Natural Products Synthesis

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Total Synthesis of Cyanolide A in the Absence of Protecting Groups, Chiral Auxiliaries, or Premetalated Carbon Nucleophiles**

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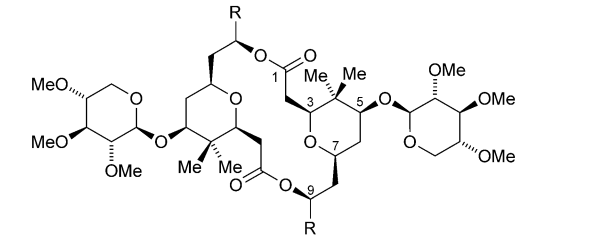
Cyanolide A is a glycosidic 16-membered macrodiolide of C_2 symmetry isolated from the Papua New Guinea cyanobacterium *Lyungbya bouillonii*[1] and is closely related in structure to the clavosolide family of natural products (Figure 1).[2] Cyanolide A exhibits potent molluscicidal activity ($LC_{50} = 1.2$ μM) against the water snail *Biomphalaria glabrata*,[1] a vector of the human parasitic disease schistosomiasis (also known as bilharziasis). Infecting more than 200 million people, schistosomiasis ranks second behind malaria among human parasitic diseases.[3] While drugs, most notably praziquantel,[4] exist to treat those infected, reinfection and the emergence of drug-resistant schistosomes are concerns.[5] Disease prevention by reducing or eliminating the population of infected water snails is more desirable.[6] The molluscicide niclosamide (bayluscide) was developed for this purpose and is utilized broadly.[7] However, it exhibits poor water solubility, is rather nonselective, adversely affects native fish, and is relatively expensive.[8] Hence, an authentic need for alternative molluscicidal agents persists, thus fueling efforts toward the synthesis of naturally occurring molluscicides.[9] Toward this end, cyanolide A has garnered significant attention from organic chemists, with several total and formal syntheses published since its isolation in 2010 (Figure 1).[10,11] Herein, we report a total synthesis of cyanolide A in the absence of protecting groups, chiral auxiliaries, or premetalated C-nucleophiles in fewer than half the steps of any previous approach.



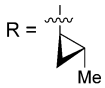
clavosolide A R = 	Lee et al. 2006, 27 Steps (LLS), 30 Steps (TS), Ref. [11a] Smith et al. 2006, 17 Steps (LLS), 23 Steps (TS), Ref. [11b] Willis et al. 2006, 16 Steps (LLS), 20 Steps (TS), Ref. [11c] Chakraborty et al. 2008, 33 Steps (LLS), 36 Steps (TS), Ref. [11d] Jennings et al. 2009, 20 Steps (LLS), 23 Steps (TS), Ref. [11e] Floreancig et al. 2012, 14 Steps (LLS), 20 Steps (TS), Ref. [11f]
cyanolide A R = Et	Hong et al. 2010, 14 Steps (LLS), 18 Steps (TS), Ref. [10a] Reddy et al. 2011, 17 Steps (LLS), 22 Steps (TS), Ref. [10b] She et al. 2011, 14 Steps (LLS), 18 Steps (TS), Ref. [10c] Pabbaraja et al. 2011, 17 Steps (LLS), 21 Steps (TS), Ref. [10d] Rychnovsky et al. 2011, 12 Steps (LLS), 18 Steps (TS), Ref. [10e] Jennings et al. 2011, 15 Steps (LLS), 19 Steps (TS), Ref. [10f]

Figure 1. The C_2-symmetric macrodiolides cyanolide A and clavosolide A, and prior total and formal syntheses. See the Supporting Information for graphical summaries of prior syntheses. LLS = longest linear sequence, TS = total steps.

