

A Formal Total Synthesis of the Marine Diterpenoid Diisocyanoadociane

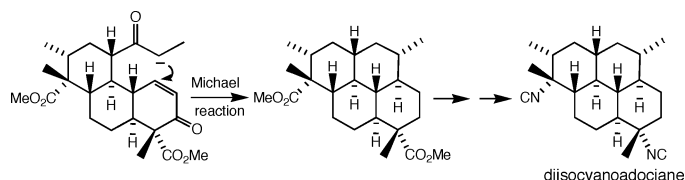
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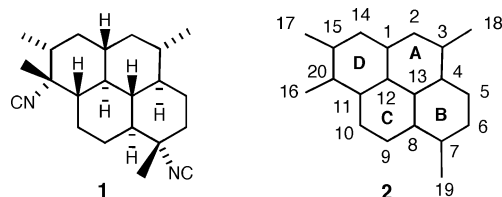
ABSTRACT



A formal total synthesis of diisocyanoadociane, a marine diterpenoid with potent antimalarial properties, has been completed. The synthesis begins with a phenanthrenoid precursor that is transformed into a pyrene-derived intermediate by means of an intramolecular Michael reaction. Nitrogen functionality is introduced via a double Curtius reaction.

Numerous diterpenes based on a wide range of carbon skeletons possessing one or more isonitrile substituents have been isolated from marine sponges.¹ Many have been shown to have significant in vitro anti-malarial activity with the most potent being diisocyanoadociane (**1**), isolated originally from an *Amphimedon* species² and subsequently from *Cymbastela hooperi*.³ The combination of biological activity⁴ with the unusual pyrene-based structure **2** has aroused the interest of synthetic chemists, and an elegant enantioselective synthesis (60% ee) based on sequential Diels–Alder cycloadditions has been reported by Corey and Magriotis.⁵ In the final stages of their synthesis, however, the isonitrile groups were introduced without diastereochemical control. This intriguing molecule had also captured our attention, and we now disclose an alternative formal synthesis of (±)-**1** in which all 10 stereogenic centers have been introduced with complete diastereoselectivity.⁶ An outline of our strategy is

provided in Scheme 1 and begins with the proposed construction of the phenanthrene derived structure **3** as illustrated.⁷



Thus, Birch reductive alkylation, then Lewis acid induced cyclization, following earlier precedents, could be expected to furnish **3** in good yield.⁸ We envisaged completion of the pyrene structure by means of the intramolecular Michael reaction **7** → **8**, and in anticipation of this step we hoped to introduce a propionyl side chain into **3** by means of a

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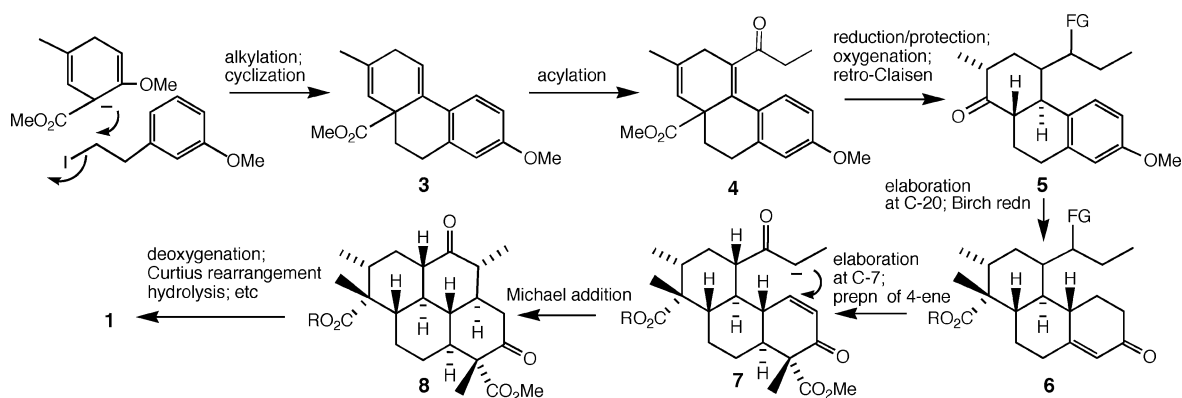
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Scheme 1



