Supporting Information

Synthesis of Filibuvir. Part II. Second Generation Synthesis of a 6,6-Disubstituted 2*H*-Pyranone via Dieckmann Cyclization of a β-Acetoxy Ester

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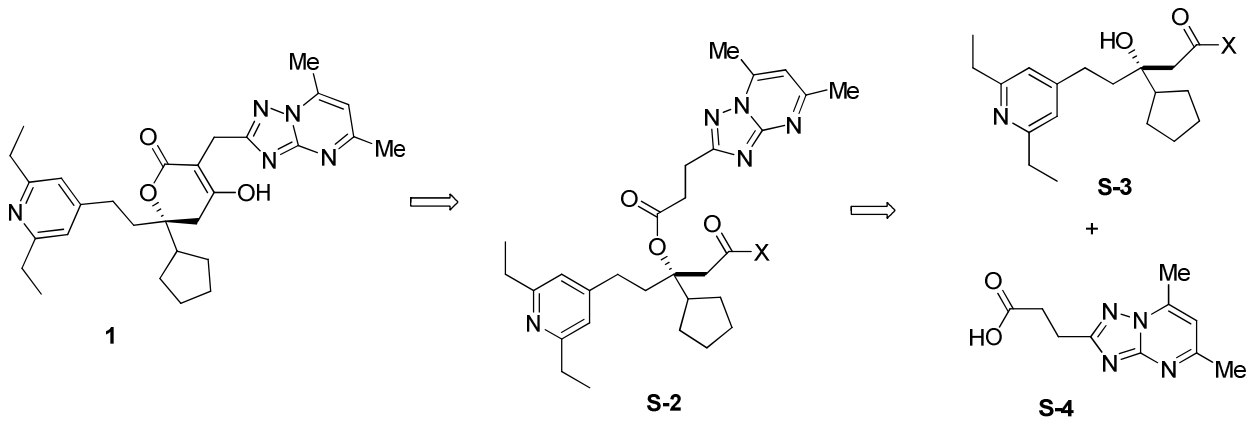
Convergent Dieckmann Approaches

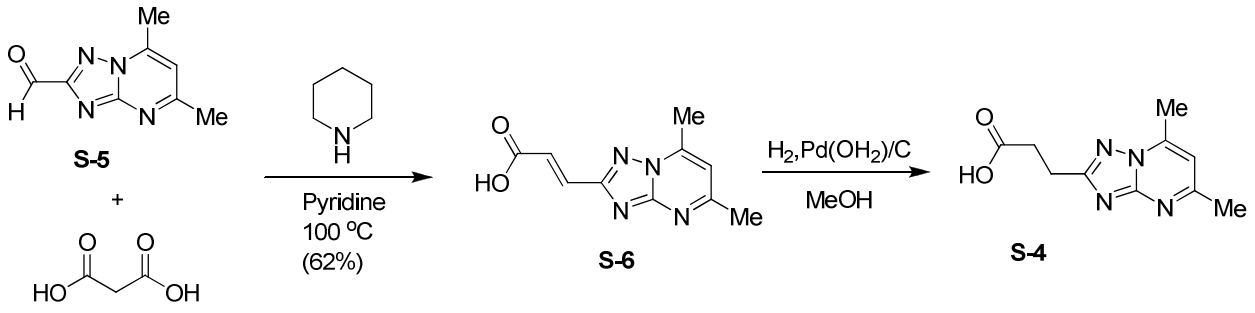
Another pyrone formation strategy we envisioned was a "convergent" Dieckmann cyclization with the triazolopyrimidine moiety installed prior to pyrone formation (Scheme 1). The most straightforward way to install the heterocycle piece is by the direct acylation of tertiary alcohol **S-3** with the homologated acid **S-4** to form ester **S-2**.

Scheme 1. Convergent Dieckmann cyclization strategy.



