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Synthesis of Molluscicidal Agent Cyanolide A Macrolactone from D-(−)-Pantolactone‡

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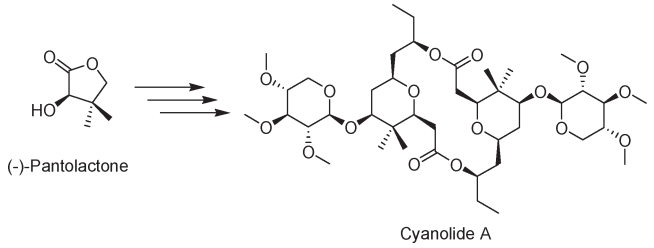

An efficient synthesis of potent molluscicidal agent cyanolide A, a glycosidic 16-membered macrolide, starting from D-(−)-pantolactone is reported. Highly stereoselective aldol, oxa-Michael addition, and Yamaguchi macrolactonization are the key steps in the present synthesis.

Schistosomiasis (also known as bilharzia or snail fever) is considered to be one of the important tropical parasitic disease, with severe socioeconomic consequences for millions of people worldwide.[1] The disease is endemic to many countries with large populations and is second only to Malaria.[2] Although it can be treated with the currently available drug praziquantel, the treatment is expensive, and also relying solely on a single drug to treat more than 200 million people is not successful.[3] One of the possible approaches to eradicate or control this disease is to interrupt the life cycle by eliminating the snail vector. Niclosamide is currently the only molluscicide recommended by WHO for snail control which kill snails at all stages of the lifecycle.[4] However, these molluscicides are toxic to nontarget animals like fish and may have long-term detrimental effects on the aquatic environment. Different groups have examined several other molluscicides to date and none have been found to be superior to niclosamide.[5] At the beginning of this year, Gerwick et al. isolated 1.2 mg of cyanolide A (**1**), a new and highly potent molluscicidal agent from a Papua New Guinea collection of *Lyngbya bouillonii*, as part of the program to screen natural products for activities to tropical diseases.[6] Compound **1** showed significant molluscicidal activity against *Biomphalaria glabrata* (LC_{50}: 1.2 μM) as well as modest brine shrimp toxicity (LC_{50}: 10.8 μM). It is relatively noncytotoxic when tested against H-460 human lung adenocarcinoma and Neuro-2a mouse neuroblastoma cell lines suggesting that it can be a potential lead compound for treating waterways infested with schistosomiasis-carrying snails of the genus *Biomphalaria*.[6]

The structure of cyanolide A (**1**) was elucidated by using extensive NMR spectroscopic analysis as a glycosidic 16-membered macrolide with structural similarities to previously known clavosolides.[7,8] Immediately, Hong's group from Duke University completed the first stereoselective synthesis of **1** in two complementary routes, dimerization−glycosylation and glycosylation−dimerization from readily available starting materials.[9] This led to the confirmation of proposed absolute configuration and provided an access to additional quantities of natural product. The interesting chemical structure and potent molluscicidal activity of cyanolide A (**1**) prompted us to undertake the synthesis of this compound. It also fits well with our group's strategy to use

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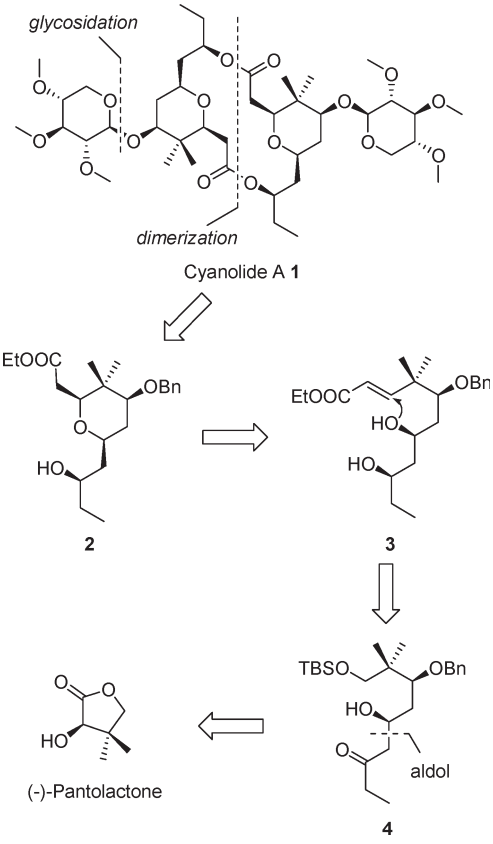
SCHEME 1. Retrosynthetic Analysis



the pantolactone chiral pool for the synthesis of biologically interesting natural products.[10]