Our synthesis plan emanates from a novel pattern of reactivity in which metal-catalyzed hydrogen exchange between alcohols and π-unsaturated reactants generates organometal/aldehyde pairs which combine to form products of carbonyl addition.[12] Direct alcohol C–H functionalization in this manner not only bypasses discrete alcohol-to-aldehyde oxidation and use of premetalated carbon nucleophiles, but enables transformations which cannot be achieved from the carbonyl oxidation level. For example, using conventional allylmetal reagents,[13] asymmetric double allylation of 1,3-dialdehydes is unknown, presumably because of a combination of factors including enolization and self-condensation.[14] In contrast, asymmetric double allylation of 1,3-diols occurs efficiently to provide C_2-symmetric adducts as single enantiomers.[15,16] Asymmetric double allylation enables rapid generation of polyacetate substructures and, hence, has proven to be an especially powerful method for the total synthesis of polyketide natural products, as illustrated in remarkably concise syntheses of roxaticin, bryostatin 7, neopeltolide, and psymberin (irciniastatin A).[17] In the case of cyanolide A, the double allylation of neopentyl glycol (**1**) to furnish the C_2-symmetric diol **2**[15a] is followed by the method from Fuwa et al. for the formation of the *cis*-2,6-disubstituted pyran **3**, which comprises a cascading ruthenium-catalyzed cross-metathesis/oxa-Michael cyclization (Scheme 1).[18,19] The conversion of the pyran **3** into cyanolide A was accomplished through two different routes, with our second-generation synthesis delivering cyanolide A in only six steps from **1** in the absence of protecting groups, chiral auxiliaries, or premetalated C-nucleophiles.

The synthesis of the pyran **3** begins with the double allylation of **1** (Scheme 2). This process employs an *ortho*-cyclometalated π-allyliridium catalyst generated in situ from [{Ir(cod)Cl}$_2$], allyl acetate, 4-chloro-3-nitrobenzoic acid, and (*S*)-Cl,MeO-biphep. Because the minor enantiomer of the monoallylated intermediate is converted into the *meso*-

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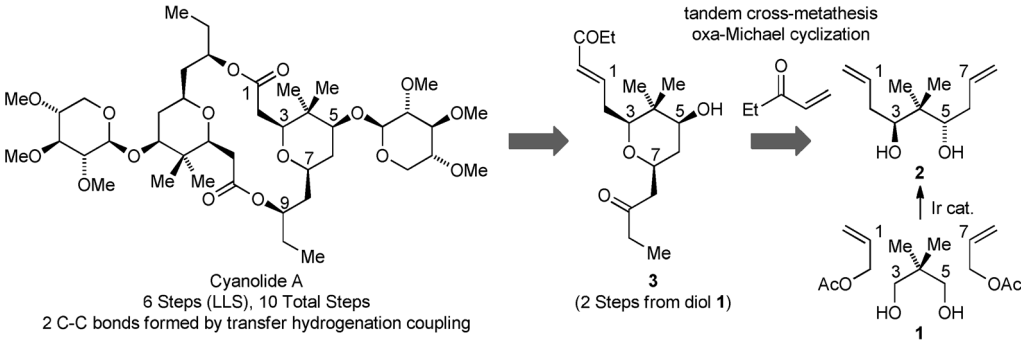
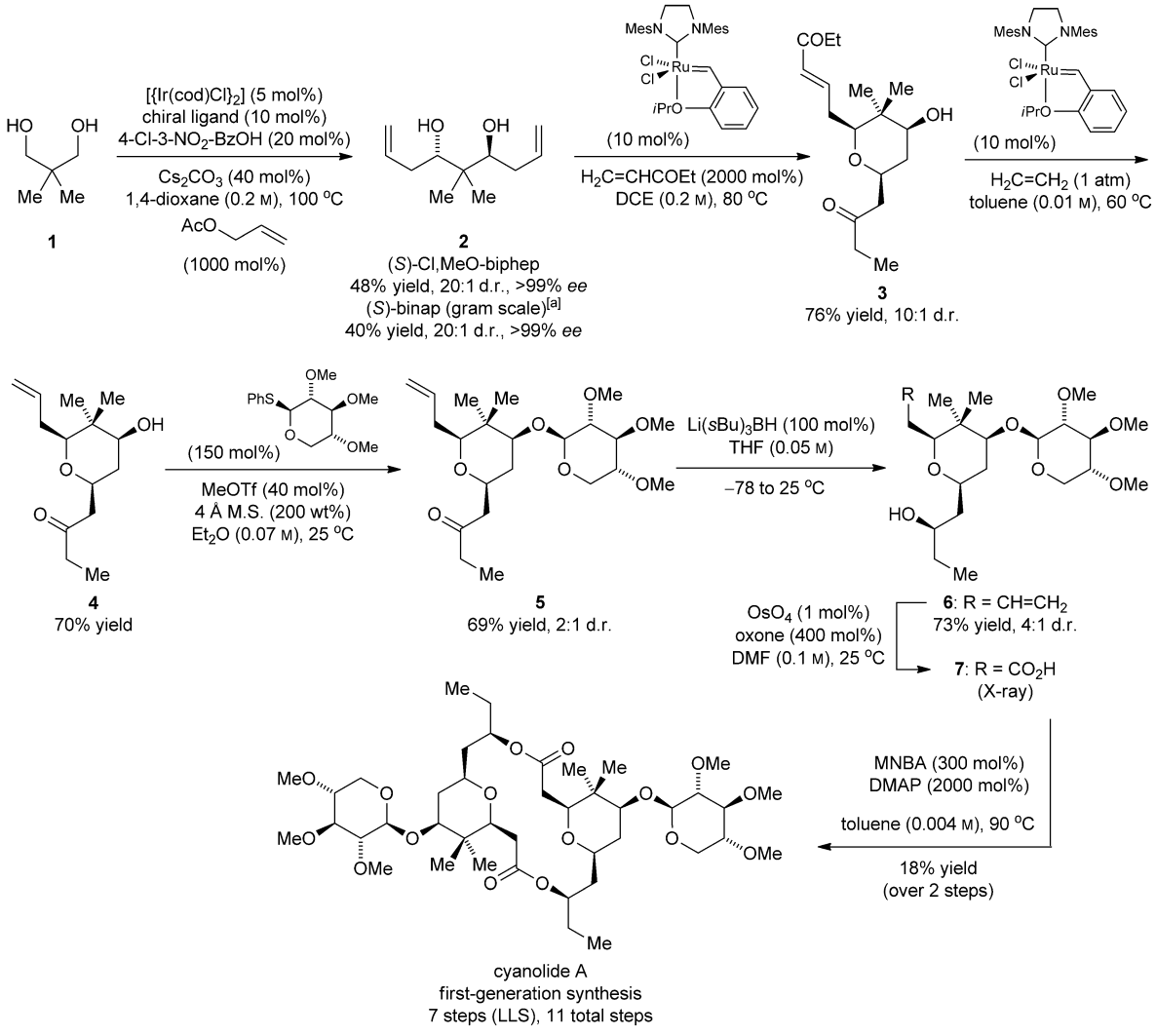


