8-20-2009

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An Efficient and Economic Asymmetric Synthesis of (+)-Nootkatone, Tetrahydronootkatone, and Derivatives

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Received May 12, 2009

ABSTRACT

A facile route to enantiomerically pure (+)-nootkatone and derivatives has been established through conjunctive stereoselective Grignard/anionic oxy-Cope (AOC) reactions.

There is a constant need for new products and applications that possess suitable termite activity without adverse health and environmental effects.1 It has been well documented that highly active compounds exuded by some plants are vital to the plants’ survival and perseverance in their natural habitat in the face of predation. Therefore, in an effort to implement Nature’s successful remedies for our own practicality, the introduction of natural active compounds into “modern” termicide formulations has received growing interest and attention in recent years. Although several botanical termicides have been identified, only pyrethrins, to date, are available for commercial use.

(+)-Nootkatone 1 (Figure 1), first isolated from the heartwood of Alaskan yellow cedar, Chamaecyparis noot-

katensis (D. Don),2 was later isolated from the peel of Citrus paradisi Macfaden3 and found to be the carrier of the grapefruit essence. In addition to its applications in the flavor and fragrance arenas, Zhu et al. recently discovered that (+)-nootkatone also possessed marked repellent and toxic activity toward the devastating Formosan subterranean termite.4,5 However, the current cost affiliated with the natural product renders it impractical for any industrial application except

Figure 1. Valencane skeletal framework.
flavors and fragrances. Also, although several research groups have synthesized compounds from the valencane family, none have been able to produce an economically viable scheme that would be appropriate for large-scale production. Therefore, it was our purpose to develop an efficient and economic asymmetric synthesis for (+)-nootkatone and analogues that could be applied to an industrial setting and utilized not only for termite (and other arthropods) control but also as a grapefruit flavor and fragrance additive.

Most synthetic approaches to the valencane skeletal framework (Figure 1) have relied on Robinson annulation reactions. However, stereospecific establishment of the vicinal cis-dimethyl substituents and their relative configuration to the isopropenyl group has proven problematic. In 1980, Yoshikoshi described a method for the enantioselective synthesis of (+)-nookatone based on the acid-mediated, tandem, cyclobutane cleavage–aldol cyclization reaction sequence depicted in Scheme 1. With such an effective method for construction of the required ring system, the problem of nootkatone synthesis is reduced to the effective method for construction of the required ring system, and utilized not only for termite (and other arthropods) control but also as a grapefruit flavor and fragrance additive.

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In lieu of nopinone, inexpensive natural product β-pinene 2, a GRAS (generally recognized as safe) compound, was chosen as the starting material for economical and environmental reasons. Although the conversion of β-pinene to nopinone could be performed via ozonolysis methods, a safer alternative was preferred. Implementing Lee’s methodology, the oxidative cleavage of β-pinene was performed with mild reaction conditions and inexpensive reagents to provide nopinone in excellent yields (Scheme 3).

Following Yoshikoshi’s procedure, nopinone was converted to the mixed aldo product 3. The resulting ketone was then subjected to Grignard reagents to provide the tertiary alcohol product 4 in excellent yields and selectivity (>20:1).

The AOC rearrangement of 4 was found to be extremely sensitive to reaction conditions, and some optimization was required to obtain acceptable yields (Scheme 4). When the AOC rearrangement was run at room temperature, an unusual fragmentation took place leading to the loss of the allyl or methallyl unit introduced in the previous Grignard addition step. Although not typical, this fragmentation is not without precedent, and has been proposed to proceed by a retro-ene mechanism. Undesired frag-

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**Scheme 1. Yoshikoshi Route: the C₄ Stereocenter Problem**

![Scheme 1](image-url)

**Scheme 2. Solving the C₄ Stereocenter Problem**

![Scheme 2](image-url)

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(4) In the USA, one Formosan subterranean termite colony, comprising up to 10 million individuals, is capable of consuming a thousand pounds of wood per year. The estimated nationwide damage reaches an excess of $1 billion dollars. In Louisiana, the damage caused by this species is valued at $500 million; New Orleans, alone, accounts for $300 million. Henderson, G.; Laine, R.; Zhu, B.; Ibrahim, S.; Crowe, W.; Sauer, A. M.; Yu, Y.; Crowe, W. E.; Laine, R. A. J. Org. Chem. 2003, 68, 2695–2701.


mentation could be avoided by lowering the reaction temperature to 0 °C. Our original plan was to treat the enolate intermediate generated in the AOC rearrangement with methyl iodide, thus converting 4 to 6 in one step. However, this plan was thwarted by the unexpected tendency of these enolates to undergo exclusively O-alkylation instead of the desired C-alkylation. An attempt to induce selectivity for C-alkylation by counterion exchange (LiBr) was partially successful, but the product yield was unacceptably low. In the end we decided to isolate ketone 5 (aqueous quench) and then introduce the methyl group in a subsequent step employing reaction conditions (NaNH₂, benzene, 45 °C) previously described by Yoshikoshi.

Subsequent Wacker oxidation (b, R = H) or oxidative cleavage (a, R = Me) of 6 produces a diketone, a known intermediate in Yoshikoshi’s route. In a chemical engineering scale-up, this oxidation step may need to be replaced to lower the expense and eliminate Hg byproduct. The remaining steps in Yoshikoshi’s synthesis, concurrent cyclobutane cleavage and aldol cyclization with subsequent dehydrochlorination, were then interdigitated to provide an efficient and economic asymmetric synthesis of (+)-nootkatone 1. However, to optimize yields, an alternative procedure for the dehydrohalogenation of the chloro enone was employed in lieu of Yoshikoshi’s alumina prep. (+)-Nootkatone was thus prepared from its hydrochloride precursor utilizing the methodologies previously described by Caine.¹¹ This modification ultimately resulted in a 21% yield increase in the last step of the reaction sequence.

In summation, the combination of the Grignard reaction and the anionic Oxy-Cope rearrangement resulted in an effective scheme to selectively generate two adjacent stereocenters, thereby providing a synthetic sequence to enantiomerically pure (+)-nootkatone. The overall yields for the eight-step syntheses were 31% (R = H) and 33% (R = Me), respectively. This route should be useful for a variety of industrial applications. Not only has (+)-nootkatone been shown effective for insects (termites, ticks, cockroaches, mole crickets, nematodes, ectoparasites, and red imported fire ants), but also for termite control with applications in wood preservatives.¹² (+)-Nootkatone synthesized also possesses substantial value in the flavor and fragrance world.

Furthermore, tetrahydronootkatone (THN) 7 and 11,12-dihydronootkatone 8 are two hydrogenation products of (+)-nootkatone (Figure 2). Both demonstrate enhanced repellent activity, with respect to their precursor, toward the Formosan subterranean termite.⁵ In addition, due to the steric nature of (+)-nootkatone’s valencane ring system, reactions of 1 often yielded products in an unprecedented high stereoselectivity. Those findings will be presented in a subsequent report.

Acknowledgment. Support of this work by funds provided by the USDA/ARS-New Orleans (58-6435-8-084) and Louisiana State University is gratefully acknowledged. We thank Drs. Dale Treleaven, Frank Zhou and Mr. Guangyu Li, all of the Department of Chemistry, Louisiana State University for assistance with 2D NMR experiments.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.