Retrosynthetically, cyanolide A (**1**) can be accessed from monomer **2** through dimerization followed by glycosidation. Compound **2** could be prepared from an acyclic intermediate **3** through an intramolecular oxa-Michael cyclization to form tetrahydropyran ring (Figure 1). The stereoselective reduction of acyclic β-hydroxy ketone **4** would provide **3** with *syn*-1,3-diol moiety (Scheme 1). Compound **4** could be prepared from commercially available D-(−)-pantolactone by using routine functional group transformations including a key stereoselective aldol reaction.

Our synthesis commenced from D-(−)-pantolactone by converting it into known aldehyde **5** essentially following the conditions reported in the literature.[11] The Mukaiyama aldol reaction of enolsilane (prepared from methyl ethyl ketone) with aldehyde **5** at −78 °C in CH_2Cl_2 by slow addition of $BF_3 \cdot OEt_2$ proceeded with an excellent 1,3-*anti* induction (>95% diastereoselectivity based on NMR) to give product **4** in moderate yield.[12] Compound **6** was prepared utilizing Evans' protocol[13] for stereoselective reduction of acyclic β-hydroxy ketone **4** to *syn*-1,3-diol (dr, 9:1, judged by HPLC)

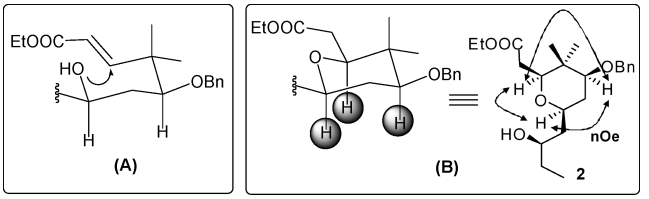
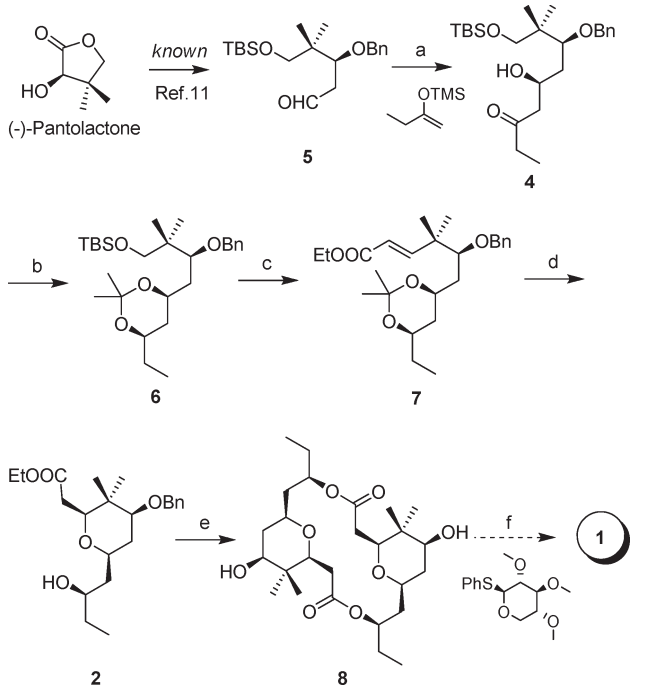


FIGURE 1. (A) Proposed transition state during oxa-Michael addition to form tetrahydropyran ring. (B) Compound **2** with highlighted protons which showed nOes.