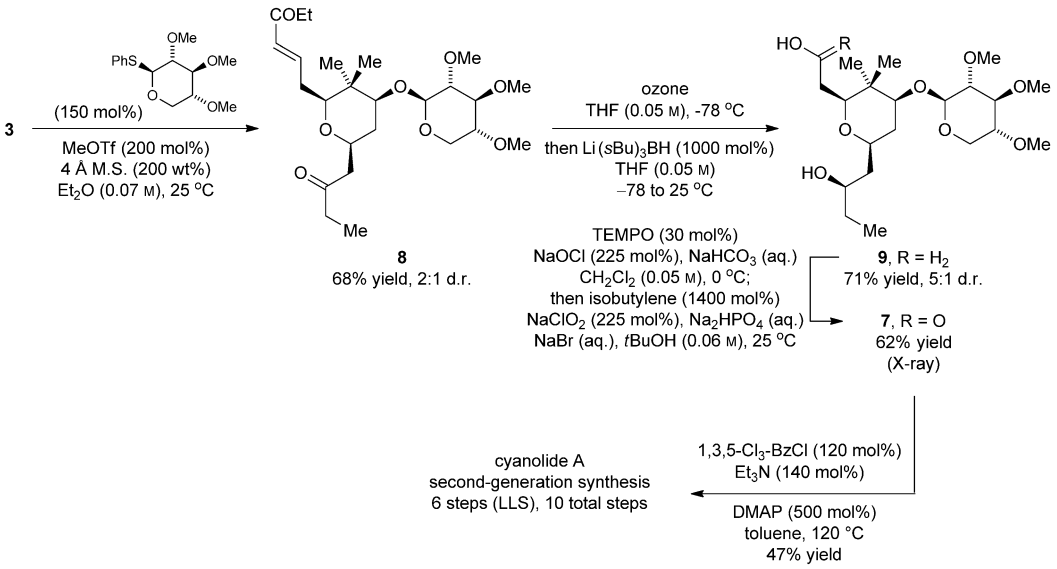
Scheme 1. Retrosynthetic analysis of cyanolide A by C—C bond-forming transfer hydrogenation.

diastereomer, the diol **2** is obtained as a single enantiomer, as determined by HPLC analysis using a chiral stationary phase.[16] For gram-scale reactions, the iridium catalyst modified by (*S*)-binap is used to mitigate cost, which delivers **2** with the same high levels of diastereo- and enantioselectivity albeit in slightly diminished yield. Conditions for cat-



