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COMMUNICATION

Total synthesis of cyanolide A†

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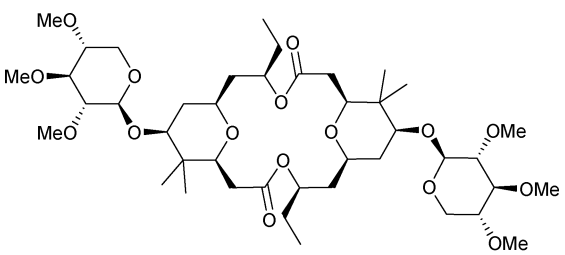
The total synthesis of cyanolide A has been achieved in 14 steps from commercially available (*S*)-2-ethyloxirane, exploiting the palladium-catalyzed intramolecular alkoxycarbonylation as the key step to construct the tetrasubstituted *cis*-tetrahydropyran ring with high stereoselectivity.

Cyanolide A (**1**) (Fig. 1), a new and highly potent molluscicidal agent against the snail vector *Biomphalaria glabrata* (LC50 = 1.2 μM), was isolated from extracts of a Papua New Guinea collection of *Lyngbya bouilloni* by Gerwick and co-workers in 2010.[1] Schistosomiasis, a disease caused by parasitic worms, is most commonly found in Asia, Africa, and South America, especially in areas where the water contains numerous freshwater snails, which may carry the parasite.[2] Although it has a low mortality rate, schistosomiasis continues to be one of the most prevalent parasitic infections worldwide, with an estimated 207 million people currently infected and 779 million people at risk of infection.[3,4] A major problem in controlling schistosomiasis infection, however, is the complex lifecycle of the worm. The helminths require both an aquatic snail host and a mammalian host to complete their reproductive cycle. Niclosamide (Bayluscide, LC100 = 4.6 μM) is the most widely used molluscicide available, effectively killing snails at all stages of the lifecycle.[5,6,7]



Cyanolide A (**1**)

Fig. 1 Structure of cyanolide A (**1**).

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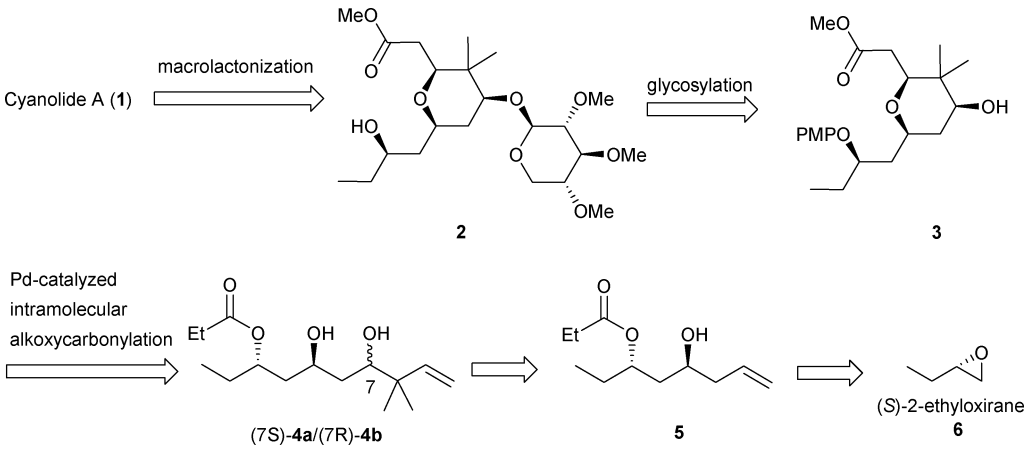
However, its high price, poor water solubility, and potential toxicity toward fish are considered major drawbacks.[8] Up to now, not any molluscicides have been proved effective enough to replace niclosamide.[6,9,10]

Cyanolide A (**1**), a glycosidic macrolide consisting of a 16-membered macrocycle, owns a C_2 symmetric structure. The interesting structure and highly potent biological activity against the snail vector *Biomphalaria glabrata* have attracted considerable interest in the synthetic community. Recently, Hong and co-workers have disclosed the first total synthesis of **1** using a tandem allylic oxidation/oxa-Michael reaction strategy to assemble the tetrahydropyran ring.[11]