SCHEME 2. Synthesis of Cyanolide A (1)[a]



[a]Reagents and conditions: (a) $BF_3 \cdot Et_2O$, CH_2Cl_2, −78 °C, 1 h, 37% (56% based on starting material recovery); (b) (i) catecholborane, THF, −10 °C, 3 h, 68%, (ii) 2,2-dimethoxypropane, PPTS, DCM, rt, 3 h, 88%; (c) (i) TBAF, THF, 60 °C, 3 h, 93%, (ii) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C, 1 h, 92%, (iii) $Ph_3P{=}CHCOOEt$, toluene, reflux, 48 h, 71%; (d) PTSA, $CHCl_3$, reflux, 20 h, 83%; (e) (i) $LiOH \cdot H_2O$, H_2O:MeOH:THF (1:1:2), rt, 18 h, 93%, (ii) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, reflux, 4 h, 48%, (iii) $Pd(OH)_2$, MeOH, H_2, rt, 20 h, 60%; (f) MeOTf, MS 4Å, Et_2O, 25 °C (known step, ref 9).

with catecholborane followed by protection of the resulting diol as acetonide. The *syn*-1,3-diol relationship was established by comparing ^{13}C chemical shifts of the acetal methyl carbons and acetal carbons of acetonides prepared from *syn*- and *anti*-1,3-diols.[14] Compound **6** was converted to α,β-unsaturated ester **7** by using the sequence of TBS deprotection, Swern oxidation followed by Horner−Wittig reaction. Having the intermediate **7** in hand, the key tetrahydropyran ring formation was attempted with use of a catalytic amount of *p*-toluenesulfonic acid. To our delight, deprotection of acetonide followed by oxa-Michael cyclization took place in a single pot to provide the fragment **2** in a highly stereoselective fashion (Scheme 2).[9,15] The observed stereoselectivity (dr > 95:5,

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judged by ^{1}H NMR) can be explained based on the transition state **A**. The stereochemistry of substituents on the tetrahydropyran ring was established by using nOe's (see highlighted protons and nOe's in **B**). Ester hydrolysis of **2** followed by dimerization with Yamaguchi's lactonization protocol[16] furnished 16-membered macrolide, which was subsequently converted to macrocyclic diol **8** by the deprotection of benzyl groups. Macrolide **8** was previously reported as a penultimate precursor in the synthesis of **1**. It was well-characterized by Hong's group, which includes X-ray crystal structure, and the same was glycosilated to yield **1**.[9] The spectral data (^{1}H and ^{13}C NMR) of the macrolide **8** from our lab were compared with those of Hong's group and both were found to be identical. Specific rotation of our sample **8** showed $[\alpha]^{23}_D$ −38.8 (*c* 0.33, $CHCl_3$) compared to that of the literature $[\alpha]^{25}_D$ −36.3 (*c* 0.56, $CHCl_3$).[9]

In short, we have achieved the formal synthesis of cyanolide A (**1**), a potent molluscicidal agent, through Hong's intermediate, macrolide **8**, starting from D-(−)-pantolactone in a highly stereoselective manner. Choosing readily available pantolactone and highly stereoselective Mukaiyama aldol reaction, oxa-Michael addition to form tetrahydropyran ring, and dimerization with Yamaguchi's lactonization are the salient features of this synthesis. As L-(+)-pantolactone is also commercially available, our route can be used for the synthesis of the unnatural enantiomer of cyanolide A and other analogues which may show improved molluscicidal activity.