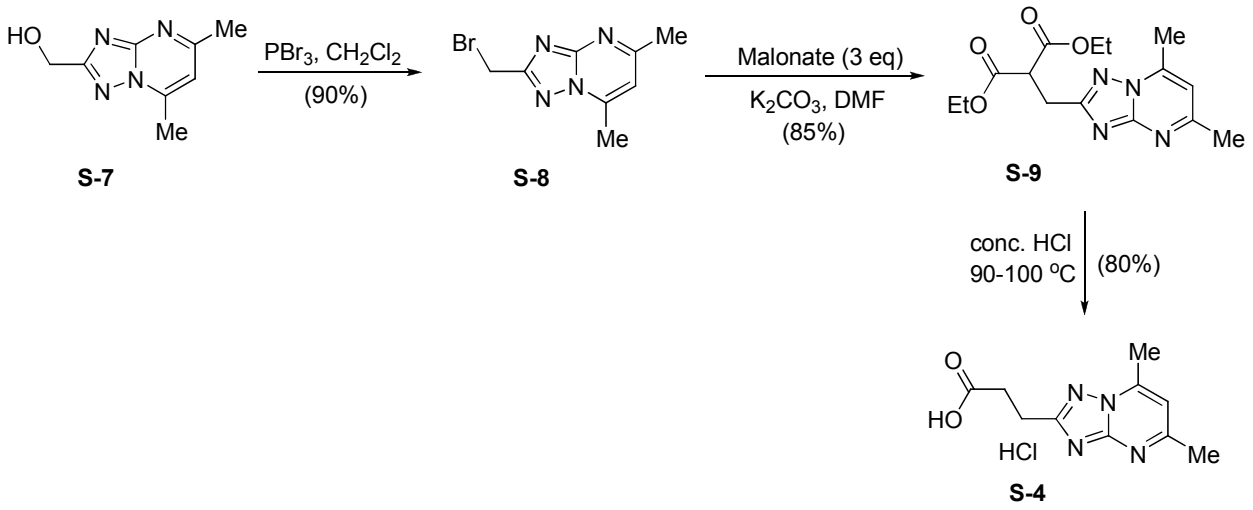
The homologated acid **S-4** had been prepared before by the Knoevenagel condensation (Doebner modification) of malonic acid with aldehyde **S-5** followed by hydrogenation of the α,β-unsaturated acid **S-6** (Scheme 2). Although this was an efficient approach, the low solubility of **S-4** presented challenges to the purification.

Scheme 2. Preparation of **S-4** from malonic acid.



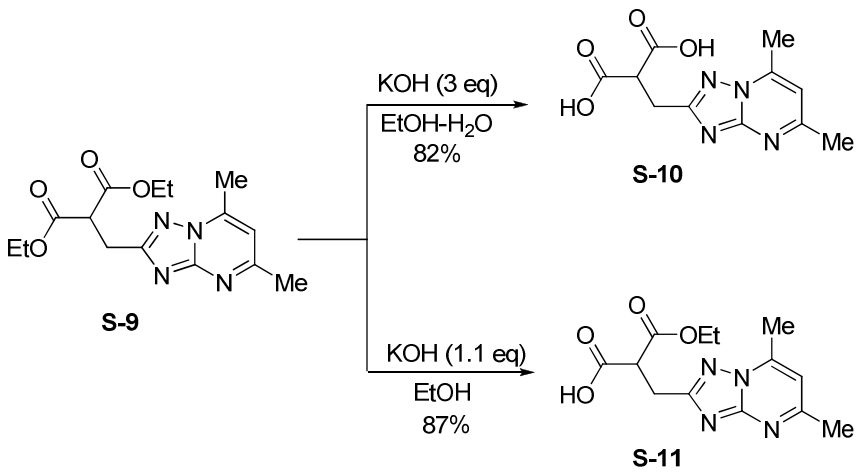
During the course of development work on alternative end games, we found that alcohol **7** could be efficiently converted to bromide **S-8** (Scheme 3) with PBr_3, which was isolated by crystallization in 90% yield. We then attempted the reaction of **S-8** with diethyl malonate. Significant bis-alkylation by-product was formed if only one equivalent of malonate was used (2:1 ratio mono-alkylation versus bis-alkylation) with potassium carbonate as base in THF. The ratio was improved to over 30:1 with 3 equivalents of malonate in DMF. After aqueous work-up, the desired product **S-9** was isolated by crystallization in 85% yield. The hydrolysis and decarboxylation were carried out in concentrated HCl at 90-100 °C, and the HCl salt of **S-4** was directly isolated from the reaction mixture in 80% yield and excellent purity.