Friedel–Crafts-type acylation of the styrene double bond. To maintain stereochemical control in the introduction of the isonitrile groups, we planned to establish the quaternary centers at C-7 and C-20 by stereochemically controlled α -methylation of methoxycarbonyl or formyl substituents at these loci and then apply the Curtius rearrangement to the corresponding acyl azides.⁹ As illustrated in Figure 1, we

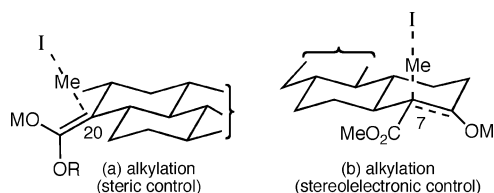


Figure 1. Stereocontrolled elaboration of the C-7 and C-20 quaternary centers.

expected simple alkylation at C-20 to proceed along the equatorial vector (steric control), whereas to achieve “axial” alkylation at C-7, we anticipated that the involvement of the C-6 carbonyl group (stereoelectronic control) would be necessary.¹⁰

Elaboration of these two centers would necessarily be under kinetic control, as would be the stereochemistry at C-8 following Li/NH_3 reduction of enone **6**. The remaining stereogenic centers, however, should be subjected to thermodynamic control by virtue of their relationship to carbonyl groups at C-2, C-6, and C-20, respectively, at the appropriate stage of the sequence.

The first stage of the synthesis is outlined in Scheme 2. Thus, Birch reduction of methyl 2-methoxy-5-methylbenzoate with lithium and in situ alkylation followed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -induced cyclization afforded **3** in good yield. Then, AlCl_3 -catalyzed acylation of the styrene alkene bond with propionyl chloride afforded **4**, provided that this last reaction

was carried out at -78°C ; at higher temperatures, the newly formed carbonyl function underwent intramolecular cyclization onto the aromatic ring B. To reduce the styrene bond, **4** was submitted to reduction by lithium in liquid ammonia, affording hydroxy ketone **9**, a somewhat surprising result given the absence of a proton source (other than ammonia). The all-cis structure was provisionally assigned as indicated from extensive NMR studies and is consistent with subsequent analyses. After masking the hydroxyl as a MOM ether, the carbonyl function was reduced (LiAlH_4) to give an epimerically pure alcohol of unspecified configuration that was protected as the benzoate **10**. Hydroboration proved to be unsatisfactory for the introduction of oxygen at C-20, so we examined epoxidation with a view to subsequent rearrangement to the 20-one. When the MOM group was found to interfere with epoxidation, it was replaced by acetate, and then the reaction proceeded smoothly to afford **11** as a mixture of epimers. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -induced rearrangement then gave **12**, again as a mixture of diastereomers. However, subsequent base-catalyzed hydrolysis of the acetate function with concomitant loss of the superfluous angular substituent (retro-aldol as planned) led to a single diastereomer, presumed to be **13** in the expectation that the product would possess the more stable trans-fused ring system with the 16-methyl group equatorial. To elaborate the quaternary center at C-20, a Wittig reaction was carried out with methoxymethylenetriphenyl phosphorane, followed by hydrolysis to aldehyde **15**. C-Methylation of the aldehyde was unsuccessful, however, and so we abandoned the original strategy (Figure 1a) and submitted the enol ether **14** to a modified Simmons–Smith methylenation.¹¹ The resulting cyclopropane derivative **16** was then treated with acid at reflux to give the desired aldehyde **17**.¹² NMR analysis again established the stereochemical relationships between the substituents on ring-D, the most salient feature of which was the cis relationship between the formyl group and H-12 as established by NOE difference spectra. It was thus established that methylenation had taken place on the more exposed exo face, leading to the desired diastereomer.

