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Sassafras oil, carrot bits and microwaves: green lessons learned from the formal total synthesis of (-)-talampanel

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A formal total synthesis of (-)-Talampanel (1), a 2,3-benzodiazepine is described. This work was undertaken to utilize greenerreaction conditions. Safrole (a renewable source) was converted to (1) in eight steps, including an enantioselective bioreduction using carrots as the key step. Microwave irradiation was also used to perform three reaction steps.

(-)-Talampanel (**1**) is an orally active antagonist of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) neuronal excitatory glutamate receptor. Excess activity of AMPA receptors results in an excess of Ca^{2+} in cells, causing cell damage and death.[1] This process is strongly related to various neurological diseases, including cerebral ischemia, epilepsy, amyotrophic lateral sclerosis (ALS) and Parkinson´s disease.[2] Inhibitors of AMPA receptors, such as 2,3-benzodiazepine derivatives, are considered potential drugs for the treatment of these neurological pathologies. Among them, talampanel is considered a promising drug candidate.[3] Thus far, talampanel has already undergone phase I and II trials for ALS, malignant gliomas and refractory epilepsy.[4]

Despite the great interest shown by several clinical and preclinical reports concerning talampanel, few synthetic strategies for this compound are available.[5] Initially, Anderson and coworkers developed an efficient and environmentally benign synthesis that affords talampanel in optically pure form.[6] The first step of Anderson´s synthesis is the stereoselective enzymatic reduction of 3,4-methylenedioxyphenylacetone (**2**) to (+)-(*S*)-a-methyl-1,3-benzodioxole-5-ethanol (**3**) with *Zygosaccharomycesrouxii* in the presence of XAD-7 resin.[6] This efficient large scale reduction suffers from some disadvantages, which are primarily a result of the microbiological requirements and the problems with concentration of solution, because it was toxic for microorganisms and it had to be changed. Several parameters, such as the quality of the cell paste and the stock culture as well as the conditions (pH, oxygen, cell concentration) used for the fermentation, are crucial to the success of this strategy.[5d] In addition, aseptic conditions and access to the microorganism must also be considered.

As an extension of our studies on the enzymatic reduction of prochiral ketones mediated by pieces of *Daucuscarota* (carrot root),[7] we planned the enantioselective reduction of 3,4-methylenedioxyphenylacetone using this inexpensive catalyst. As the biocatalysis using a resin and yeast,[6] the bioreduction of **2** with carrot has not been previously employed to obtain **3**.

Additionally, to further utilize green principles compared to Anderson´s route, we were concerned with energy and time efficiency as well as the use of renewable starting materials. Thus, we report herein the formal total synthesis of (-)-talampanel using sassafras oil as a starting material and utilizing microwave energy for the reactions when possible.

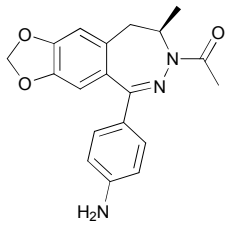

Figure 1. Talampanel (**1**)

Distillation of sassafras oil (kindly provided by Professor Massuo J. Kato – University of São Paulo) afforded substantial quantities of safrole, which was submitted to Wacker oxidation (Scheme 1).[8]Thus, treatment of safrole with $PdCl_2$ in methanol followed by the addition of benzoquinone in water furnished 3,4-methylenedioxyphenylacetone (**2**) in 60% isolated yield.Bioreduction of ketone **2** was easily accomplished by simply reacting with carrot bits in water.[9]Berkowitz and coworkers used a commercial alcohol dehydrogenase from *Candida parapsilosis* and a cofactor for stereoselectivebioreduction of **2**.[10] The use of this edible

