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Total Synthesis of Clavosolide A via Asymmetric Alcohol-Mediated Carbonyl Allylation: Beyond Protecting Groups or Chiral Auxiliaries in Polyketide Construction**

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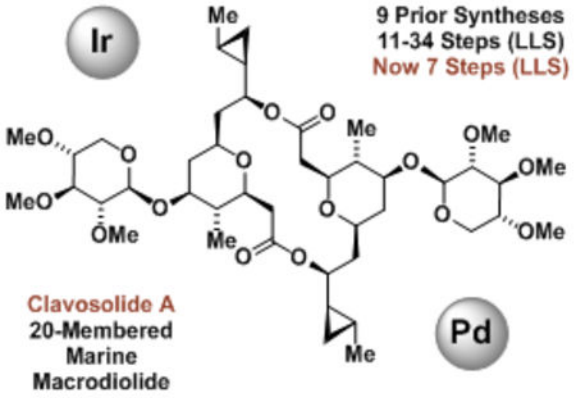
Graphical Abstract

Less is more. The 20-membered marine macrodiolide clavosolide A is prepared in 7 steps (LLS) in the absence of protecting groups or chiral auxiliaries via enantioselective alcohol-mediated carbonyl addition. In 9 prior total syntheses, 11-34 steps (LLS) were required.



Keywords

Enantioselective; C-C Bond Formation; Iridium; Hydrogen Transfer; Homogenous Catalysis

Polyketide natural products and their semisynthetic congeners are used more frequently in human medicine than any other class of secondary metabolites.[1,2] With one exception (eribulin®),[3] manufacturing routes to commercial polyketide drugs invariably rely on fermentation. These data suggest available methods for *de novo* polyketide construction do not adequately meet the challenges evoked by the synthesis of such stereochemically complex compounds. Carbonyl additions, in particular asymmetric aldol reactions[4] and allylmetallations,[5] figure prominently among methods for polyketide total synthesis, yet often require multi-step preparations of preformed enol(ate) or allylmetal reagents that

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involve numerous sacrificial reagents. To address these limitations, our laboratory has developed a suite of metal-catalyzed carbonyl reductive couplings and related hydrogen auto-transfer processes that convert lower alcohols to higher alcohols.[6] The redox-economy of these processes and the ability to directly deploy feedstock pronucleophiles in a stereo- and site-selective manner has been shown to streamline polyketide construction, enabling total syntheses in significantly fewer manipulations than previously required.[7] The bidirectional asymmetric allylation of 1,3-diols[8] represents one especially valuable method of this type, as it directly assembles triketide substructures, and has no counterpart in classical carbonyl addition chemistry as the corresponding 1,3-dialdehydes are unstable. For example, a 7-step total synthesis of cyanolide A was completed via bidirectional asymmetric allylation of neopentyl glycol[9g] - the shortest among 8 other total syntheses ranging between 12-19 steps (Figure 1).[9] Clavosolide A is a structurally related but more complex macrodiolide, for which 9 total syntheses exist that range between 11-34 steps (LLS) (Figure 1).[10,11] Here, we report a 7-step (LLS) total synthesis of clavosolide A in the absence of protecting groups[12] or chiral auxiliaries via bidirectional asymmetric allylation of 2-methyl-1,3-propane diol.

Clavosolide A, a C_2-symmetric 20-membered glycosidic macrodiolide, was isolated in trace quantities from the marine sponge *Myriastra clavosa*, which is found in the Philippines.[13] The structure initially proposed for clavosolide A was misassigned and later revised by total syntheses.[10a,14] While the biological properties of clavosolide A have yet to be determined, the structurally related natural product cyanolide A[9,15] displays potent molluscicidal activity (LC_{50} = 1.2 μM) against the water snail *Biomphalaria glabrata*, a vector of the human parasitic disease schistosomiasis. Additionally, in 2016, the closely related macrodiolide xylopyranoside was discovered, cocosolide (not shown), which exhibits immunosuppressive activity.[16] The structure of cocosolide was verified by total synthesis through a 17-step route (LLS).[16]

