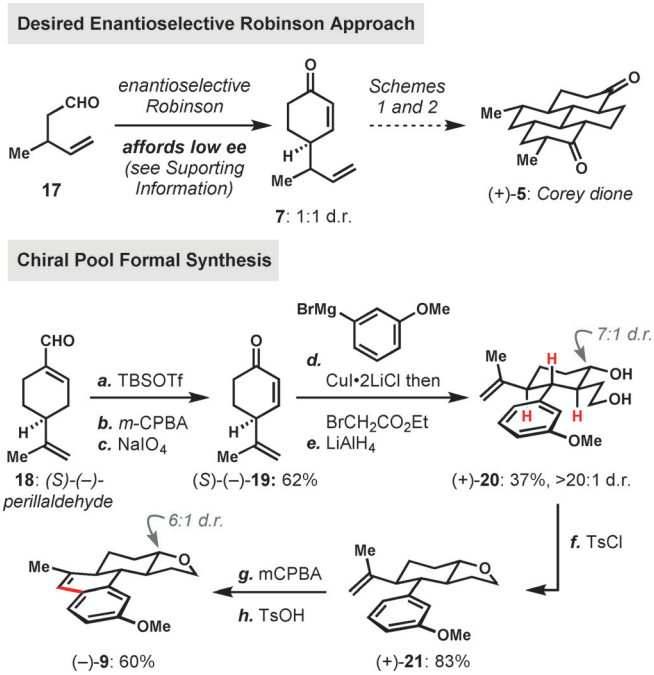
to the discovery that reductions with Rh/C were highly *trans*-selective (d.r. 15:1).

The crude *trans*-fused hydrogenation product, which contained some over-reduced C20 alcohol, was oxidized to the lactone/ketone **13** (Scheme 2).[19] The moderate yield of the oxidation accounts for virtually all of the losses in the two-stage process. This ether-to-lactone oxidation was necessitated by the failure of a planned Lewis acid mediated tetrahydrofuran ring opening that had worked on simpler model systems. This oxidation needed to be heavily optimized[15] before we arrived at the conditions shown (Fieser's reagent in $MeNO_2$), which provided **13** in 38 % yield over the two steps.[20] An overall efficient five-step sequence was carried out to open the lactone to differentiated diol **14**, the primary alcohol of which was oxidized to permit aldol condensation to close the final ring in **15**. The cross-conjugated dienolate derived from enone **15** was methylated at C15 with a moderate axial preference; after enone hydrogenation/benzyl ether hydrogenolysis and oxidation of the C7 alcohol, base-mediated equilibration afforded the Corey dione (**5**). Access to this target, which completes a formal synthesis of DICA, was achieved in a total of 18 steps from **7**,[21] but with only eight chromatographic purifications and with excellent relative stereochemical control at all eight centers of the perhydropyrene scaffold.



Scheme 2. Synthesis of the Corey dione (**5**). Reagents and conditions: g) 500 psi H_2, cat. Rh/C, EtOAc; h) CrO_3, aq. AcOH, $MeNO_2$, 38 % over 2 steps; i) cat. TsOH, ethylene glycol, Dean–Stark, benzene (reflux); j) $LiAlH_4$, THF (0 °C→RT); k) TrCl, NEt_3, cat. DMAP, DCE (70 °C); l) KH, BnCl, cat. TBAI, THF (50 °C); m) cat. TsOH, cat. PPTS, aq. acetone (70 °C), 75 % over 5 steps; n) DMP, $NaHCO_3$, CH_2Cl_2; o) cat. TsOH, Hickman still, benzene (reflux), 72 % over 2 steps; p) LDA, MeI, HMPA, THF (−78 °C→RT), 85 %; q) 900 psi H_2, cat. Pd/C, EtOAc; r) PCC, Celite, CH_2Cl_2; NaOH, MeOH (50 °C), 65 % yield over 2 steps. Tr = triphenylmethyl, DMAP = 4-dimethylaminopyridine, DCE = 1,2-dichloroethane, Bn = benzyl, TBAI = tetrabutylammonium iodide, PPTS = pyridinium *para*-toluenesulfonate, DMP = Dess–Martin periodinane, LDA = lithium diisopropylamide.

