

Total synthesis of 1-(*Z*)-atractylodinol

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Abstract—The total synthesis of 1-(*Z*)-atractylodinol, a natural polyacetylenic alcohol with several biological activities, has been achieved using a newly developed telluride synthon and a novel use for the Negishi type coupling reaction employing vinyl tellurides. © 2006 Published by Elsevier Ltd.

Vinylic tellurides are important due to their usefulness as intermediates in organic synthesis, including the synthesis of natural products.¹ Of the two isomers, the *Z*-vinylic tellurides have been employed more frequently as intermediates because they are easily accessible.² The hydrometalation of alkynes usually affords *E*-alkenes; however, hydrotelluration, the most important method for the preparation of vinylic tellurides, yields *Z*-alkenes in a high regio- and stereoselectivity. Recently, new applications of the *Z*-vinylic tellurides using palladium-catalyzed cross-coupling have been described.³ In these cross-coupling reactions, a *Z*-vinylic telluride acts as a pseudohalide in a similar manner to vinyl halides or triflates used in the Sonogashira et al.,⁴ Heck and Dieck,⁵ Suzuki,⁶ and Stille and co-workers⁷ cross-coupling reactions. A new methodology based on the Negishi cross-coupling reaction⁸ using vinylic- and aryl-tellurides and heteroarylzinc chlorides catalyzed by PdCl₂/CuI was also described.⁹ This cross-coupling reaction is quite general and allows the formation of a new sp²–sp² carbon bond in good yields and high stereoselectivity.

Herein, we describe the application of this methodology in the synthesis of 1-(*Z*)-atractylodinol (**1**), a natural product isolated from the dried rhizomes of *Atractylodes lancea* De Candolle (Chinese: Cangzhu) widely used in China and Japan against rheumatic diseases, digestive disorders, night blindness, and influenza.¹⁰ *A. lancea*

produces these antiulcer effects¹¹ and inhibits gastric secretion.¹² The aqueous extract of *A. lancea* also improves the delay in gastric emptying¹³ and the *n*-hexane extract of the rhizome exhibits good inhibitory activities in both 5-lipoxygenase (5-LOX) and cyclooxygenase-1 (COX-1) enzymatic in vitro assays.¹⁴

Typical recoveries from 570 g of dried and powdered *A. lancea* rhizomes gives 9.6 mg with about 70% of (*E*)-atractylodinol—the already described isomer.¹⁰ The ¹H NMR spectral data suggested that the newly isolated compound differed mainly in the lower chemical shift values for vinyl protons together with smaller coupling constants. Therefore, the authors identified the compound as the *Z*-isomer. The question arises whether the *Z*-isomer was the genuine constituent of the drug, or whether it was generated from its *E*-isomer during the extraction or isolation procedures.¹⁴

Our retrosynthetic approach for 1-(*Z*)-atractylodinol (**1**) is outlined in Figure 1.

The vinyl telluride that was required for assembling the *Z*-double bond was prepared according to Scheme 1.

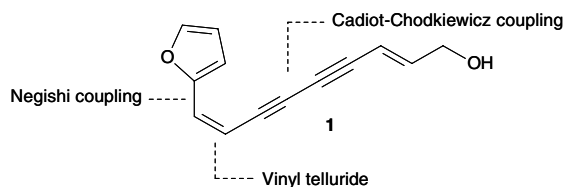
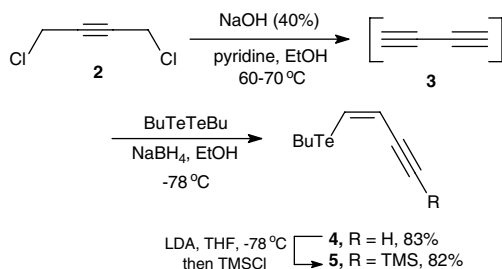


Figure 1. Retrosynthetic analysis for 1-(*Z*)-atractylodinol.

Keywords: Atractylodinol; Vinyl tellurides; Negishi cross-coupling.

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Scheme 1.

1,3-Butadiyne **3** was prepared in situ from 1,4-dichlorobut-2-yne **2**¹⁵ and stereoselectively hydrotellurated¹⁶ to give vinylic telluride **4** in a 83% yield (Scheme 1).

The stereochemistry of (*Z*)-telluride **4** was established by the double doublet at 6.40 ppm with coupling constants of 10.5 and 2.4 Hz and a doublet of doublets at 7.46 ppm with coupling constants of 10.5 and 0.6 Hz, attributed to the *cis*-related olefinic hydrogens.

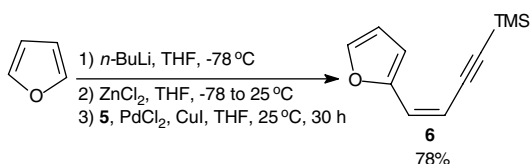
The protection of the alkyne terminus as its trimethylsilyl derivative **5** followed by a cross-coupling reaction with an excess of 2-furylzinc chloride (3 equiv)⁹ gave **6** in a 78% yield (Scheme 2).