Retrosynthetically, clavosolide A was envisioned to arise through dimerization of the hydroxy acid **11**, which is prepared from pyran **3** by glycosylation using the permethylated D-xylose trichloroacetimidate **4** and subsequent introduction of the cyclopropyl moiety using iodide **8** (Scheme 1). Pyran **3** is potentially accessible in only two steps via bidirectional asymmetric allylation of 2-methyl-1,3-propane diol[8a] **2** followed by Fenton-Semmelhack alkoxypalladation-carbonylation of the resulting C_2-symmetric diol **2**.[17,18,19] The feasibility of assembling pyran **3** in this manner was rendered uncertain due to the presence of the methyl-bearing chirotopic nonstereogenic center at C4. However, in related halocyclizations of olefinic alcohols, highly stereoselective desymmetrization is achieved owing to the preference of the latent methyl-bearing stereocenter to reside equatorially in the nascent pyran.[8b,20]

The synthesis of pyran **3** begins with the bidirectional allylation of 2-methyl-1,3-propane diol (Scheme 2). The reported procedure involves generation of the cyclometallated catalyst *in situ* and utilizes (*S*)-Cl,MeO-BIPHEP as ligand.[8a] To improve scalability, an effort was made to optimize the reaction using the inexpensive ligand (*S*)-BINAP. Ultimately, it was found that using the preformed π-allyl-*C,O*-benzoate complex modified by (*S*)-BINAP, (*S*)-Ir-BINAP (10 mol%), and 4-cyano-3-nitrobenzoic acid (20 mol%) as an additive, the desired

C_2-symmetric diol **2** could be obtained in 53% yield on 10 mmol scale, which is roughly equivalent to the yield previously obtained using (*S*)-Cl,MeO-BIPHEP. Notably, an earlier synthesis of the corresponding desmethyl diol required a 7-step sequence involving three protecting group manipulations, two separate alcohol oxidations and two separate carbonyl asymmetric allylborations was required.[21] Initial attempts at Fenton-Semmelhack alkoxypalladation/carbonylation[17,18,19] of the C_2-symmetric diol **2** using $Pd(OAc)_2/CuCl_2$ in acetonitrile-methanol solvent provided the desired pyran **3**, but with poor levels of diastereocontrol at the C4 methyl-bearing chirotopic nonstereogenic center. Improved stereocontrol (6:1 dr) was achieved upon slow addition of diol **2** (over 10 min) and use of benzonitrile as cosolvent. Lower diastereoselectivity was observed using other Pd catalysts ($PdCl_2$, PdI_2, $Pd(dppf)Cl_2$, $Pd(PPh_3)_2Cl_2$).

In prior syntheses of clavosolide A,[10] direct formation of the trimethyl xylopyranoside moiety suffered from poor levels of β-selectivity. Specifically, in Schmidt-type glycosylations of trichloroacetimidates promoted by BF_3•OEt_2 or TMSOTf, a 1:1 ratio of α- vs β-anomers was observed.[10a,b,d,f] Aggarwal's synthesis exploited neighbouring group participation in a tribenzoyl-protected xylopyranosyl donor to guide β-anomer formation,[10i] however, this approach incurred two additional chemical manipulations to transform the tribenzoate into permethylated xylopyranoside. A recent report from the Fairbanks group showed that chiral phosphoric acids catalyze β-selective Schmidt-type glycosylations of trichloroacetimidates.[22] Inspired by this work, glycosylation of pyran **3** catalyzed by (*R*)- and (*S*)-**PA-I** and **PA-II** were attempted in dichloromethane and toluene solvent using the trimethyl xylopyranoside trichloroacetimidate **4** (Scheme 3).[10a] Reactions catalyzed by the parent BINOL phosphoric acids (*R*)- and (*S*)-**PA-I** were inefficient and did not significantly influence β-selectivity. However, in accord with Fairbanks' report, glycosylations catalyzed by (*R*)-**PA-II** displayed good levels of β-diastereoselectivity, with reactions conducted in toluene displaying slightly higher yields. The structure of β-xylopyranoside **5** was corroborated by single crystal X-ray diffraction analysis.