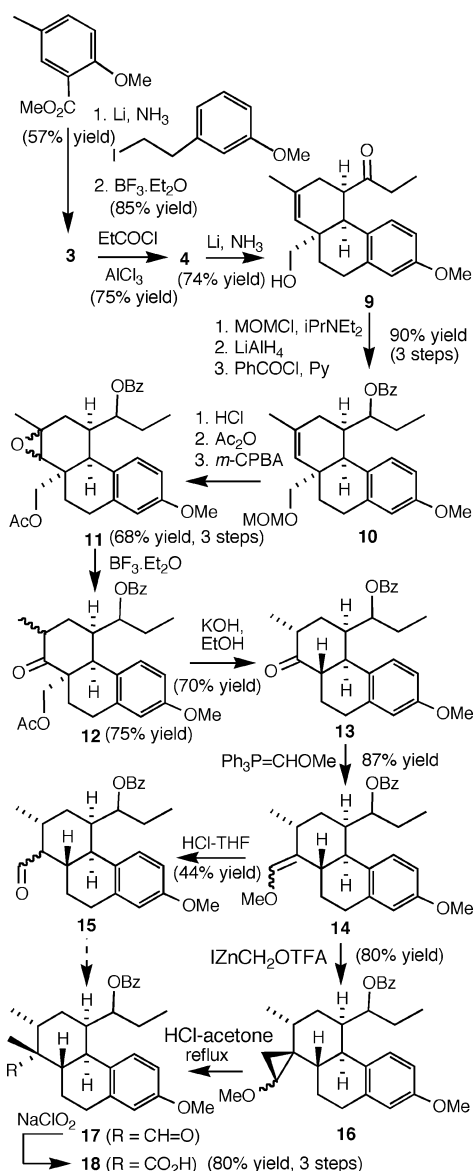
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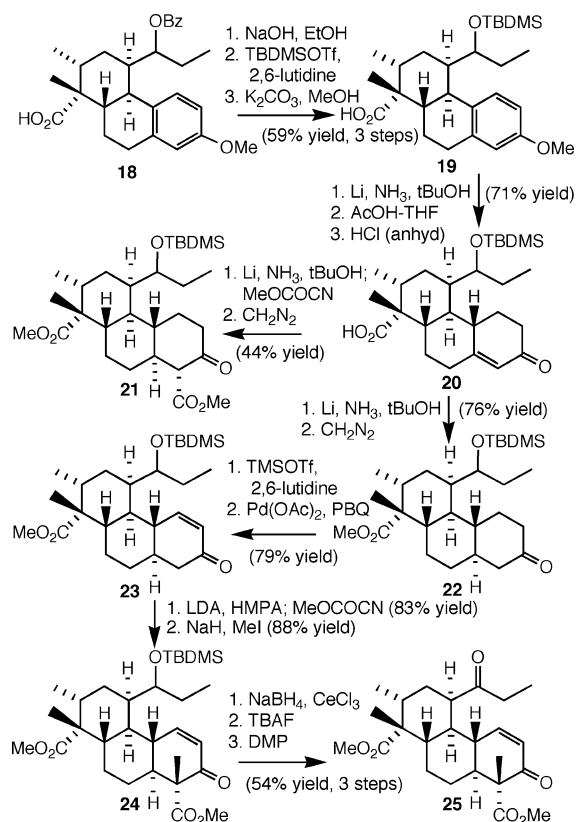
Scheme 2



The next stage of the synthesis, as outlined in Scheme 3, involved extensive functional group manipulation, including repeated lithium in ammonia reductions and establishment of the second quaternary center at C-7. Thus, aldehyde **17** was oxidized to acid **18** (NaClO_2 , 80% yield from **14**)¹³ and the benzoate group replaced with a TBDMS function, following which, Birch reduction and hydrolysis in acetic acid of the dihydroanisole product afforded the expected β,γ -unsaturated enone which could be isomerized by anhydrous HCl in THF to enone **20**. A second lithium/ammonia reduction with trapping of the resulting lithium enolate by methyl cyanofornate¹⁴ afforded a modest yield of the β -keto ester **21**, but C-methylation of this intermediate using a variety of bases gave none of the desired product.

Alternatively, enone **20** was simply reduced with Li/NH_3 to **22** and the isomeric enone **23** prepared using the Saegusa

Scheme 3



procedure.¹⁵ Subsequent acylation with methyl cyanofornate,¹⁶ followed by C-methylation, then proceeded in excellent yield to afford **24**. From model studies, we expected that removal of the TBDMS group with TBAF would almost certainly result in cyclization of the liberated hydroxyl onto the enone function. The enone was therefore reduced with $\text{NaBH}_4/\text{CeCl}_3$ ¹⁷ prior to deprotection. After desilylation, a double oxidation with the Dess–Martin periodinane¹⁸ afforded dione **25** in preparation for the pivotal Michael reaction (Scheme 4).

