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Dynamic kinetic Asymmetric Transformations with Hard Nucleophiles: Cyclopentens for Anti-tuberculosis and Antibiotics

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Introduction

Asymmetric additions of alkyl nucleophiles to racemic allylic chlorides will be used to access derivatives of important cyclopentene containing natural products. We describe in this paper the asymmetric additions of alkyl nucleophiles to racemic allylic chlorides, to access cyclopentenyl fatty acids. These natural products have timely biological activity and the eventual synthesis of derivatives will help develop structure-activity relationships. Cyclopentene natural products Alepric acid [1], aleprestic acid [1], and gorlic acid [1], have not previously had their synthesis reported. The asymmetric addition reaction is a dynamic kinetic asymmetric transformation (DYKAT) to a racemic allylic chloride to give cyclopentenes with high level of ee [2]. The bioassay results showed that gorlic acid has unusual selectivity against positive gram bacteria.

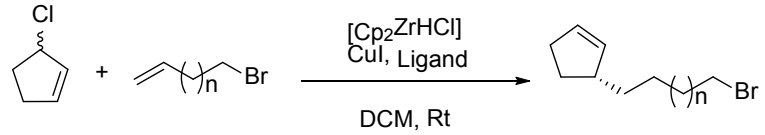
Copper-catalyzed asymmetric 1, 4-addition to α, β- unsaturated compounds is now well developed, but cyclopentenone remains a special case and addition of hard nucleophiles is notoriously difficult. Yields are generally limited by competitive reactions of the highly reactive enolate generated in the reaction, and much lower ee values than observed with other substrates are obtained. This commonly attributed to the "flatness" of the 5-memberd ring substrate.

Fletcher group [2] recently demonstrated that alkyl nucleophiles can be used with racemic allylic chlorides in dynamic kinetic asymmetric transformations (DYKATs) to give cyclopentenes with high levels of ee (Scheme 1). These reactions work at room, rather than cryogenic-temperatures, which is unusual for asymmetric reactions with hard nucleophiles and practically significant.

Fletcher group [2] applied the method to short, straightforward, enantioselective syntheses of three natural products **(Figure 1)** which compare favorably to previously reported syntheses, and will facilitate the preparation of analogues, these acids have been first isolated from *Hydnocarpus wightiana* oil (chaulmoogric oil) by Cole and Cardoso [1] in 1939, this oil had been used in the East against leprosy and various skin conditions for many hundreds of years, and was the standard remedy [3,4] for leprosy.

Hydnocarpic acid and chaulmoogric acid were used in ancient and traditional medicine, particularly as leprosy treatments; in both cases the cyclopentenyl ring is a requirement for biological activity. (1) is believed to act by blocking the activity of biotin or inhibiting microbial biotin synthesis [5], while the activity of (2) is likely due to incorporation into the cell wall lipids of *M. leprae* [6]. A recent report shows that (2) and anthelminthicin C (3) significantly inhibit *M. tuberculosis* growth with MIC values of 9.82 and 4.38 µM respectively [7]. (3) also inhibits *para*-aminobenzoic acid biosynthesis (*P*ABA) [7], inhibitors of *p*ABA are important leads for new antibiotics, as this pathway is not found in humans [8].

In our project, we prepared three cyclopentenyl fatty acids, which



Scheme 1 Alkyl Nucleophiles can be used with Allylic Chlorides in Asymmetric transformations (DYKATs) to give Cyclopentenes.

never been synthesized, Alepric acid (4), Aleprestic acid (5) and Gorlic acid (6) **(Figure 2)**.

In the literature, it is believed that aleprestic acid has an inhibitory activity against glycolysis [9] and gorlic acid has an anti-bacterial activity [9,10]. These natural products are supposed to have an anti-bacterial, anti-leprosy and anti-tuberculosis activity.

Our bioassay results showed an interesting activity of gorlic acid 3.91 µg/mL towards the positive gram bacteria *Staphylococcus aureus*.

The goal of this study is to use DYKATs to rapidly access a variety of new natural products, it is hoped that these will be used in Structure activity relationship studies and as possible leads for new anti-tuberculosis and anti-biotic agents.

The syntheses of (4), (5) start from commercially available bromo alkene (b_1), (b_3) to give bromo-substituted (d_1), (d_3) which is converted to (f_1), (f_3) (by hydrolysis, then oxidation) (Scheme 2).

We followed the same method to synthesize (f_2) which was subjected to Wittig reaction [10,11] in the presence of the Wittig reagent (h) prepared [12,13] from bromocyclohexanoic acid (g) with triphenyphosphine (Scheme 3). Gorlic acid (6) was obtained selectively (one isomer: cis) with good yields 69 % by using NaHDMS as base (Scheme 3). In contrary, in case [14] of NaH, the yields and selectivity shut down (yields= 13%) obtaining a mixture of two isomers E/Z: 3/2 (Scheme 3), while the using of n-BuLi [14] didn't led to the desired product.

Finally, we succeeded to prepare three natural products never been synthesized previously by selective methods (See supplementary information for full details).

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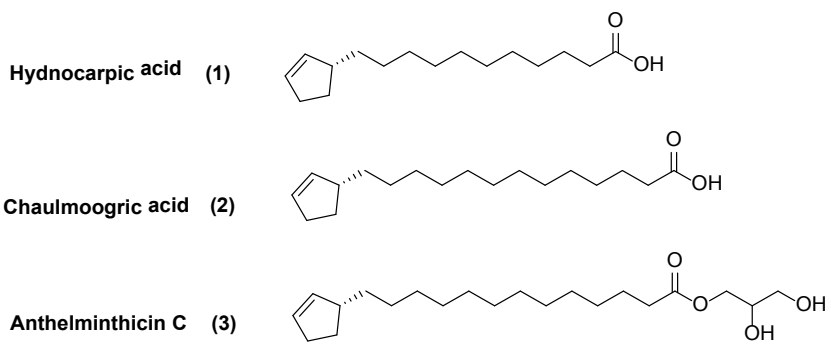


Figure 1 Synthesis of Three Natural Products.