Scheme 3. Preparation of acid **S-4** via bromide **S-8**.

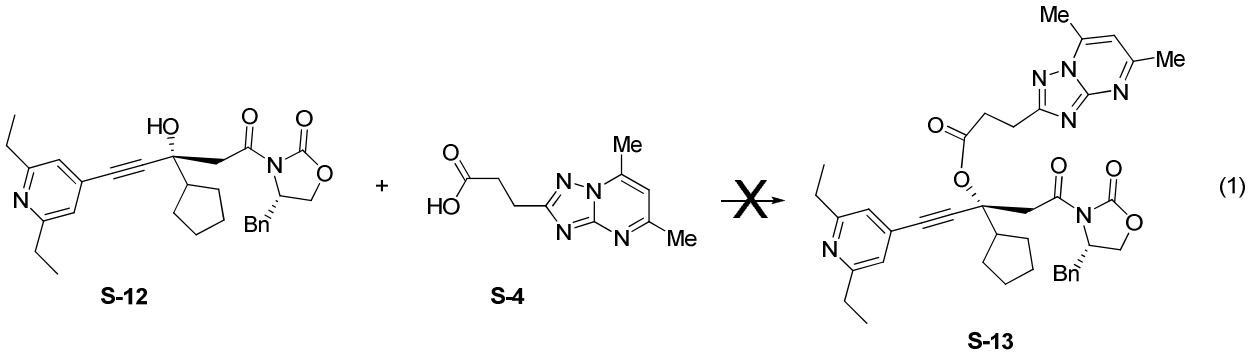


Alternatively, the hydrolysis of **S-9** under basic conditions (KOH) generated either the diacid **S-10** or the monoacid monoester **S-11** depending on the stoichiometry of base used (Scheme 4). Both compounds were also isolated by crystallization in good yields.

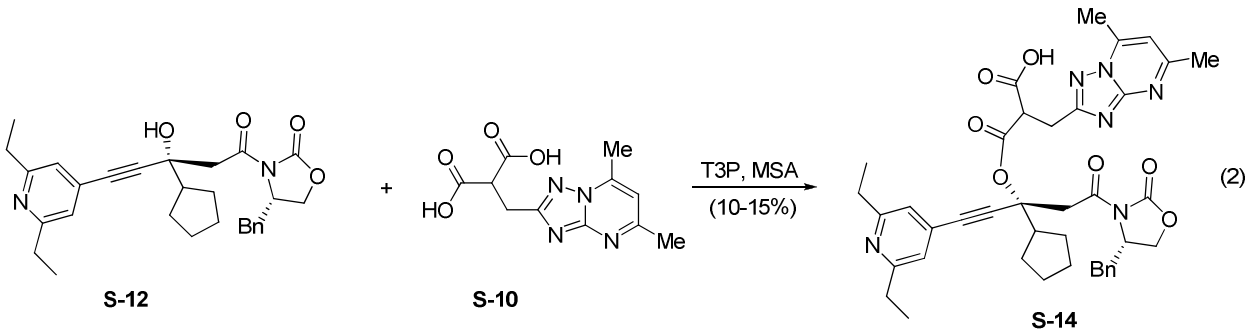
Scheme 4. Preparation of diacid **S-10** and acid-ester **S-11**.



We first attempted the direct acylation of tertiary alcohol **S-12** with **S-4** under various conditions (eq 1). Unfortunately, none of the desired product **S-13** was detected with activation methods such as EDCI, T3P, and acyl chloride (prepared from $(COCl)_2$), likely due to the hindered nature of the tertiary hydroxyl group.