Experimental Section

[(2*S*,4*S*,6*R*)-4-Benzyloxy-6-((*R*)-2-hydroxybutyl)-3,3-dimethyltetrahydropyran-2-yl]acetic Acid Ethyl Ester (2). To a stirred solution of (*E*)-(*S*)-5-benzyloxy-6-((4*R*,6*R*)-6-ethyl-2,2-dimethyl[1,3]dioxan-4-yl)-4,4-dimethyl-hex-2-enoic acid ethyl ester **7** (110 mg, 0.3 mmol) in chloroform (5 mL) was added *p*-toluenesulfonic acid monohydrate (8 mg, 0.15 mmol) then the mixture was refluxed for 20 h. The reaction mixture was cooled to room temperature, diluted with chloroform, washed with saturated sodium bicarbonate solution, water, and brine, dried over anhydrous sodium sulfate, concentrated, and purified by column chromatography (9% ethyl acetate in hexanes) to give 82 mg (83%) of [(2*S*,4*S*,6*R*)-4-benzyloxy-6-((*R*)-2-hydroxybutyl)-3,3-dimethyltetrahydropyran-2-yl]acetic acid ethyl ester **2** as a colorless oil. $[\alpha]^{22.5}_D$ +9.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3H), 0.91 (s, 3H), 0.95 (s, 3H), 1.26 (t, J = 6.8 Hz, 3H), 1.40−1.54 (m, 4H), 1.57−1.67 (m, 1H), 1.85−1.89 (m, 1H), 2.38−2.48 (m, 2H), 3.17 (dd, J = 11.6, 4.8 Hz, 1H), 3.49 (br s, 1H), 3.53 (dd, J = 9.2, 3.2 Hz, 1H), 3.62 (t, J = 10.0 Hz, 1H), 3.79 (dd, J = 13.2, 6.8 Hz, 1H), 4.11−4.21 (m, 2H), 4.43 (d, J = 12.0 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 7.28−7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.9, 13.6, 14.3, 22.7, 30.2, 33.8, 35.1, 38.5, 42.0, 61.1, 71.2, 73.4, 77.9, 81.0, 82.0, 127.6, 127.7, 128.5, 138.8, 172.5; IR (neat) 1733, 3533 cm^{-1}; LCMS = 379.3 $[M + H]^+$; HRMS (ESI) m/z calcd for $C_{22}H_{35}O_5$ $[M + H]^+$ 379.2484, found 379.2482.

(1*S*,5*R*,7*S*,9*S*,11*S*,15*R*,17*S*,19*S*)-5,15-Diethyl-9,19-dihydroxy-10,10,20,20-tetramethyl-4,14,21,22-tetraoxatricyclo[15.3.1.1^{7,11}]docosane-3,13-dione (8). To a stirred solution of [(2*S*,4*S*,6*R*)-4-benzyloxy-6-((*R*)-2-hydroxybutyl)-3,3-dimethyltetrahydropyran-2-yl]acetic acid ethyl ester **2** (75 mg, 0.2 mmol) in a mixture of THF:methanol:water (2:1:1, 2.0 mL) was added lithium hydroxide monohydrate (33 mg, 0.8 mmol) at room temperature. After the mixture was stirred for 20 h, volatiles were evaporated under reduced pressure. The resulting residue was taken in water and washed with *n*-pentane. Then the aqueous layer was acidified by 1.0 N HCl and extracted with ethyl acetate. The ethylacetate layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated to give 64 mg (93%) of [(2*S*,4*S*,6*R*)-4-benzyloxy-6-((*R*)-2-hydroxybutyl)-3,3-dimethyltetrahydropyran-2-yl]-acetic acid as a white solid. Mp 162−163 °C; $[\alpha]^{22.1}_D$ +11.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 7.6 Hz, 3H), 0.90 (s, 3H), 0.95 (s, 3H), 1.42−1.58 (m, 4H), 1.65 (dd, J = 20.4, 10.0 Hz, 1H), 1.85 (d, J = 12.0 Hz, 1H), 2.43 (s, 2H), 3.17 (dd, J = 11.2, 3.2 Hz, 1H), 3.54 (dd, J = 8.4, 3.6 Hz, 1H), 3.67 (t, J = 10.4 Hz, 1H), 3.87−3.90 (m, 1H), 4.43 (d, J = 11.6 Hz, 1H), 4.64 (d, J = 11.6 Hz, 1H), 4.95 (br s, 1H), 7.27−7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.6, 13.6, 22.7, 29.7, 33.7, 34.9, 38.6, 40.9, 71.3, 74.1, 77.8, 81.3, 81.9, 127.6, 127.7, 128.5, 138.8, 174.4; IR (neat) 1728, 3459 cm^{-1}; LCMS = 351.2 $[M + H]^+$.