Scheme 2. First-generation synthesis of cyanolide A. Cited yields are of diastereomeric mixtures isolated after silica gel chromatography. Enantiomeric ratios were determined by HPLC analysis using a chiral stationary phase. Diastereomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. Diastereomers were separated at the stage at which they were generated. See the Supporting Information for additional experimental details. [a] THF was used as the solvent. Cl,OMe-biphep = (5,5′-dichloro-6,6′-dimethoxy-1,1′-biphenyl)-2,2′-diyl-bis(diphenylphosphine), binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, Bz = benzoyl, cod = cyclo-1,5-octadiene, DCE = 1,2-dichloroethane, DMAP = 4-(dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, MNBA = 2-methyl-6-nitrobenzoic anhydride, M.S. = molecular sieves, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

alyst recovery and recycling have been identified and will be presented as part of a systematic study in due course. Gratifyingly, upon exposure of **2** to the reaction conditions from Fuwa et al. for cascading cross-metathesis/oxa-Michael cyclization using ethyl vinyl ketone,[18,19] the desired *cis*-2,6-disubstituted pyran **3** was generated in 76% yield as a 10:1 mixture of diastereomers. It was our intent to convert the enone **3** directly into the terminal olefin **4** by purging the reaction vessel with ethylene gas. In practice, the conversion of **2** into **3** became slow when lower loadings of ethyl vinyl ketone were used, and the presence of excess vinyl ketone inhibited ethylene cross-metathesis. For this reason, **3** was first isolated and then subjected to ethylene cross-metathesis to furnish the terminal olefin **4**. In all but one prior synthesis of cyanolide A,[10c] glycosidation of the C5 alcohol is conducted subsequent to macrodiolide formation, thus resulting in a complex mixture of anomers. To circumvent this issue, **4** was exposed to the indicated phenyl thioglycoside[20] in the presence of methyl triflate[21] to furnish the product of glycosylation, **5**, in 69% yield as a 2:1 mixture of diastereomers favoring the β anomer. In accord with the revision, by Evans et al., of Cram's polar model for the reduction of β-alkoxy ketones,[22] Li(*s*Bu)$_3$BH reduction of the C9 ketone of **5** exhibits 1,3-*syn*-diastereoselectivity (4:1 d.r.) and provides the alcohol **6**.[23] Finally, oxidative cleavage of the terminal olefin **6** to form the carboxylic acid **7**[24] and subsequent macrodiolide formation under the reaction conditions of Shiina et al.[25] delivers cyanolide A.



Scheme 3. Second-generation synthesis of cyanolide A. As described for Scheme 2. TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl.

Glycosylation of **3** and subsequent direct ozonolytic cleavage of the enone **8** with concomitant reduction of the ozonide and C9 ketone moieties potentially provides more concise access to cyanolide A, especially if the resulting diol **9** were amenable to oxidative macrodiolide formation (Scheme 3).[27] In the event, the glycosylation of **3** occurred uneventfully under the aforementioned reaction conditions to furnish **8**.[21] Exposure of **8** to ozone followed by an excess Li(*s*Bu)$_3$BH led to the formation of **9** in 71% yield as a 5:1 mixture of diastereomers at C9.[26] Attempted oxidative macrodiolide formation from **9**, however, was not successful.[27] Hence, **9** was subjected to reaction conditions for site-selective oxidation to form the hydroxy acid **7**,[28] which was converted into the macrodiolide using reaction conditions reported by Yamaguchi and co-workers,[29] thus constituting a total synthesis of cyanolide A in only six steps from neopentyl glycol (**1**).

In summary, a concise total synthesis of the glycosidic macrodiolide cyanolide A was achieved in the absence of protecting groups, chiral auxiliaries, or premetalated C-nucleophiles. As the lexicon of synthetic methods expands, so does the spectrum of strategic possibilities, thus underscoring the need for practitioners of the art to expand their vocabulary beyond first-generation solutions to the challenges of chemical synthesis. Here, through sequential application of two recently developed methods, the double allylation of 1,3-glycols[15] and Fuwa's cascading cross-metathesis/oxa-Michael cyclization,[18] neopentyl glycol (**1**) is rapidly transformed into the complex pyran core of the cyanolide and clavosolide families. Future studies will focus on the development of new catalytic processes and, therefrom, new strategies which can shift the retrosynthetic paradigm to simplify longstanding challenges in chemical synthesis.

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