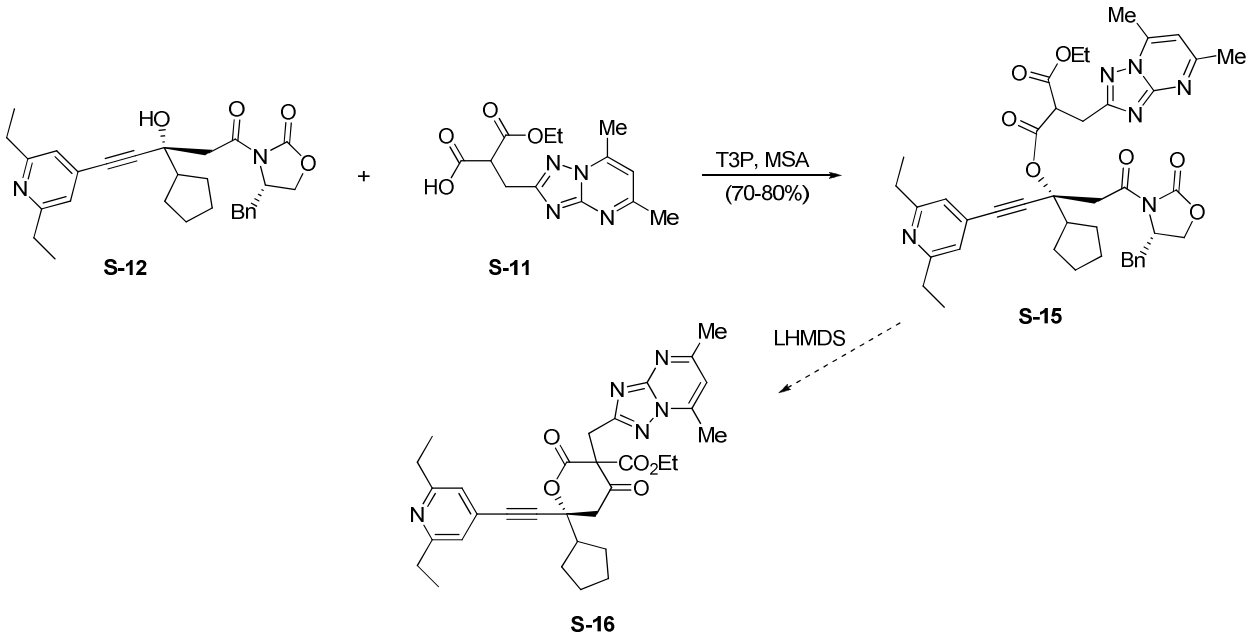


With the successful acylation of **S-12** with malonic acid and T3P (*vide supra*), we next carried out the acylation with **S-10** (eq 2). Although we did observe the desired product **S-14**, the yield was only 10-15%. Significant decarboxylation of **S-10** to **S-4** occurred under the acidic reaction conditions.



To minimize the decarboxylation of **S-10**, the acylation was then attempted with the monoacid monoester **S-11**. The reaction gave ~70% conversion with one equivalent of **S-11**, and could be improved to ~83% conversion with 1.5 equivalent of **S-11** (Scheme 5). However, attempted cyclization of the acylated compound **S-15** did not provide any of the desired product **S-16**. This was likely due to the steric hindrance in the cyclization substrate (**S-15**).