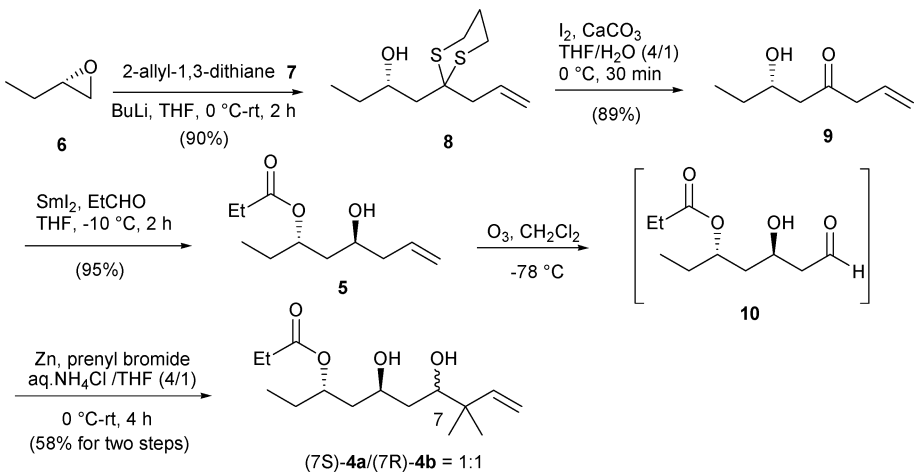
Our retrosynthetic analysis was illustrated in Scheme 1. We envisioned that **1** would be accessible by dimerization of its monomer **2**, which itself might be generated *via* glycosylation of alcohol **3**. Critically, we anticipated that *cis*-tetrahydropyran ring structure could be obtained by means of palladium-catalyzed intramolecular alkoxycarbonylation of diol **4a** or **4b**, which would be derived from ester **5**. For ester **5**, it could be easily prepared from commercially available (*S*)-2-ethyloxirane (**6**) *via* SmI_2-promoted Evans-Tishchenko reduction.

An efficient synthesis of diols **4a** and **4b** from commercially available (*S*)-2-ethyloxirane is outlined in Scheme 2. Treatment of **6** with the lithium anion of 2-allyl-1,3-dithiane **7** afforded alcohol **8** in 90% yield. Removing the 1,3-dithiane group of **8** followed by a SmI_2-promoted Evans-Tishchenko reduction[12] generated **5** in 85% yield for two steps. Ozonolysis of **5** gave the crude aldehyde **10**, which was subjected directly to Barbier-type reaction[13] with prenyl bromide to yield diols **4a** and **4b** (1 : 1 mixture, 58% total yield for two steps), which were separated by column chromatography.

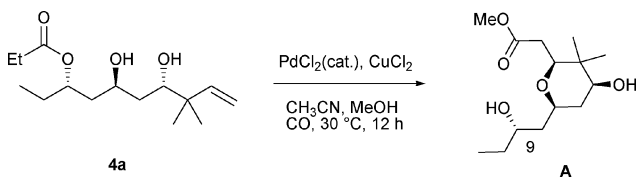
In our first attempts, we made an effort to reduce the use of protecting group in our synthesis. Thus, the Pd-catalyzed intramolecular alkoxycarbonylation[14] was carried out with **4a**. It was unfortunate that the propionate protecting group was cleavaged to give diol **A** (Scheme 3), in which two unmasked secondary hydroxyl groups were difficult to be discriminated for further functionalization. Moreover, the stereochemistry of C9 in diol **A** should be inverted to meet the required stereochemistry of natural cyanolide A (**1**). For this consideration, we decided to conduct the C9 stereochemistry inversion before conduction of the palladium-catalyzed intramolecular alkoxycarbonylation. As depicted in Scheme 4, treatment of diol **4a** with 2,2-dimethoxypropane followed by $LiAlH_4$ easily produced alcohol **12** in 89% yield for two steps. Using a Mitsunobu reaction with



Scheme 1 Retrosynthetic analysis of cyanolide A (**1**).



Scheme 2 Synthesis of diols **4a** and **4b**.



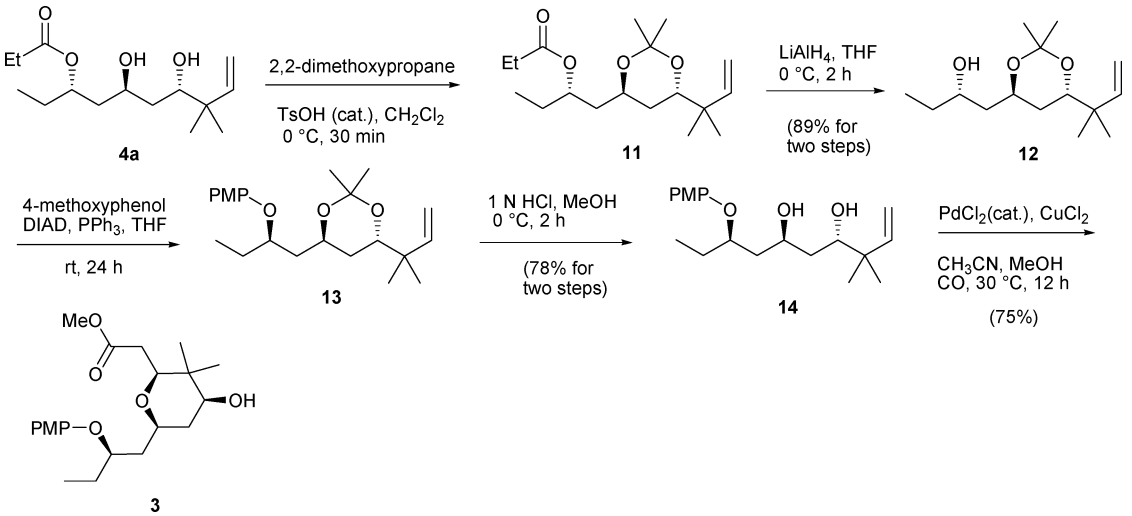
Scheme 3 Pd-catalyzed intramolecular alkoxycarbonylation with **4a**.