With xylopyranoside **5** in hand, a carbonyl addition strategy for stereoselective introduction of the cyclopropane moiety spanning C10-C13 was undertaken, which necessitated preparation of cyclopropyl iodide **8** (Scheme 4). To this end, allyl alcohol **6** was subjected to Charette's enantioselective iodocyclopropanation mediated by the indicated commercially available boronate ester.[23] The resulting cyclopropylcarbinyl alcohol **7** was converted to the tosylate and exposed to $LiBH_4$ in ether solvent to furnish cyclopropyl iodide **8**. Cyclopropyl iodides participate in lithium-halogen exchange and may be captured by diverse electrophiles with complete retention of configuration.[23b,24] Conversion of **8** to the corresponding cyclopropyl lithium followed by treatment with aldehyde **9** (prepared via DIBAL reduction of xylopyranoside **5**) delivered the desired carbonyl addition product **10**, but as an equimolar mixture of C9 epimers across a range of solvents. Based on chelation control or the Cram-Reetz model, additions to β-alkoxy aldehydes are anticipated to favor the undesired 1,3-*anti*-diastereomer.[25] Hence, the observed lack of diastereoselectivity was actually encouraging as it suggested the feasibility of utilizing a chirally modified cyclopropyl lithium reagent to bias formation of the desired 1,3-*syn*-diastereomer. Indeed, after screening a range of chiral diamines, including (*1S,2S*)-N^1,N^1,N^2,N^2-

tetramethylcyclohexane-1,2-diamine[26] and (*1S,2S*)-N^1,N^1,N^2,N^2-tetramethyl-1,2-diphenylethane-1,2-diamine,[27] it was found that aldehyde addition in the presence of (−)-sparteine[28] enabled formation of cyclopropylcarbinyl alcohol **10** in a 4:1 diastereomeric ratio. The major and minor diastereomers could be separated by column chromatography on basic alumina. Exposure of **10** to $KMnO_4$/$NaIO_4$ affected chemoselective alkene oxidative cleavage to form carboxylic acid **11** without oxidation of the C9 alcohol.[29] Finally, mixed anhydride-mediated esterification-macrolactonization delivered clavosolide A in 7 steps (LLS).[30]

To summarize, through bidirectional asymmetric diol allylation, a 7-step (LLS) total synthesis of the 20-membered marine macrodiolide clavosolide A has been achieved in the absence of protecting groups or chiral auxiliaries. In the longest linear sequence, 5 of 7 reactions represent skeletal construction events, 3 of which are stereoselective catalytic processes. The remarkably concise nature of this route is underscored by the fact that in 9 previously reported total syntheses 11-34 (LLS) were required. Future studies will focus on the development of related metal-catalyzed C-C bond formations that streamline polyketide construction by directly transforming lower alcohols to higher alcohols using abundant π-unsaturated pronucleophiles.[30]

