A Formal Enantiospecific Synthesis of 7,20-Diisocyanoadociane

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Abstract: 7,20-Diisocyanoadociane (DICA) is a potent antimalarial isocyanoterpenic 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 isocyanoterpenes 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 missions (s) of action combine to elevate the importance of the isocyanoterpenes (ICTs, 1–4, Figure 1) for detailed study. 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 Angererhofer 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.[5] 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.[6] Rather, tetracyclic dione 5 (“Corey dione”) was subjected to double nucleophilic methylation and activation of the corresponding tertiary carbinols as trifluoracetate 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 featured completely stereocontrolled introduction of the tertiary carbamolamine precursors to the C7 and C20 isonitriles by using Curtius degradation of carboxylic acid precursors.[7] In 2011, Miyaoaka 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.[8] Piers and co-workers completed syntheses of amphilectane and cycloamphilectane ICTs with isonitriles located at ring junctions,[9] and Miyaoaka and Okubo made an amphilectane natural product related to 3.[10] Finally, the stunning 2014 synthesis of (±)-amphilectene 3 by Pronin and Shenvi in approximately 10 steps raised the bar for synthesis in this area.[11] Moreover, they introduced an important tool for stereocontrolled introduction of the tertiary isonitriles, namely a largely invertive displacement of tertiary trifluoracetates.[12]

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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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 interaction 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 tetrahydropyran ring as a means of internally protecting both groups; two-stage oxidative alkene cleavage and acid-mediated Friedel–Crafts-type cyclodehydration afforded dihydroxynaphthalene 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 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/NH₃, the major product was cis-protonated 12 with 2:1 selectivity (entry 1). A screen of alkali-metal reductants and the use of tBuOH as a bulky proton source had little impact on the selectivity (entries 2–4). Homogeneous hydride reagents such as Karstedt’s catalyst[17] and tBuCu/DIBAL[18] only enhanced the cis-selectivity (entries 5–6). Fortunately, heterogeneous reducing agents provided mixtures significantly enriched in the trans product (entries 7–9). A small screen of hydrogenation catalysts led

Figure 2. A potentially general synthesis plan for ICTs.

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, BrCH₂CO₂Et; b) LiAlH₄, Et₂O (0°C−RT), 56% yield over 2 steps; c) TsCl, pyridine (40°C); d) cat. OsO₄, NMO, aq. acetone; NaIO₄, aq. THF; e) cat. TsOH, Dean–Stark, toluene (reflux), 80% over 3 steps; f) Li, MeOH, NH₃, THF (−40°C); HCl, aq. MeOH, 65%. The diastereoselectivity for each reaction is shown in the scheme. THF = tetrahydrofuran, HMPA = hexamethylphosphoramide, Ts = para-toluensulfonyl.

Figure 3. Comparison of protonation events to explain the preference for cis-reduced 12 over trans-reduced 11 with dissolving metals.
An overall efficient five-step sequence was sought (Scheme 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reduction Conditions</th>
<th>Yield [%]</th>
<th>11/12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Li, NH₄, THF (−40°C)</td>
<td>64</td>
<td>1:2</td>
</tr>
<tr>
<td>2</td>
<td>Na, NH₄, THF (−78°C)</td>
<td>85</td>
<td>1:1</td>
</tr>
<tr>
<td>3</td>
<td>K, NH₄, THF (−78°C)</td>
<td>82</td>
<td>1:1</td>
</tr>
<tr>
<td>4</td>
<td>K, rBuONa, NH₄, THF (−78°C)</td>
<td>80</td>
<td>1:3</td>
</tr>
<tr>
<td>5</td>
<td>K, Dess–Martin (70°C)</td>
<td>92</td>
<td>1:5</td>
</tr>
<tr>
<td>6</td>
<td>t-BuCu, DIBAI, HMPA, THF (−50°C)</td>
<td>86</td>
<td>&lt;1:20</td>
</tr>
<tr>
<td>7</td>
<td>H₂, Pd/C, EtOAc</td>
<td>94</td>
<td>6:1</td>
</tr>
<tr>
<td>8</td>
<td>H₂, Rh/alumina, EtOAc</td>
<td>93</td>
<td>8:1</td>
</tr>
<tr>
<td>9</td>
<td>H₂, Rh/C, EtOAc</td>
<td>93</td>
<td>13:1</td>
</tr>
</tbody>
</table>

[a] Yields of isolated product after column chromatography. [b] Followed by TBAF, THF. [c] i. 400–500 psi H₂; ii. PCC, Celite, CH₂Cl₂ (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.

The crude trans-fused hydrogenation product, which contained some over-reduced C20 alcohol, was oxidized to the lactone/ketone 13 (Scheme 2). 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 before we arrived at the conditions shown (Fieser’s reagent in MeONO₂), which provided 13 in 38% yield over the two steps. 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 methyalted 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, but with only eight chromatographic purifications and with excellent relative stereochemical control at all eight centers of the perhydropyrene scaffold.

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. Unfortunately, we could not uncover conditions for efficient ring-closing aldol condensations without significant erosion of enantio purity, and an alternative entry to the asymmetric manifold was sought (Scheme 3).

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

**Scheme 2.** Synthesis of the Corey dione (5). Reagents and conditions:
- g) 500 psi H₂, cat. Rh/C, EtOAc; h) CrO₃, aq. AcOH, MeNO₂, 38% over 2 steps; i) cat. TsOH, ethylene glycol, Dean–Stark, benzene (reflux); j) LIAH₄, THF (0°C → RT); k) TlCl, N₂, 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, NaHCO₃, CH₂Cl₂; o) cat. TsOH, Hickman still, benzene (reflux), 72% over 2 steps; p) LDA, Me₃SiCl, HMPA, THF (−78°C → RT), 85%; q) 900 psi H₂, cat. Pd/C, EtOAc; r) PCC, Celite, CH₂Cl₂, NaHCO₃, 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.

**Scheme 3.** Chiral-pool synthesis of dihydronaphthalene (−). Reagents and conditions: a) TBSOTf, NEt₃, CH₂Cl₂ (0°C); b) m-CPBA, aq. NaHCO₃, Et₂O; c) NaIO₄, aq. HF, MeCN, 62% over 3 steps; d) ArMgBr, cat. C₂Cl₂O, THF (−78°C → RT) then HMPA, Br₂, CH₂CO₂Et; e) Li₂H₂P₃, Et₂O (0°C → RT), 37% yield over 2 steps; f) TsCl, pyridine (40°C), 83%; g) mCPBA, NaHCO₃, CH₂Cl₂; 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 dehydrogenated alkene via net oxidation. This insight identified the known cyclohexenone (→)–19, which is available in enantio-pure 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 tetrahydronaphthalenone (→)–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 perhydropropirole intermediate. A shift in strategy away from poorly enantioselective Robinson annulation toward the adoption of a chiral-pool starting material assures the production of enantio-pure 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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[12] 3-Methyl-4-pentenal has been prepared many times, and we used elements of several known preparations. See the the Supporting Information for details.
[15] Please see the Supporting Information for more details.
[21] Cyclohexenone 7 was made in three steps with two purifications, each by distillation. See the the Supporting Information for details.
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