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Catalytic Asymmetric Synthesis of (+)-Anthecotulide Using Enyne and Meyer–Schuster Rearrangements

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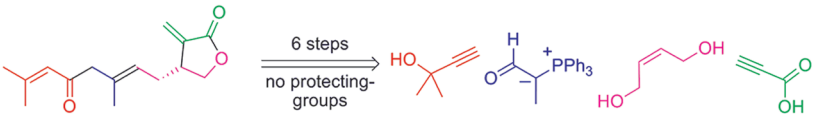
ABSTRACT



(+)-Anthecotulide **1**

The bioactive sesquiterpene lactone (+)-anthecotulide (1) is synthesized for the first time, in a six-step sequence devoid of protecting groups. The key transformations are a novel Rh(I)-catalyzed asymmetric enyne rearrangement of a terminal alkynyl ester (4), to form the α-methylene-γ-butyrolactone core, and a final-step mild Au(I)-catalyzed Meyer–Schuster rearrangement

Anthecotulide (**1**) is an optically active irregular sesquiterpene lactone first isolated in 1969 from *Anthemis cotula* L. (stinking chamomile).[1] At the time, the structure was assigned from analysis of spectroscopic data. In 2005, a more detailed analysis, which included a NOESY experiment to determine the configuration of the stereogenic double bond, corroborated the original structural assignment.[2] Anthecotulide has attracted interest due to its contact allergen properties[3] (contamination of chamomile preparations by *A. cotula* is to be avoided)[2] and its unusual biosynthesis for a sesquiterpene, involving head-to-middle coupling of geranyl diphosphate and dimethylallyl diphosphate.[4] More recently, anthecotulide demonstrated antibacterial,[5] antimalarial,[6] trypanocidal, and leishmanicidal activity[7] and has been shown to inhibit the activation pathway of the transcription factor NF-*k*B which regulates pro-inflammatory mediators (cytokines, nitric oxide, prostaglandins).[8]

Due to the emerging biological activity profile, and as part of our ongoing interest in the synthesis of α-methylene-γ-butyrolactones,[9] we communicate here the first synthesis of anthecotulide.

In this synthesis we aimed to address the synthetic challenge of assembling the sensitive α-methylene-γ-butyrolactone[10] and deconjugated ketone functionality in an efficient and stereocontrolled manner. Specifically, we envisaged accessing the natural product **1** by a Meyer–Schuster rearrangement from propargylic alcohol **2** (Scheme 1). This alcohol **2** would be derived by Wittig homologation of aldehyde **3**, which was anticipated to be accessible from cycloisomerization of enyne **4**.

So as to examine this chemistry, enyne **4** was first prepared (83% yield) by DCC coupling[11] of commercially available (*Z*)-but-2-ene-1,4-diol (**6**) with propiolic acid (**5**)

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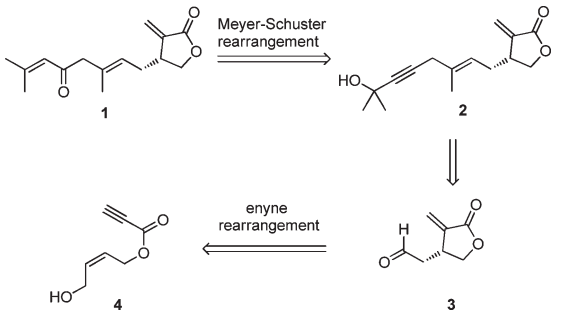
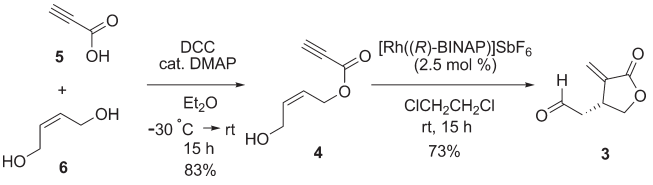
Scheme 1. Retrosynthetic Strategy to Anthecotulide (**1**)



(Scheme 2). Although metal catalyzed Alder-ene reactions of 1,6-enynes have been well-studied,[12] to the best of our knowledge only a single isolated example to form an α-methylene-γ-butyrolactone has been reported, using an achiral ruthenium(I) catalyst ($CpRu(NCCH_3)_3PF_6$).[13]

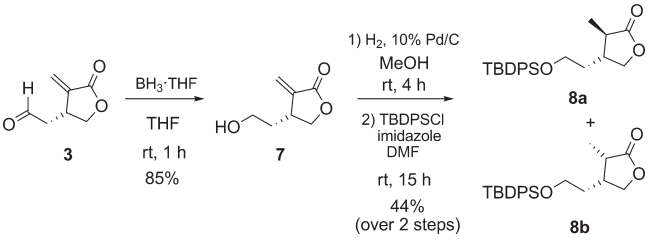
Scheme 2. Synthesis and Cycloisomerization of Enyne **4**



Considering the prospects for asymmetric catalysis, we decided to investigate the synthesis of the α-methylene-γ-butyrolactone core under rhodium(I) catalysis, which was originally developed by Zhang and co-workers with internal alkynes.[14] Using Zhang's conditions ($[Rh(cod)Cl]_2$/*rac*-BINAP/$AgSbF_6$, (0.025:0.05:0.05), $ClCH_2CH_2Cl$, rt, 15 h), enyne **4** gave the desired aldehyde **3**, albeit in low yields (20−30%) which were difficult to reproduce. On the basis that polymerization might be a competitive side reaction, we lowered the reaction concentration from 0.2 to 0.1 M and 0.05 M, but these experiments also gave low yields (23% and 15%, respectively). However, modifying the conditions to those used by Nicolaou and co-workers, where preforming the catalyst [Rh(*rac*)-BINAP)]SbF_6 was found optimal for the synthesis of α-methylene-γ-butyrolactams,[15] gave aldehyde **3** in much improved yield (71%). Finally, using [Rh((*R*)-BINAP)]SbF_6 gave (+)-aldehyde **3** in 73% yield and 96:4 er by chiral HPLC (Scheme 2).[16]

