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A Formal Synthesis of Antimalarial Diterpenoid 7,20-Diisocyanoadociane

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A formal synthesis of antimalarial diterpenoid 7,20-diisocyanoadociane, isolated from marine sponge *Adocia* sp., was achieved. The authors synthesized Corey's synthetic intermediate **2** for 7,20-diisocyanoadociane. This synthesis involves the synthesis of a perhydropyrene derivative using a sequential isomerization–intramolecular Diels–Alder reaction as the key step.

7,20-Diisocyanoadociane (**1**) is a marine diterpenoid isolated from a marine sponge of the genus *Adocia* collected in Australia, on the Great Barrier Reef.[1] 7,20-Diisocyanoadociane (**1**) has a unique all-*trans*-perhydropyrene ring system (Figure 1). The relative configuration of **1** was demonstrated by single-crystal X-ray analysis[1] and the absolute configuration of **1** was determined by its total synthesis by Corey.[2] 7,20-Diisocyanoadociane strongly inhibits proliferation of the malaria parasite *Plasmodium falciparum*.[3–5] The biological activity and unique structural features prompted the synthetic chemists to undertake its preparation.[6] Total synthesis of **1** using the intramolecular Diels–Alder reaction by Corey[2] and formal synthesis of **1** using the intramolecular Michael reaction by Mander[7] have been reported. The authors achieved the synthesis of Corey's synthetic intermediate **2** via the construction of all-*trans*-perhydropyrene derivative by the sequential isomerization–intramolecular Diels–Alder reaction as the key step.

cis-Decalin **11** was synthesized from (*S*)-4-methyltetrahydro-2*H*-pyran-2-one (**3**)[8] (Scheme 1). Lactone **3** was treated with LDA in the presence of HMPA followed by allyl bromide to give *trans*-lactone **4** as a sole product in 79% yield. Lactone **4** was reduced to the hemiacetal with DIBAH and treatment with benzyl alcohol and *p*-TsOH gave benzyl acetal **5** as a diastereomeric mixture (3:2). Hydroboration–oxidation of the terminal olefin in **5** provided the primary alcohol, and protection of the hydroxy group as a TBS ether afforded TBS ether **6**. Following deprotection of the benzyl acetal in **6** by hydrogenolysis, the resulting hemiacetal was treated with allylmagnesium bromide to afford diol **7** as a diastereomeric mixture (5:3). The hemiacetal did not react with the Wittig reagent or Horner–Wadsworth–Emmons reagent, the hemiacetal was recovered. The primary hydroxy group in diol **7** was protected as a Tr ether and the secondary hydroxy group was converted to tosylate **8**. Treatment of tosylate **8** with NaH in DMSO resulted in elimination of tosylate to give (*E*)-diene and deprotection of TBS with TBAF gave alcohol **9**. Oxidation of alcohol **9** with IBX gave the aldehyde and subsequent vinylation with vinylmagnesium chloride afforded allylic alcohol **10**. Allylic alcohol **10** was oxidized with IBX in DMSO via the spontaneous *endo*-selective intramolecular Diels–Alder reaction of the generated enone to afford *cis*-decalin **11** as a sole product in 74% yield.[9]