It is noteworthy that when the reaction was performed with unprotected telluride **4**, a complex mixture of compounds was observed.

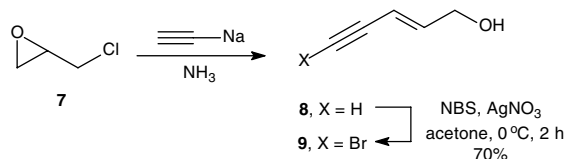
The analysis of the ¹H and ¹³C NMR spectra of **6** showed that the data are in full agreement with the assigned structure. The stereoisomeric purity of the product was identical to that of the starting vinyl telluride, indicating the complete retention of the configuration during the coupling reaction.

(*E*)-2-Penten-4-yn-1-ol **8** was prepared from epychlorohydrin **7** as a 9:1 mixture of *E* and *Z* stereoisomers according to a known procedure, where sodium acetylide reacts with **7** in liquid ammonia to give **8**.¹⁷ This is converted to the bromo-derivative **9** in a 70% yield through the treatment of **8** with NBS and a catalytic amount of AgNO₃ in acetone¹⁸ (Scheme 3).

Attempts to obtain **1** by treating **6** with sodium carbonate in methanol followed by Cadiot–Chodkiewicz coupling¹⁹ reaction with **9** were unsuccessful and only a complex mixture of compounds was observed. This is probably due to the high instability of **6** in the presence of amines. A similar coupling reaction in the synthesis of (–)-Nitidon²⁰ was also unsuccessful using the standard



Scheme 2.



Scheme 3.

Cadiot–Chodkiewicz conditions as well as the method employed by Saalfrank et al.²¹

Unfortunately, a second route also based on the transformation of trimethylsilylacetylene **6** into the corresponding haloacetylene²² **6a** followed by Cadiot–Chodkiewicz coupling with **8** was also unsuccessful (Scheme 4).

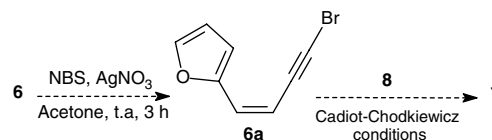
In view of these unsatisfactory results, another approach²³ based on the use of hydroxylamine hydrochloride, diethylamine and copper(I) chloride was employed to give the desired compound in a low yield (Scheme 5).

The obtained compound **1**, however, proved to be extremely unstable and when dissolved in deuteriochloroform rapidly polymerized to a pale orange solid. This behavior was observed before, and the authors attributed this instability to the furan moiety, which promotes polymerization due to its susceptibility for addition reactions.¹⁴

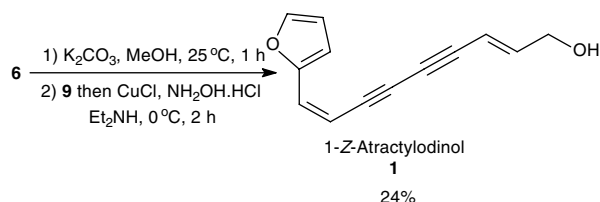
In an effort to improve the yield and avoid intra-molecular addition reactions, **9** was converted into its *tert*-butyldimethyl silyl derivative²⁴ **10** in a good yield (Scheme 6).

When the coupling reaction was performed using **10**, the desired product **11** was also obtained in a low yield (Scheme 7). In this case, the product showed a higher stability when compared to **1**.

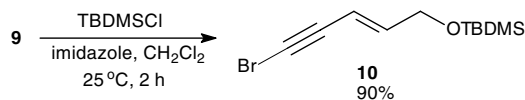
Interestingly, the (*Z*)-isomer rapidly isomerized to the energetically more favorable (*E*)-isomer during the puri-



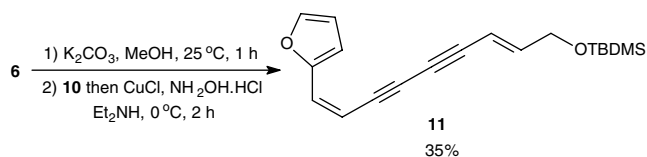
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

fication process in a ratio of 3:1 (*Z*:*E*), according to the NMR data, indicating that the *Z*-isomer could be the genuine constituent of the *A. lancea* rhizomes, but the *E*-isomer could be formed during the isolation procedure.

In summary, our synthesis of 1-(*Z*)-atractylodinol is convergent, allowing for the preparation of analogs with ease. The synthesis features a newly developed telluride synthon and a novel use for the Negishi type coupling reaction employing vinyl tellurides. Finally, the first use of this methodology in the total synthesis of a natural product offers future possibilities in the development of new organometallic approaches to the compounds containing *Z*-double bonds.

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Supplementary data

Supplementary data associated with this article can be found online at ScienceDirect, at [doi:10.1016/j.tetlet.2006.08.130](https://doi.org/10.1016/j.tetlet.2006.08.130).

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