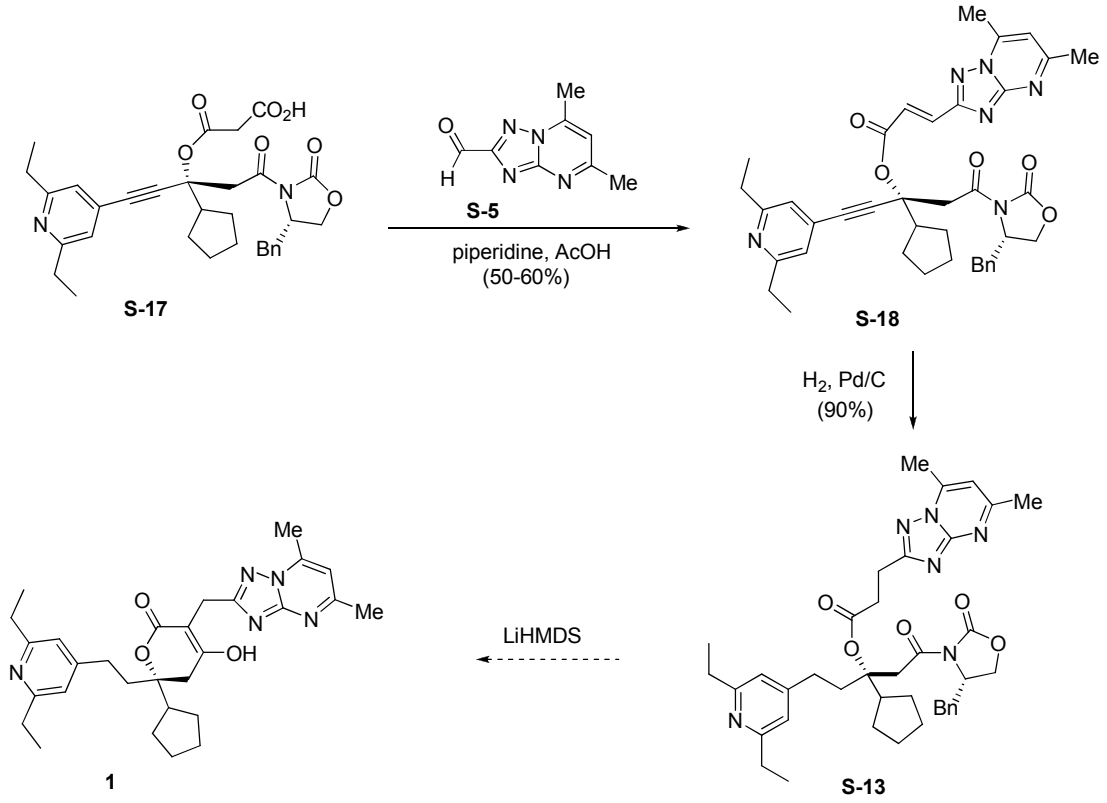
Scheme 5. Preparation and attempted cyclization of ethyl malonate **S-15**.



We next turned to an indirect approach employing the malonic acid acylated product **S-17**. We found that **S-17** underwent Knoevenagel condensation (Doebner modification) with aldehyde **S-5**