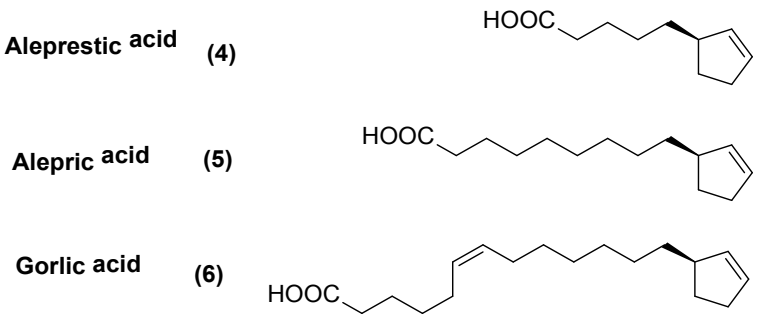
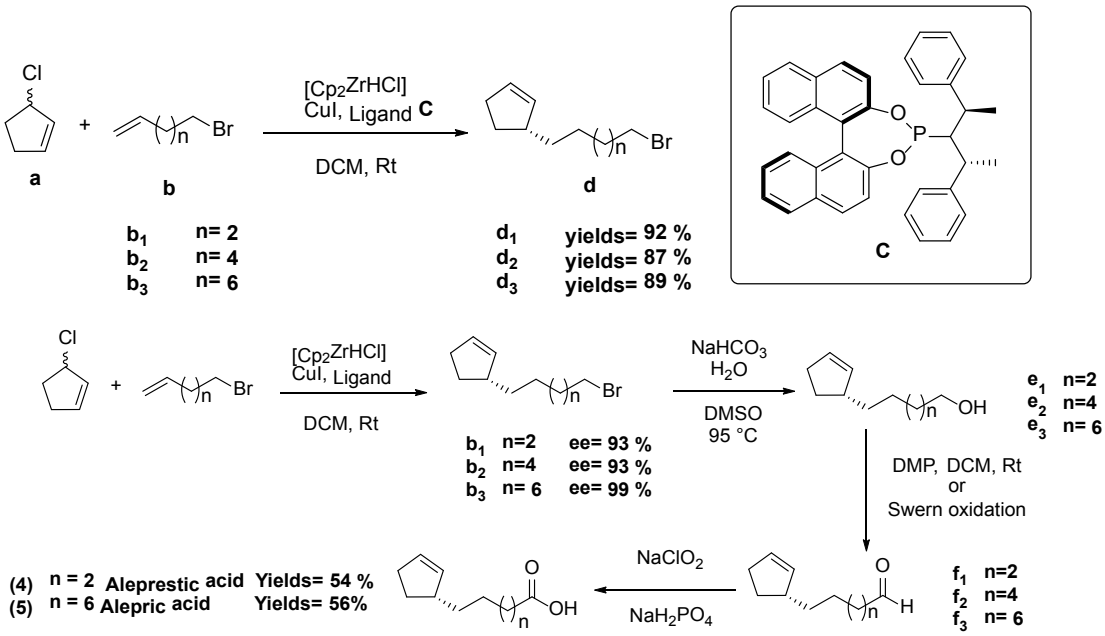
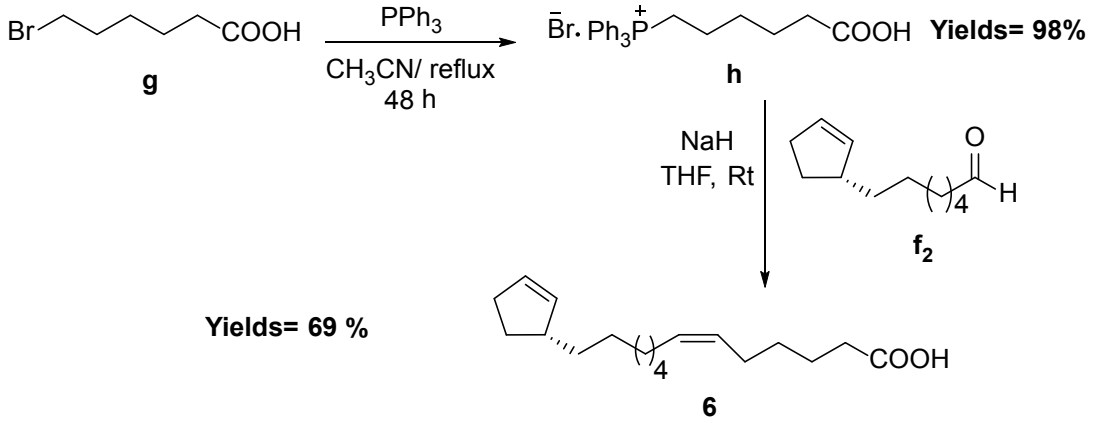


Figure 2 Synthesis of three Cyclopentenyl Fatty Acids.



Scheme 2 The Synthesis of Alepresticacid and Alepric aid start from Bromo Alkene (b_1), (b_3) to give Bromo-substituted (d_1), (d_3) which is converted to (f_1), (f_3) (by hydrolysis, then oxidation).



Scheme 3 Synthesize (f_2) in the presence of the Wittig reagent (**h**) prepared from Bromocyclohexanoic acid (**g**) with Triphenyphosphine. Gorlic acid was obtained selectively by using NaHDMS as base. In case of NaH, the yields and selectivity shut down obtaining a mixture of two isomers.

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