

A Concise Enantioselective Synthesis of (+)-endo-Brevicomin Accomplished by a Tellurium/Metal Exchange Reaction

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Um homoenolato gerado pela reação de troca telúrio/lítio foi aplicado na síntese enantioselectiva do (+)-endo-brevicomin com 70% de rendimento isolado e 84,4% de *e.e.*

A homoenolate generated by tellurium/lithium exchange reaction was employed in a straightforward enantioselective synthesis of (+)-endo-brevicomin in 70% yield and 84.4% *e.e.*

Keywords: tellurium/lithium exchange, homoenolate, epoxide opening

Introduction

Organometallics are among the most commonly used reagents in both organic and inorganic chemistry. Because of their importance for preparative purposes many organometallics are commercially available. Among them, organolithiums are probably the most popular and versatile, because they can act as bases and nucleophiles as well as precursors of many other organometallics by transmetallation. Commonly, organolithium reagents are prepared by direct lithiation via acid / base reaction, reduction of halides with elemental lithium,¹ by tin/lithium exchange or by reductive cleavage of sulphides.² Complementary to these methodologies, is the tellurium/lithium exchange reaction.³ Previously we demonstrated the synthetic application and efficacy of the tellurium/lithium exchange reaction to generate functionalized organolithium reagents⁴ as well as to prepare other classes of organometallics, including organomagnesium,⁵ organocoper,⁵⁻⁷ and organocerium⁷ reactive reagents. Herein, we report the enantioselective synthesis of the pine beetle pheromone (+)-endo-brevicomin⁸ (**1**) and its racemic mixture using a telluride as the key precursor of a functionalized organometallic reagent.

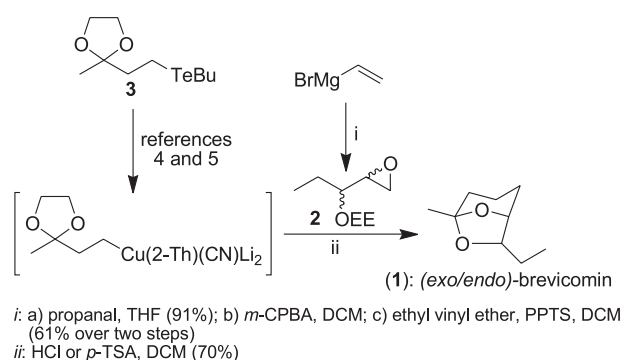
Results and Discussion

The racemic synthesis of (+/-)-(exo/endo)-brevicomin was performed by the sequence presented in Scheme 1. Epoxy-ether **2**, was prepared in 55 % overall isolated yield as follows: Vinyl magnesium bromide was reacted with propanal, followed by epoxidation with *m*-CPBA and finally, the crude epoxy-alcohol was treated with ethyl vinyl ether in the presence of pyridinium *p*-toluenesulfonate (PPTS) in dichloromethane. With **2** in hand, telluride **3**⁷ was treated with one equivalent of *n*-butyl-lithium promoting the instantaneous tellurium/lithium exchange reaction. It is worth to mention that the tellurium/lithium exchange reaction can be easily verified by TLC analysis, since the consumption of **3** is accompanied by formation of the non polar di-butyltelluride. The resulting organolithium was converted into the higher order cyanocuprate in the usual way, and then reacted with **2**.^{5,6,9} The hydroxy-ketal originated from this reaction was directly treated with hydrochloric acid or *p*-TSA resulting in the racemic mixture of (+/-)-(endo/exo)-brevicomin (**1**) in 70% isolated yield.

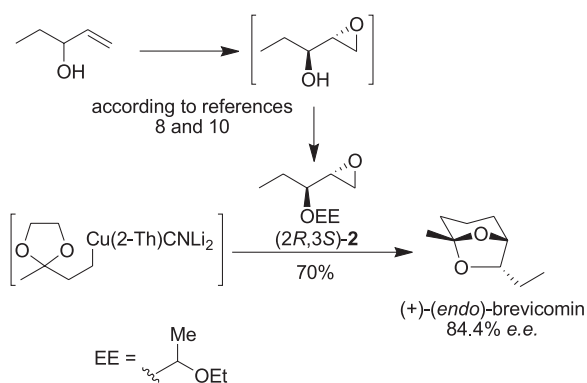
The enantioselective synthesis of (+)-endo-brevicomin was carried out using the enantioenriched epoxide (2*R*,3*S*)-**2** which was prepared from 1-penten-3-ol by kinetic resolution epoxidation according to the procedure reported by Sharpless *at al*¹⁰ and applied latter by Mori⁸ for the same substrate (Scheme 2).

The enantiomeric purity of **2** could not be directly measured by chiral capillary gas chromatography.

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Scheme 1. Racemic synthetic route of (*exo/endo*)-brevicomine.



Scheme 2. Kinetic resolution epoxidation of 1-penten-3-ol (+69.3°, *c* = 1.0, diethyl ether, 84.4% e.e.).

However, the reaction of **2** with the higher order cyanocuprate, prepared from telluride **3**, as described before, yielded the enantioenriched *endo*-brevicomine which was subjected to chiral capillary gas chromatography revealing an optical purity of 84.4% e.e. This value was confirmed by polarimetric analysis ($[\alpha]_D^{20} +69.3^\circ$ (*c* = 1.0, diethyl ether), comparing with literature data.⁸ In this way we can conclude that (2*R*,3*S*)-**2** was obtained with the same optical purity, i.e. 84.4% e.e., on the kinetic Sharpless epoxidation since no racemisation has been observed by Mori *at al.*⁸ for this substrate under the same experimental conditions employed by us.

Conclusion

In conclusion, (+)-*endo*-brevicomine was synthesized in one step and 70% isolated yield starting from the known enantioenriched epoxy-ether **2**⁷ by using a tellurium/metal exchange reaction. Currently, some functionalized organotellurides are being used in our laboratory in the

synthesis of some other bioactive compounds, including pheromones.

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