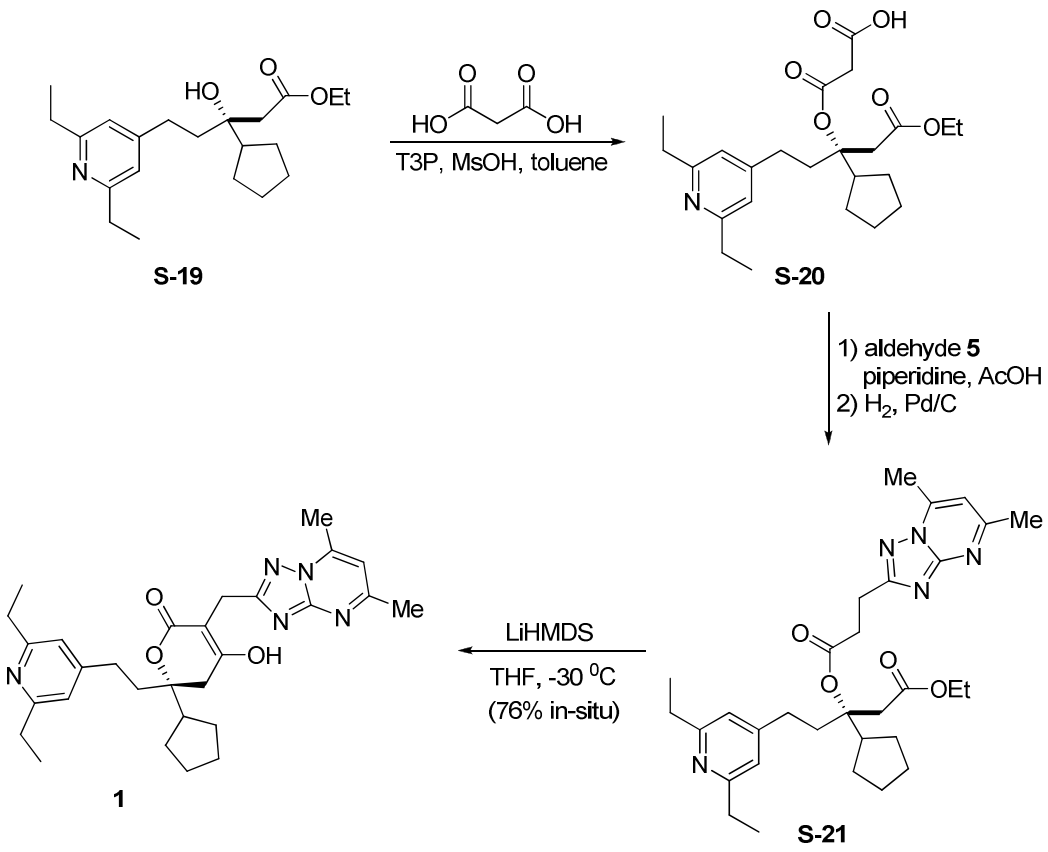
to give ester **S-18** in an unoptimized 50-60% yield after flash chromatography purification (Scheme 6). Hydrogenation of both the double and triple bonds gave compound **S-13** cleanly. We then subjected **S-13** to cyclization using LHMDS. Unfortunately, the reaction generated multiple products by LCMS, and only trace amount of the desired product **1**.

Scheme 6. Preparation and attempted cyclization of ester **S-13**.



Given the better Dieckmann cyclization result with esters (*vide infra*), the same strategy was applied to the ethyl ester substrate **S-19** to prepare malonic acid **S-20** and ethyl ester substrate **S-21** (Scheme 7). The Dieckmann cyclization of **S-21** did provide **1** in 76% in-situ yield. Nevertheless, due to the longer linear sequence, the convergent Dieckmann approach was not further pursued.

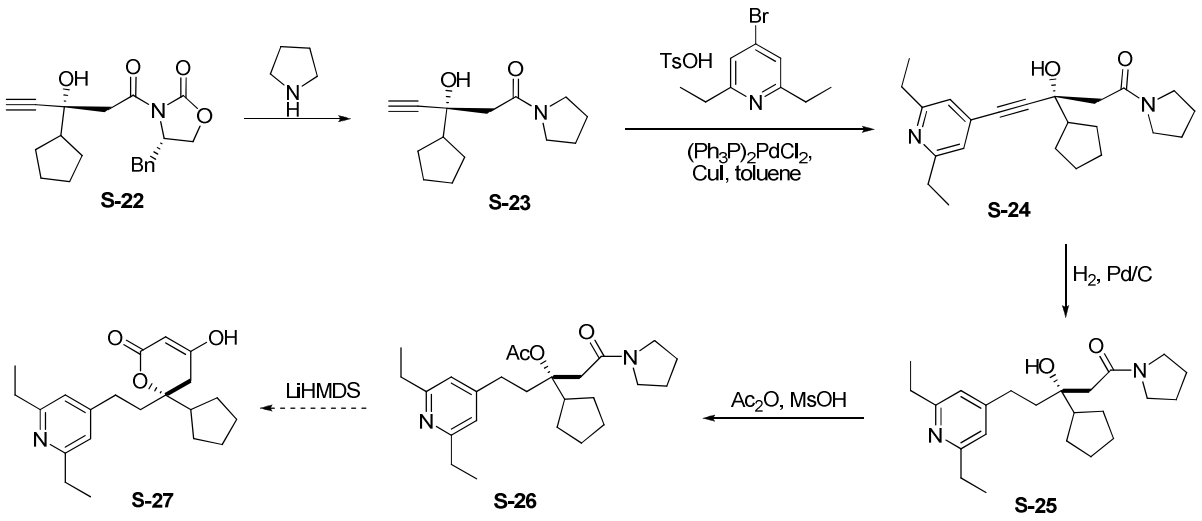
Scheme 7. Preparation and attempted cyclization of ethyl ester **S-21**.