An inspection of molecular models indicated that the Michael reaction was unlikely to take place with **25** since it would require the D-ring to adopt a boat conformation to bring the participating functions within bonding distance, and even then orbital overlap between the reacting centers would be poor. It appeared that an α -configured side chain could assume the necessary geometry, however. When treatment of **25** with a variety of bases returned starting material, it seemed that the axially oriented side chain was more stable in the β -configuration, despite its axial nature. Nevertheless, one could expect there to be a sufficient amount of the α -epimer in equilibrium to undergo the desired cyclization. After extensive experimentation, it was found that heating a solution of **25** in ethanediol and triethylamine for 4 days at 70 °C effected cyclization, conditions that were selected in

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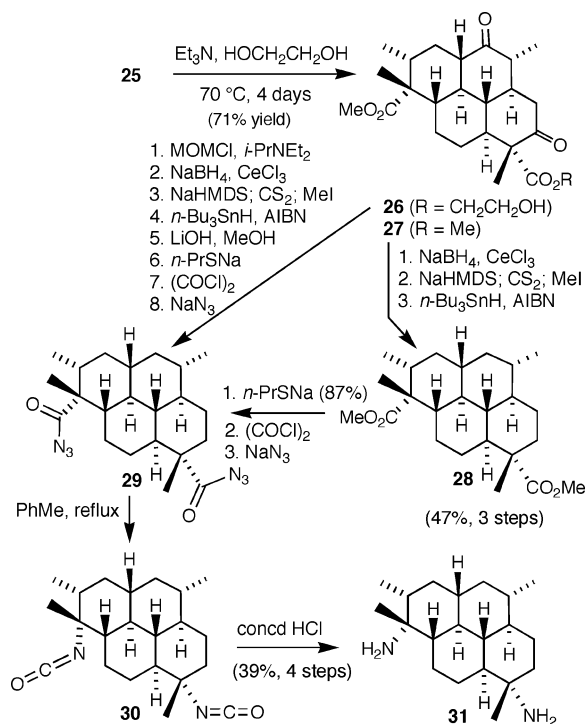
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Scheme 4



view of those reported by Corey et al. for a difficult intramolecular Michael reaction during the synthesis of longifolene.¹⁹ No other solvent was effective, and unfortunately, trans-esterification of the 7-ester function with the glycol had occurred, resulting in a 4:3 mixture of **26** and **27**, complicating subsequent manipulations. After confirming the structure of the latter compound by single-crystal X-ray analysis,²⁰ the diketone was converted into the deoxy derivative **28** by applying the Barton–McCombie deoxygenation procedure to the dixanthate derived from the 2,6-diol.²¹ After protecting **26** as the MOM ether, this product was similarly deoxygenated. Demethylation of both ester

groups in **28** was effected with sodium propanethiolate,²² while the deoxygenated ester from **26** was treated with lithium hydroxide to hydrolyze the C-7 ester function before liberating the C-20 carboxyl with propanethiolate. Preparation of the diacyl chloride and thence the diacyl azide **29** proceeded smoothly, as did the Curtius rearrangement to **30**, which was effected by heating in toluene at reflux.²³ Hydrolysis in concd HCl then afforded diamine **31**, which gave identical mass spectra as well as ^1H and ^{13}C NMR spectra (measured on the TFA salts) to those obtained from an authentic sample obtained by hydrolysis of **1**. Since **31** has been reconstituted to **1**,²⁴ the formal total synthesis of diisocyanoadociene (**1**) is complete. While all 10 stereogenic centers have been introduced with the correct relative stereochemistry, we have yet to address the question of enantioselectivity. However, the initial Birch reductive alkylation, if carried out on an appropriate chiral benzamide,²⁵ should resolve this remaining stereochemical issue.

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Supporting Information Available: Experimental details and copies of selected ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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