To a stirred solution of the above [(2*S*,4*S*,6*R*)-4-benzyloxy-6-((*R*)-2-hydroxybutyl)-3,3-dimethyltetrahydropyran-2-yl]-acetic acid (70 mg, 0.2 mmol) in THF (1.0 mL) was added triethylamine (40 μL, 0.3 mmol) followed by 2,4,6-trichlorobenzoyl chloride (40 μL, 0.3 mmol), then the mixture was stirred at room temperature for 3 h. The solid was filtered and the filtrate was diluted with toluene (6 mL) and then added dropwise to a solution of 4-dimethylaminopyridine (122 mg, 1.0 mmol) in toluene (40 mL) at reflux (125 °C) over a period of 3 h. After refluxing for an additional 4 h, the reaction mixture was cooled to room temperature and concentrated. The crude product was partitioned between water (15 mL) and ethyl acetate (30 mL), and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, concentrated, and purified by column chromatography (10% ethyl acetate in hexanes) to give 32 mg (48%) of (1*S*,5*R*,7*R*,9*S*,11*S*,15*R*,17*R*,19*S*)-9,19-bis-benzyloxy-5,15-diethyl-10,10,20,20-tetramethyl-4,14,21,22-tetraoxatricyclo[15.3.1.1^{7,11}]docosane-3,13-dione. $[\alpha]^{22.3}_D$ +9.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85−0.89 (m, 12H), 0.94 (s, 6H), 1.30 (ddd, J = 12.0, 12.0 Hz, 2H), 1.58−1.67 (m, 6H), 1.86−1.93 (m, 2H), 2.04−2.10 (m, 2H), 2.29 (dd, J = 15.2, 9.2 Hz, 2H), 2.39 (d, J = 14.0 Hz, 2H), 3.16 (dd, J = 11.6, 4.4 Hz, 2H), 3.36−3.41 (m, 4H), 4.44 (d, J = 12.0 Hz, 2H), 4.67 (d, J = 12.0 Hz, 2H), 4.90 (ddd, J = 8.0, 6.8, 6.8 Hz, 2H), 7.26−7.34 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.4, 13.2, 22.3, 27.9, 33.1, 35.1, 38.3, 41.1, 70.8, 73.2, 74.6, 80.9, 82.0, 127.2, 128.0, 138.6, 172.1; IR (neat) 1738 cm^{-1}; LCMS = 665.5 $[M + H]^+$; HRMS (ESI) m/z calcd for $C_{40}H_{57}O_8$ $[M + H]^+$ 665.4053, found 665.4047.

Palldium hydroxide (10 mg) was added to a solution of (1*S*,5*R*,7*R*,9*S*,11*S*,15*R*,17*R*,19*S*)-9,19-bis-benzyloxy-5,15-diethyl-10,10,20,20-tetramethyl-4,14,21,22-tetraoxatricyclo-[15.3.1.1^{7,11}]docosane-3,13-dione (30 mg) in methanol (4 mL) then the mixture was stirred under hydrogen atmospheric pressure (using balloon) for 20 h. The reaction mixture was then filtered through a Celite bed. Filtrate was concentrated and purified by column chromatography (60% ethyl acetate in hexanes) to give 13 mg (60%) of (1*S*,5*R*,7*S*,9*S*,11*S*,15*R*,17*S*,19*S*)-5,15-diethyl-9,19-dihydroxy-10,10,20,20-tetramethyl-4,14,21,22-tetraoxatricyclo[15.3.1.1^{7,11}]docosane-3,13-dione **8** as a white solid. Mp 132−134 °C; $[\alpha]^{22.7}_D$ −38.8 (*c* 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (s, 6H), 0.87 (dd, J = 7.2, 7.2 Hz, 6H), 0.93 (s, 6H), 1.33 (ddd, J = 12.0, 11.6, 11.6 Hz, 2H), 1.52−1.60 (m, 6H), 1.83−1.91 (m, 4H), 2.29 (dd, J = 15.6, 8.8 Hz, 2H), 2.40 (dd, J = 15.6 Hz, 2H), 3.40 (d, J = 8.0 Hz, 2H), 3.43−3.49 (m, 4H), 4.91 (ddd, J = 7.6, 6.8, 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.7, 12.6, 22.4, 28.3, 35.4, 37.3, 38.8, 41.0, 73.8, 75.1, 75.4, 80.8, 172.2; IR (neat) 1726, 3409 cm^{-1}; LCMS = 485.4 $[M + H]^+$; HRMS (ESI) m/z calcd for $C_{26}H_{45}O_8$ $[M + H]^+$ 485.3114, found 485.3097. The spectral

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data (^{1}H and ^{13}C NMR) of the macrolide **8** from our lab were compared with those of Hong's group[9] and both were found to be identical.

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Supporting Information Available: Experimental procedures, spectral data, and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.