4-methoxyphenol, alcohol **12** was converted into PMP ether **13** accompanying the stereoinversion. Deprotection of the acetonide group afforded the corresponding 1,3-diol **14** in a reasonable 78% yield for two steps. At this point, we turned our attention to the construction of tetrahydropyran ring. Fortunately, subjecting diol **14** to the Pd-catalyzed intramolecular alkoxycarbonylation reaction smoothly provided the desired intermediate **3** in 75% isolated yield as a single isomer.

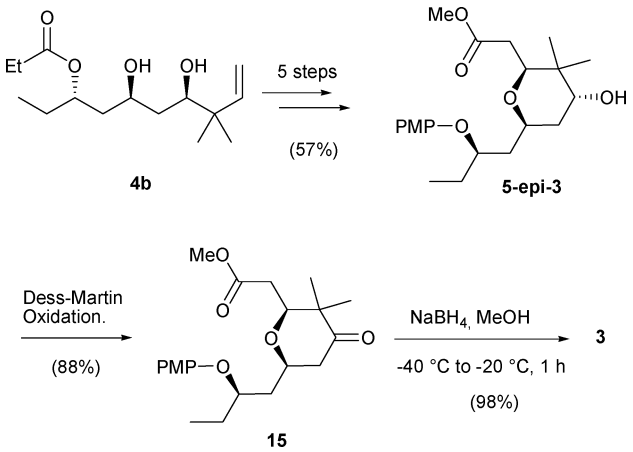
Similarly, diol **4b** was transformed to **5-*epi*-3** in five steps with excellent 57% total yield. Oxidation of **5-*epi*-3** with Dess–Martin periodiane and subsequent $NaBH_4$-reduction of the corresponding ketone **15** gave alcohol **3** in 86% yield for two steps (Scheme 5).

With key intermediate **3** in hand, we proceeded to the synthesis of natural product **1** (Scheme 6). Glycosylation of **3** with phenyl thioglycoside **16** in the presence of MeOTf furnished the desired β-anomeric monomer **17** in 62% isolated yield along with a small amout of α-anomeric monomer (~5 : 1).[11] Deprotecting the PMP group of **17** with ammonium cerium(IV) nitrate (CAN) provided alcohol **2** in 80% yield.[15] Its optical rotation ($[\alpha]_D^{20} = -42.0$, c 0.66, $CHCl_3$) was essentially identical to the value reported by Hong and co-workers ($[\alpha]_D^{25} = -46.6$, c 0.66, $CHCl_3$). Then alcohol **2** was converted to the natural cyanolide A (**1**) in two steps as described by Kim and Hong (ref. 11). The optical rotation of our synthetic ($[\alpha]_D^{20} = -50.0$, c 0.42, $CHCl_3$) was in agreement with the isolated natural product ($[\alpha]_D^{23} = -59.0$, c 0.60, $CHCl_3$) and the value reported by Hong and co-workers ($[\alpha]_D^{25} = -55.5$, c 0.33, $CHCl_3$).[11]

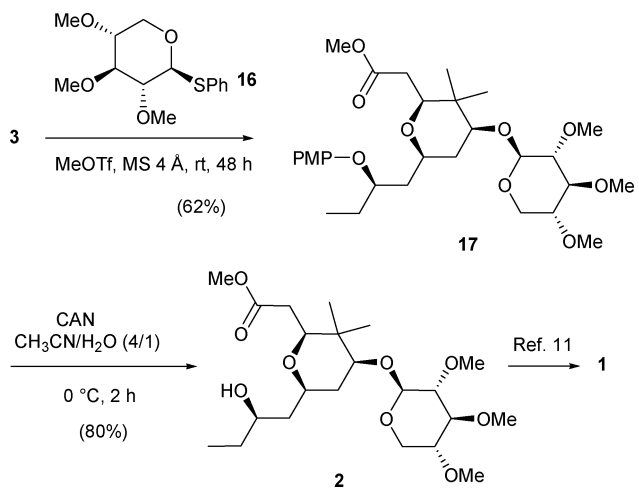
In summary, an enantioselective total synthesis of cyanolide A (**1**) has been achieved with the longest linear sequence of 14 steps. Central to this venture was the efficient Pd-catalyzed intramolecular alkoxycarbonylation to construct the tetrasubstituted *cis*-tetrahydropyran ring core with high stereoselectivity. The application of SmI_2-promoted Evans-Tishchenko reduction, Barbier-type



Scheme 4 Synthesis of alcohol **3**.



Scheme 5 Synthesis of alcohol **3** from **4b**.



Scheme 6 Total synthesis of cyanolide A (**1**).

reaction and Mitsunobu reaction, reduced the use of protecting groups to some certain extent. Synthesis toward cyanolide A (**1**) further demonstrates the value of Pd-catalyzed cyclyzation technology. It is flexible and therefore should be suitable for the synthesis of several other similar natural products.[16]

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