Supplementary Material

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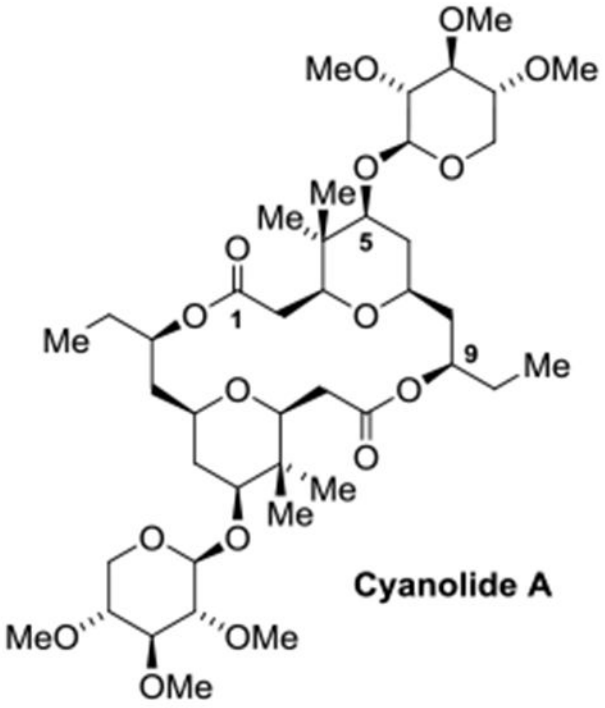
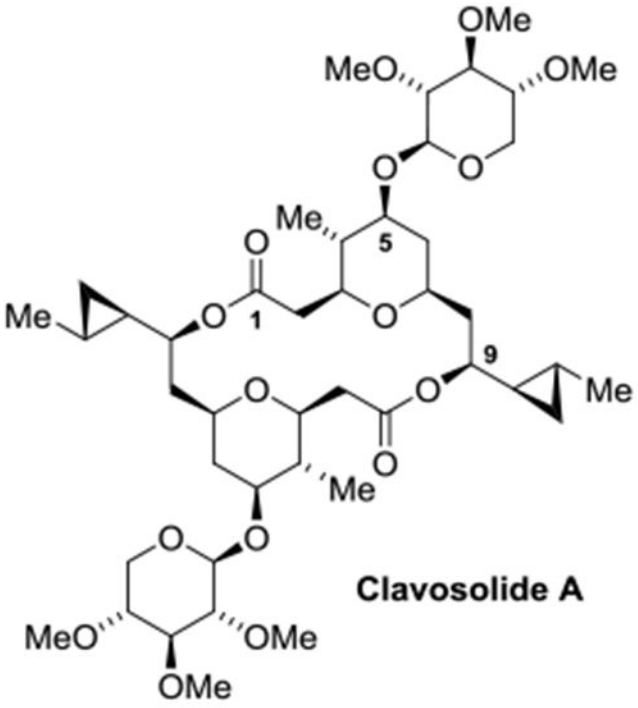