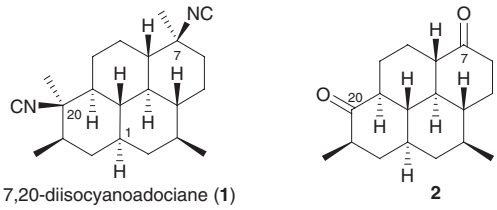
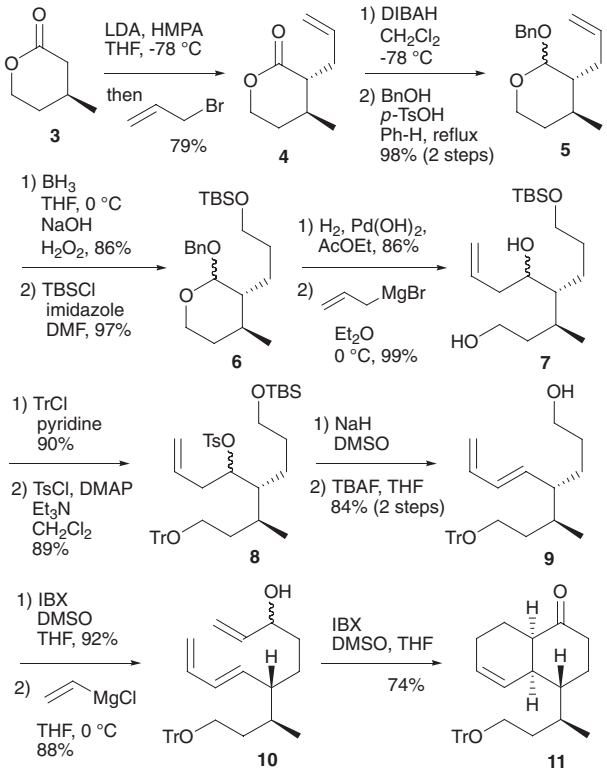
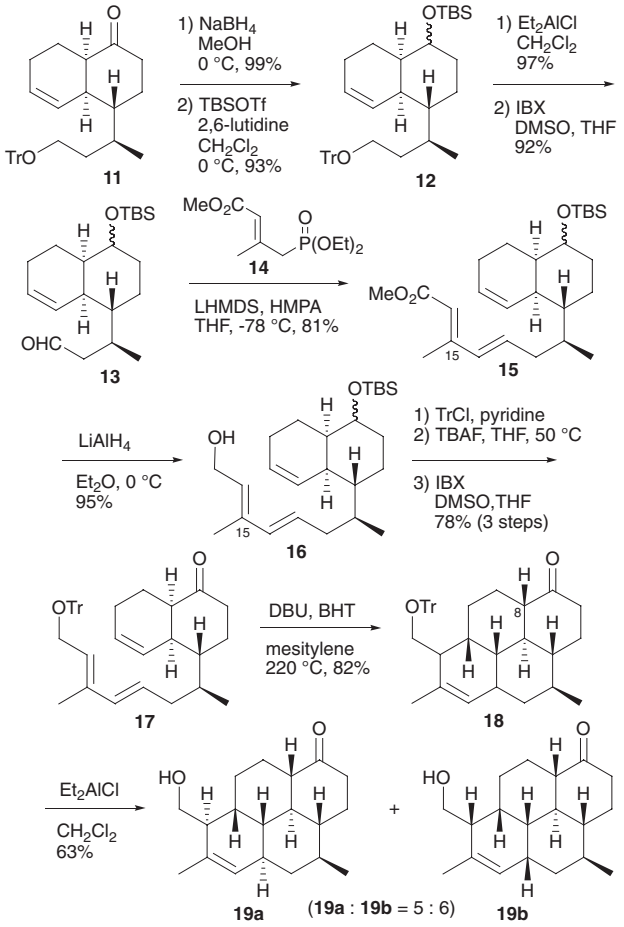


Figure 1. Structures of 7,20-diisocyanoadociane (**1**) and Corey's synthetic intermediate **2**.



Scheme 1. Synthesis of *cis*-decalin **11**.