Preparation of amide S-26, thioester S-30, Weinreb amide S-31, and ethyl ester S-32

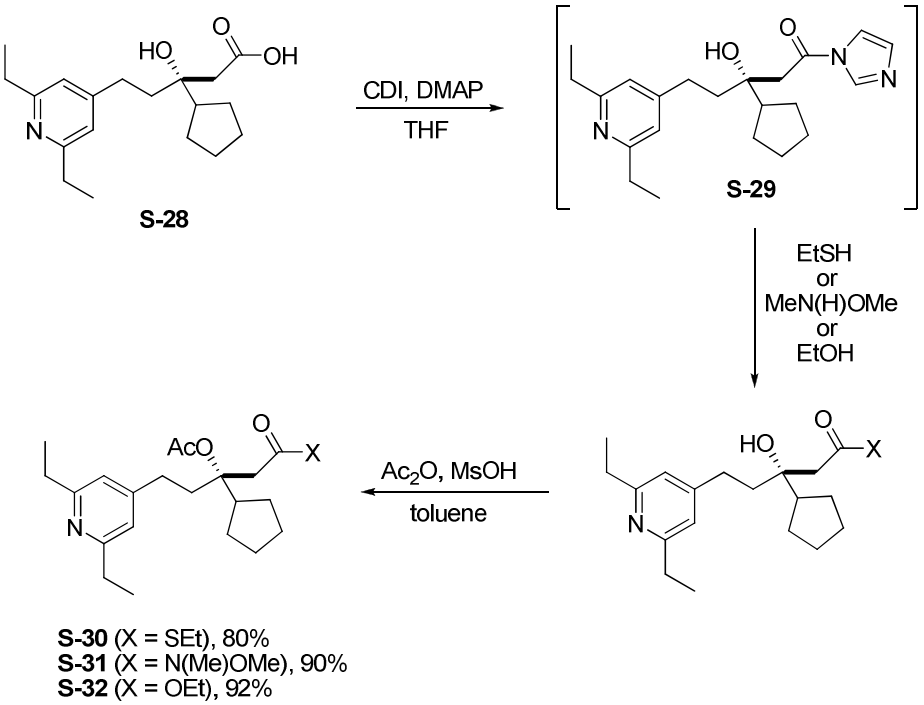
The pyrrolidine amide substrate **S-26** was prepared by a similar sequence as the current route (Scheme 8). The oxazolidinone of **S-22** could be efficiently exchanged with excess pyrrolidine to give alkyne amide **S-23**. The Sonogashira reaction of **S-23** with 4-bromo-2,6-diethylpyridine tosic acid salt, followed by hydrogenation of **S-24** and acetylation of **S-25**, gave the substrate **S-26** for the Dieckmann cyclization.

Scheme 8. Preparation of pyrrolidine amide **S-26**.



The other three substrates were prepared from the alcohol acid **S-28**, an intermediate in the enabling route. After activating the carboxylic acid with CDI, the acyl imidazole intermediate (**S-29**) was treated with ethanethiol, Weinreb amine, or ethanol for the coupling reaction, followed by acetylation with the current conditions ($MeSO_3H/Ac_2O$) to give the corresponding substrates **S-30**, **S-31**, and **S-32** (Scheme 9) in good yields.

Scheme 9. Preparation of thioester **S-30**, Weinreb amide **S-31**, and ethyl ester **S-32**.



S-30 (X = SEt), 80%
S-31 (X = N(Me)OMe), 90%
S-32 (X = OEt), 92%