Cyanolide A

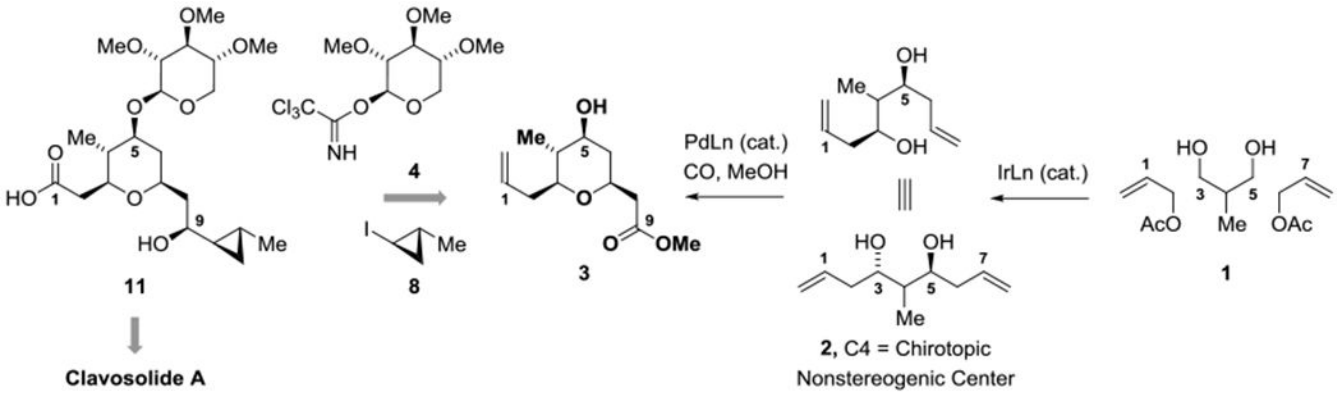


Clavosolide A

Total or Formal Syntheses	LLS (TS)	Total or Formal Syntheses	LLS (TS)
Hong, 2010 (ref. 9a)	14 (21)	Lee, 2006 (ref. 10a)	26 (31)
Reddy, 2011 (ref. 9b)	17 (21)	Smith, 2006 (ref. 10b)	19 (28)
She, 2011 (ref. 9c)	15 (18)	Willis, 2006 (ref. 10c)	16 (20)
Pabbaraja, 2011 (ref. 9d)	17 (21)	Chakraborty, 2008 (ref. 10d)	34 (36)
Rychnovsky, 2011 (ref. 9e)	12 (19)	Jennings, 2009 (ref. 10e)	21 (23)
Jennings, 2011 (ref. 9f)	15 (19)	Floreancing, 2012 (ref. 10f)	14 (21)
Krische, 2013 (ref. 9g)	7 (9)	Hong, 2015 (ref. 10g)	16 (25)
Bates, 2014 (ref. 9h)	13 (18)	Breit, 2015 (ref. 10h)	11 (16)
Zhou, 2019 (ref. 9i)	19 (22)	Aggarwal, 2016 (ref. 10i)	14 (24)

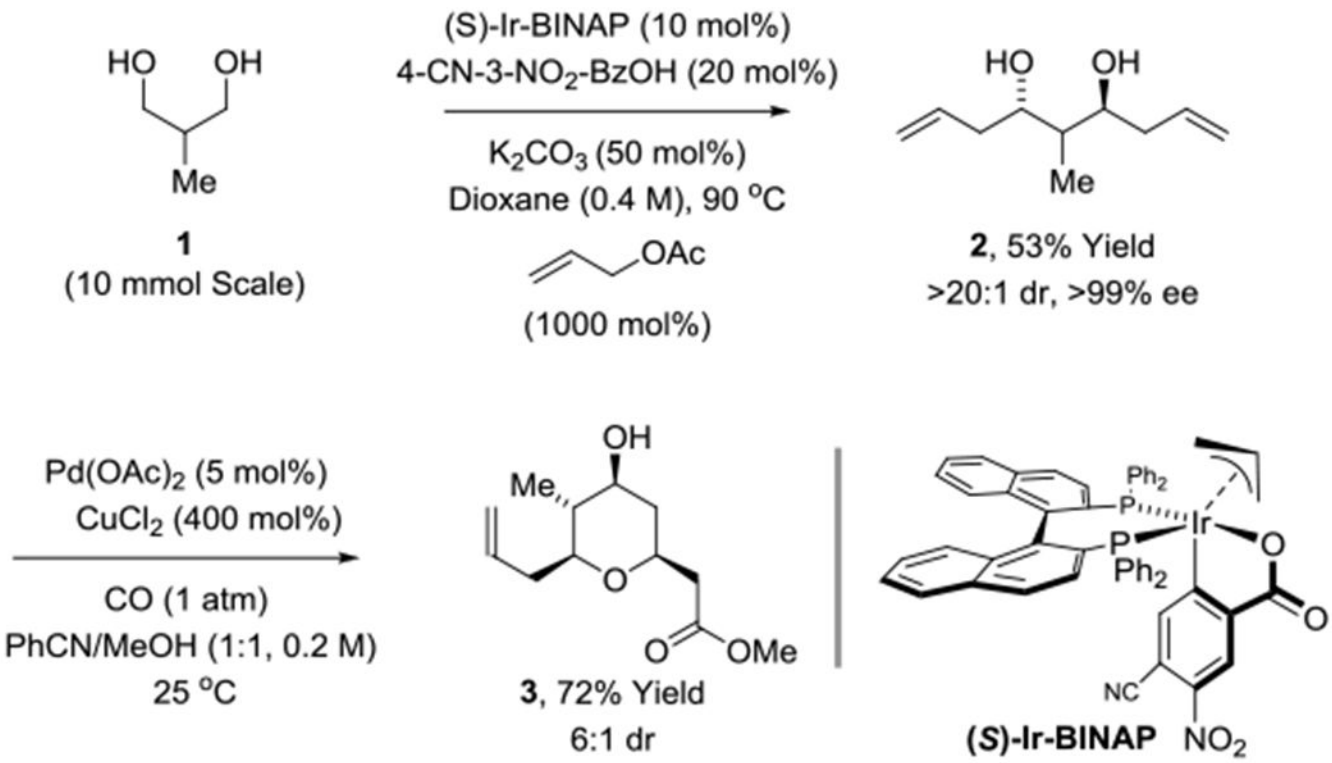
Figure 1.