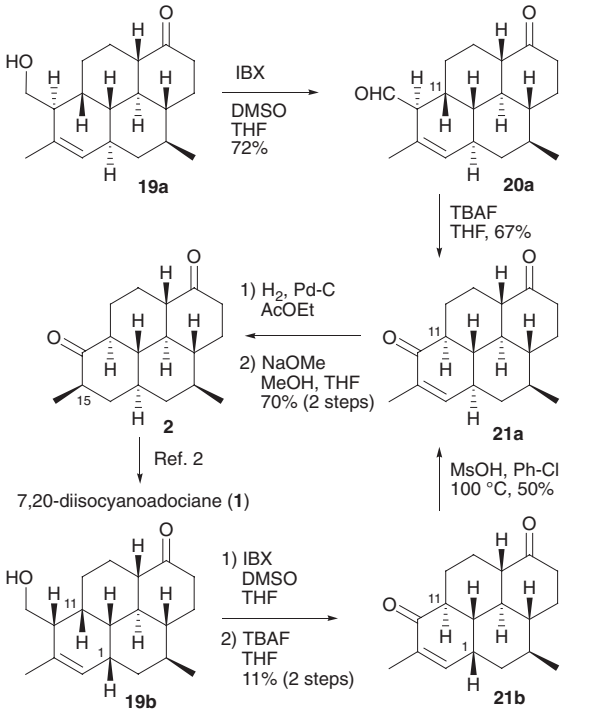
Construction of the perhydropyrene skeleton was performed by a sequential isomerization–intramolecular Diels–Alder reaction (Scheme 2). The ketone in *cis*-decalin **11** was reduced with $NaBH_4$ and the resulting secondary hydroxy group was protected to give TBS ether **12** as a diastereomeric mixture. The Tr group in **12** was deprotected by treatment with Et_2AlCl to give the primary alcohol, which was then oxidized with IBX to afford aldehyde **13**. Aldehyde **13** was treated with the Horner–Wadsworth–Emmons reagent **14**[10] and LHMDS in the presence of HMPA to give (*E*,*E*)-$\alpha,\beta,\gamma,\delta$-unsaturated ester **15** in 81% yield (*E*,*E*:*E*,*Z* = 21:1). Unsaturated ester **15** was reduced with



Scheme 2. Synthesis of perhydropyrene derivative **19**.

$LiAlH_4$ to allylic alcohol **16**, whose hydroxy group was protected as a Tr ether. The TBS group was removed by treatment with TBAF and the resulting secondary alcohol was oxidized with IBX to give ketone **17**. Ketone **17** is a substrate of the sequential isomerization–intramolecular Diels–Alder reaction as the key step. When ketone **17** was heated in the presence of DBU and BHT in mesitylene at 220 °C, an intramolecular Diels–Alder reaction following isomerization at C-8 occurred to afford a diastereomeric mixture of perhydropyrene derivative **18** (*exo*:*endo* = 5:6) in 82% yield. This sequential reaction did not occur in the absence of DBU. This is the first example of a sequential isomerization–intramolecular Diels–Alder reaction in the presence of a base. Since chromatographic separation of the *exo*/*endo* mixture of **18** was difficult, the mixture was subjected to deprotection of the Tr group by treatment with Et_2AlCl which then allowed for chromatographic separation to provide *exo*-adduct **19a** and *endo*-adduct **19b** (**19a**:**19b** = 5:6), respectively.

Corey's synthetic intermediate was synthesized from perhydropyrene derivatives **19a** and **19b** (Scheme 3). Alcohol **19a** was oxidized by IBX to give aldehyde **20a**, which was then deformylated[11] and isomerized at C-11 by treatment with TBAF to afford diketone **21a**. On the other hand, conversion of alcohol **19b** to enone **21a** via isomerization at C-1 was examined. Alcohol **19b** was converted to diketone **21b** by similar methods via the aldehyde. Isomerization of C-1 in diketone **21b** was



Scheme 3. Formal synthesis of 7,20-diisocyanoadociane.

achived by treatment with methanesulfonic acid (MsOH) in chlorobenzene at 100 °C to give diketone **21a** as a major product (**21a**:**21b** = 25:4) in 50% yield. Diketone **21a** was hydrogenated and isomerized at C-15 to afford all-*trans*-perhydropyrene derivative **2**, which was Corey's synthetic intermediate.[2] Spectral data and sign of the optical rotation of synthetic **2**, $[\alpha]_D^{25}$ +13.0 (*c* 0.91, $CHCl_3$), were identical with those of Corey's intermediate, $[\alpha]_D^{23}$ +7.5 (*c* 2.5, $CHCl_3$), ca. 60% ee.[2] Therefore the formal synthesis of 7,20-diisocyanoadociane was achieved.[12]

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12 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