Having successfully procured the Corey dione in racemic form, we aimed to render the synthesis asymmetric. The choice of cyclohexenone **7** as a starting material was intentional to take advantage of our group's experience with the organocatalytic asymmetric Robinson annulation, which had served well in our kalihinol B synthesis.[2,13] Unfortunately, we could not uncover conditions for efficient ring-closing aldol condensations without significant erosion of enantiopurity, and an alternative entry to the asymmetric manifold was sought (Scheme 3).



Scheme 3. Chiral-pool synthesis of dihydronaphthalene (−)-**9**. Reagents and conditions: a) TBSOTf, NEt_3, CH_2Cl_2 (0 °C); b) *m*-CPBA, aq. $NaHCO_3$, Et_2O; c) $NaIO_4$, aq. HF, MeCN, 62 % over 3 steps; d) ArMgBr, cat. CuI·2 LiCl, THF (−78 °C→RT) then HMPA, $BrCH_2CO_2Et$; e) $LiAlH_4$, Et_2O (0 °C→RT), 37 % yield over 2 steps; f) TsCl, pyridine (40 °C), 83 %; g) *m*CPBA, $NaHCO_3$, CH_2Cl_2; h) cat. TsOH, Hickman still, benzene (reflux), 60 % yield over 2 steps. TBSOTf = tert-butyldimethylsilyl triflate, *m*CPBA = *meta*-chloroperoxybenzoic acid.

Inspiration for a new starting point came from analysis of the synthesis in hand. While the preparation of dihydronaphthalene **9** requires oxidative cleavage of an alkene precursor to generate an aldehyde for Friedel–Crafts cyclodehydration, the intermediate aldehyde could instead arise from a dehomologated alkene via net oxidation. This insight identified the known cyclohexenone (−)-**19**, which is available in enantiopure form,[22] as an attractive chiral-pool starting material. Conversion of the inexpensive terpene (−)-perillaldehyde into cyclohexenone (−)-**19** on a gram scale has been previously reported;[22b] however, to improve throughput, we found that purification by distillation was preferable (Scheme 3). In an unoptimized sequence, conjugate addition and alkylation selectively installed the three stereogenic centers with desired diastereoselectivity as seen in (+)-**20**, in a similar manner as we previously showed to make **8**. Condensation of diol (+)-**20** via the tosylate furnished *trans*-fused tetrahydrofuran (+)-**21**. Alkene epoxidation is followed by heating at reflux with acid, which presumably triggered epoxide rearrangement to the aldehyde followed by in situ cyclodehydration to dihydronaphthalene (−)-**9**. This sequence intersects our racemic synthesis of DICA (Schemes 1 and 2), thereby permitting access to all later intermediates in enantiopure form. Because of our desire to improve several aspects of the overall synthesis, we elected not to revisit our formal DICA synthesis using this optically active material, though it is clear that this chiral-pool approach is suitable for doing so with respect both to control of absolute configuration and material throughput. In its current form, this route ends up at 21 steps from perillaldehyde with only 10 purifications.

Our formal synthesis of DICA that intersects with the Corey dione features the highly diastereoselective introduction of the eight stereogenic centers of this perhydropyrene intermediate. A shift in strategy away from poorly enantioselective Robinson annulation toward the adoption of a chiral-pool starting material assures the production of enantiopure material through an enantiospecific route.[23] As we move toward an improved complete synthesis of DICA, the challenges that remain include differentiating the C7 and C20 carbonyl groups so that the salient isonitriles can be installed with stereochemical control, and further streamlining the route by obviating some of the less attractive functional-group interconversions and protecting-group manipulations. These issues notwithstanding, with this work we have clearly demonstrated that our strategy beginning with chiral cyclohexenones is applicable not just to the kalihinanes, but also more broadly within the ICT family.

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