Summary of prior total and formal syntheses of cyanolide A and clavosolide A. For graphical summaries of total syntheses, see Supporting Information. Longest Linear Sequence (LLS), Total Steps (TS).



Scheme 1.

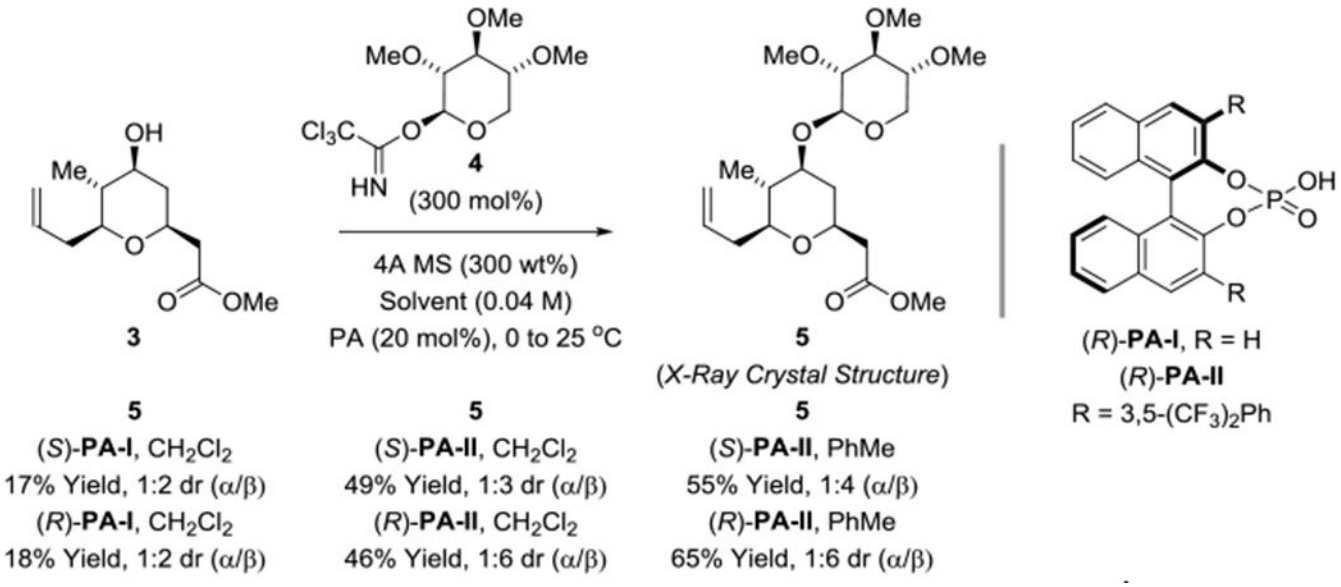
Retrosynthetic analysis of clavosolide A via bidirectional allylation of 2-methyl-1,3-propane diol.



Scheme 2.

Enantioselective synthesis of pyran **3**.