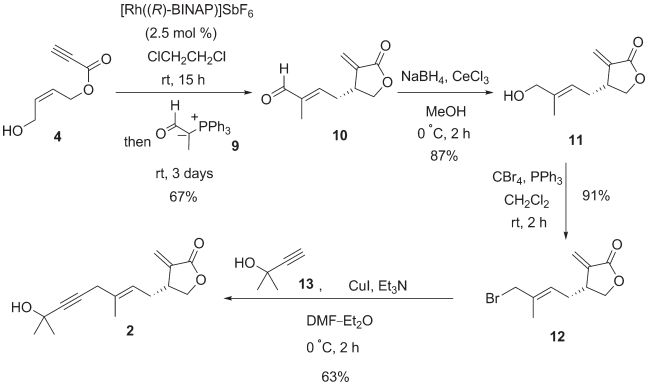
The sense of asymmetric induction in the cycloisomerization above using (*R*)-BINAP was determined by conversion of (+)-aldehyde **3** to the *trans*-lactone **8a**[17] of previously established absolute configuration and comparison of specific rotation values (Scheme 3). Chemoselective reduction of aldehyde **3** using BH_3,[18] followed by hydrogenation of the α-methylene group in lactone **7** and silylation of the resulting primary alcohol, gave a cis−trans mixture of lactones **8** from which *trans*-lactone **8a** could be obtained by careful chromatography. This correlation established that the *R*-configured aldehyde **3** was obtained from enyne **4** when using (*R*)-BINAP, and this corresponds to the same sense of asymmetric induction observed in Zhang's and Nicolaou's studies.[14,15]

Scheme 3. Configuration of Aldehyde (+)-**3** by Conversion to *trans*-Lactone (+)-**8a**



With a catalytic and highly enantioselective synthesis of aldehyde **3** established we examined its conversion to the propargylic alcohol **2** for the projected Meyer−Schuster rearrangement. Structurally related (internal) alkynes have been recently shown to undergo one-pot cycloisomerization−Wittig reaction.[19] In the present case, addition of ylide **9**[20] (1.3 equiv) following the Alder-ene reaction gave the *E*-α,β-unsaturated aldehyde **10** (67% from enyne **4**, Scheme 4).

Scheme 4. Synthesis of Propargylic Alcohol **2**



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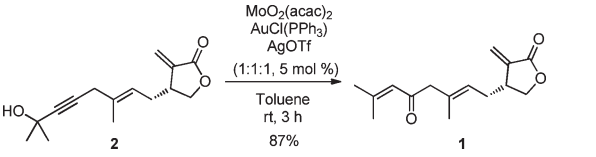
1,2-Reduction of aldehyde **10** with Luche's conditions,[21] followed by an Appel reaction[22] using PPh_3 and CBr_4, gave allylic bromide **12** (79% yield from **10**). Of various procedures examined for the displacement of the allylic bromide **12** by terminal alkynes,[23] conditions developed by White and co-workers were found to work best.[24] Propargylic alcohol **2** was obtained (63%) by addition of the allylic bromide **12** at 0 °C to the alkynylcopper species from alkynol **13**, prepared by mixing with stoichiometric CuI and Et_3N in a 2:1 mixture of Et_2O and DMF.

Mild methods for the conversion of propargyl alcohols into α,β-unsaturated ketones (Meyer−Schuster rearrangements) have recently been developed.[25] Akai and co-workers reported an effective catalytic combination of $MoO_2(acac)_2$ with $AuCl(PPh_3)$−AgOTf, where rearrangement is considered to proceed by [3,3] sigmatropy of an intermediate molybdate which is facilitated by alkyne coordination to an *in situ* generated cationic Au catalyst.[26] Using these conditions propargylic alcohol **2** gave (+)-anthecotulide (**1**) in excellent yield (87%) (Scheme 5). No isomerization of the β,γ-trisubstituted alkene into conjugation with the ketone was observed. The spectroscopic data were in full agreement with those in the literature,[2,16] and the specific rotation of synthetic anthecotulide $[\alpha]^{23}_D$ +81.1 (*c* 0.15, $CHCl_3$) is of comparable magnitude to that reported for the natural product $[\alpha]^{23}_D$ +76.9 (*c* 0.032, $CHCl_3$).[27]

In summary, the first and asymmetric synthesis of (+)-anthecotulide (**1**) has been achieved in six steps from commercially available materials, which additionally establishes the absolute configuration of the natural product as *R*- and provides a strategy for analog synthesis. Aside from its brevity, which stems from only one oxidation level change[28] and the absence of protecting-group chemistry,[29] the synthesis is noteworthy for the first example of an enantioselective enyne cycloisomerization to a α-methylene-γ-butyrolactone and the tolerance of the latter functionality to Au(I)-catalyzed Meyer−Schuster rearrangement.

Scheme 5. Anthecotulide (**1**) by Meyer−Schuster Rearrangement



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Note Added after ASAP Publication. The version published ASAP on October 7, 2011 contained typographical errors in two specific rotations related to Scheme 5. The correct version reposted on October 11, 2011.

Supporting Information Available. Full experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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