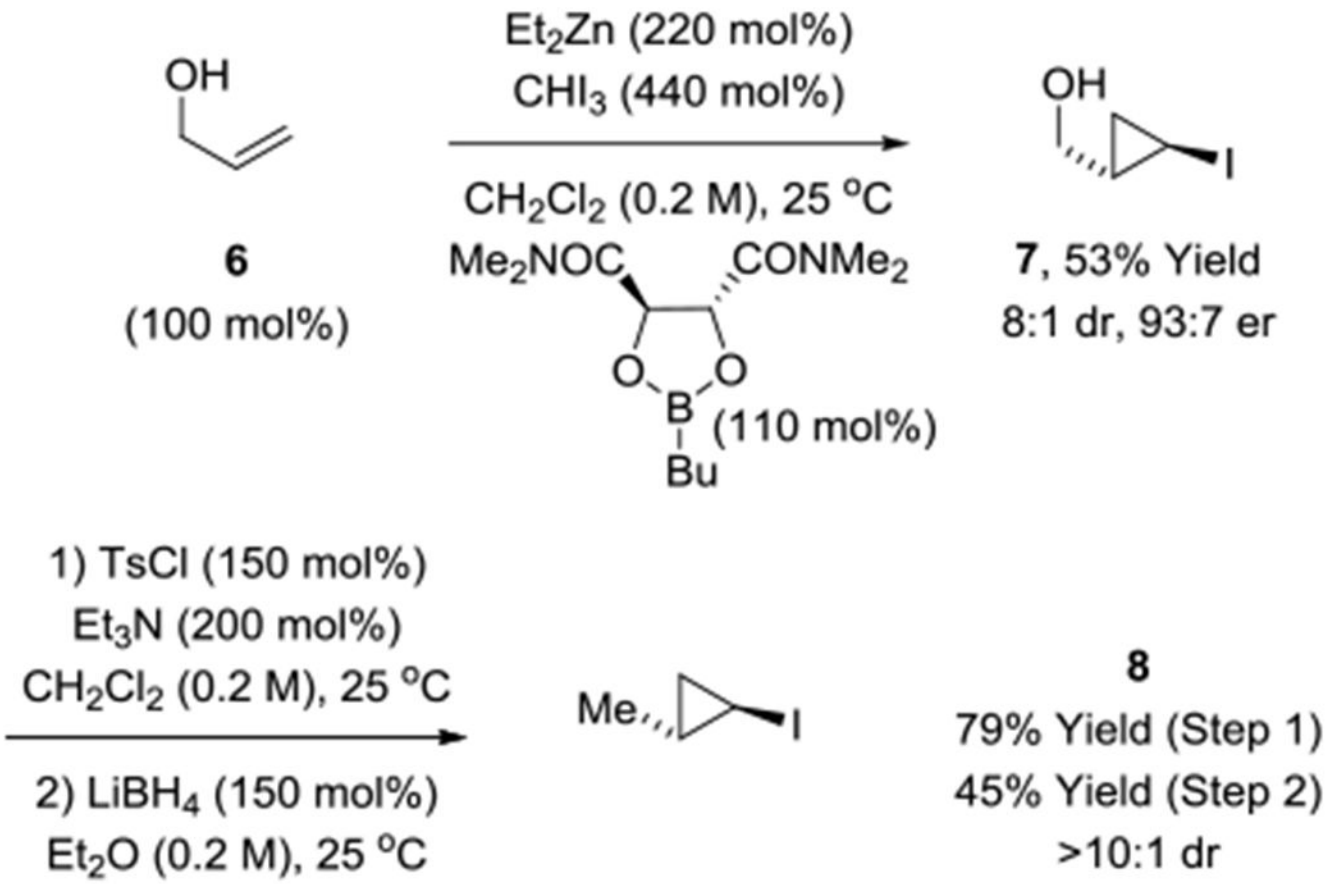
[a]Yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR analysis of crude reaction mixtures. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.



Scheme 3.

Chiral phosphoric acid-catalyzed Schmidt glycosylation of pyran **3** to form trimethyl xylopyranoside **5**.[a]

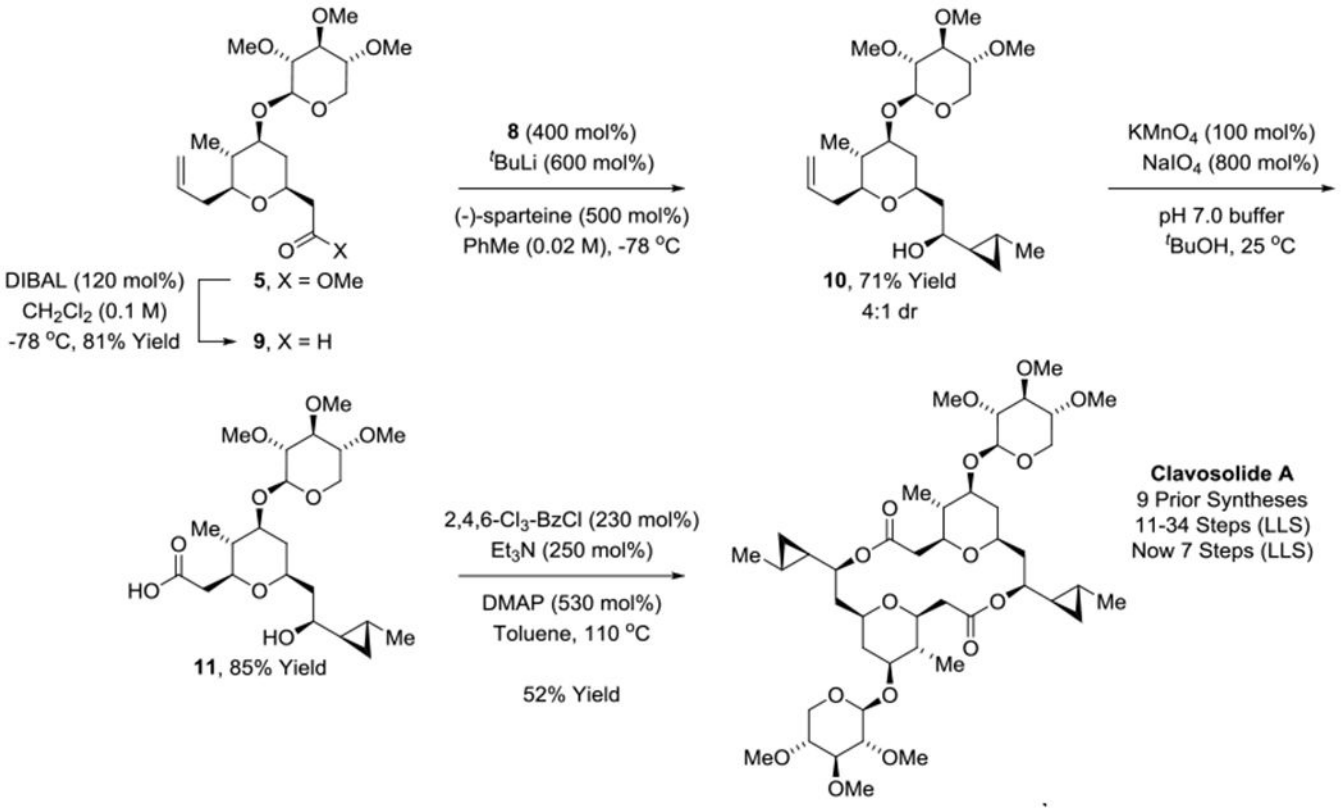
[a]Yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR analysis of crude reaction mixtures. See Supporting Information for further experimental details.



Scheme 4.

Enantioselective synthesis of iodide **8**.

[a]Yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR analysis. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.



Scheme 5.

Total synthesis of clavosolide A.

[a]Yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR analysis of crude reaction mixtures. See Supporting Information for further experimental details.