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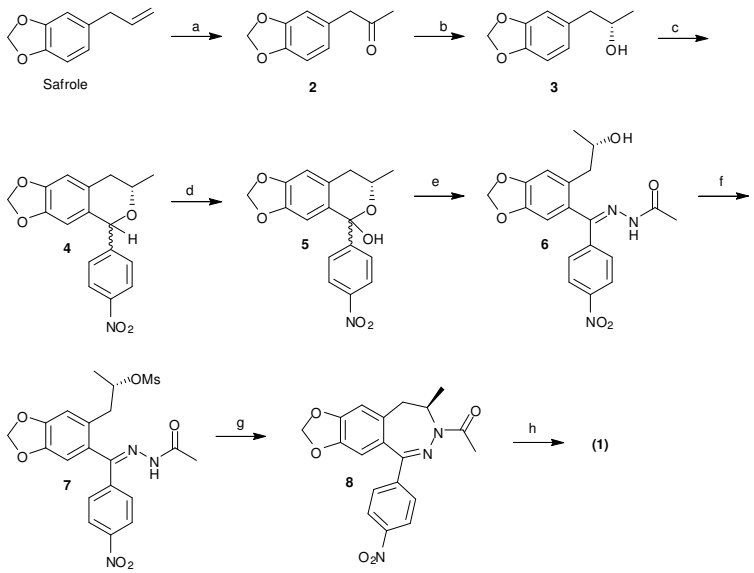

Scheme 1. Reaction conditions: (a) *p*-benzoquinone, $PdCl_2$, MeOH/H_2O (60%); (b) *D. carota* bits, H_2O (80%, >95% e.e.); (c) *p*-$NO_2C_6H_4CHO$, PTSA, Microwave -150 W, 110ºC (71%); (d) DDQ, H_2O/CH_2Cl_2 (72%); (e) H_2NNHAc, Microwave 200 W, 114ºC (82%); (f) CH_3SO_2Cl, Et_3N, CH_2Cl_2 (89%); (g) Cs_2CO_3, DMF, Microwave - 150 W, 70ºC (94%); (h) Steel wool, EtOH/vinegar, sonication (60%)

catalyst, which can be obtained easily in local markets, often provides high levels of enantioselectivity, and the reaction can be carried out under extremely mild conditions with a straightforward work-up and eco-friendly procedurescompared with other biocatalytic systems.[11] Therefore, (+)-(*S*)-a-methyl-1,3-benzodioxole-5-ethanol (**3**) was obtained in 80% isolated yield and 99% *ee*.[12]Synthesis of this alcohol in the optically active form typically requires four steps from piperonal.[5c]

An alternative solvent-free attachment of nitroaryl fragments *via* an *oxa*-Pictet Spengler reaction was elegantly accomplished by treatment of **3** with *p*-nitrobenzaldehyde and *p*-toluenesulfonic acid (PTSA) under microwave irradiation, yielding isochroman**4**.[13] The next step we used a procedure developed by Sólyom.[14] It was a faster and simple procedure to obtaining **5** than we found on Anderson protocol.[15] When **4** was treated with DDQ in dichloromethane/water (95:5), compound **5** was obtained in 72% isolated yield. The following step, the opening of the cyclic hemiketal**5** with acetylhydrazine, must be performed in refluxing ethanol or toluene for a few hours, according to the methods reported in the literature, We found that this reaction time could be reduced to five minutes if microwave irradiation was applied under solvent-free conditions. Under these conditions, hydrazone**6** was obtained in 82% isolated yield.

The mesylation of **6** to generate compound **7** was the only step of this talampanel synthesis performed in the same manner as Anderson´s route. Treatment of alcohol **6** with mesyl chloride and triethylamine provided the desired mesylate**7** in slightly higher isolated yield (89%) compared to Anderson´s synthesis. Next, our attention turned to the intramolecular SN_2 cyclization, and we first investigated two protocols published by Anderson and Sólyom. Unfortunately, both of these methods, which used NaOH and *t*-BuOLi, failed in our hands; we therefore investigated the possibility of again utilizing microwave irradiation to obtain penultimate intermediate **8**. Treatment of **7** with cesium carbonate in DMF under microwave irradiation successfully afforded the desired product **8** after only 10 minutes and in an excellent isolated yield (94%).[16]

To complete the synthesis, we examined reduction of the nitroaryl group. Countless reduction methods are available, and the use of palladium on carbon for catalytic hydrogenation is generally suitable, as shown in Anderson´s route. However, at large scale, the large amounts of the catalyst that are necessary can ignite upon exposure to air, particularly when the catalyst contains adsorbed hydrogen, readily causing ignition of flammable solvents. Other notable methods using metal catalysis with dilute acids or acetic acid promoted by ultrasound have been reported. Based on the protocol reported by Keller,[17] we found that the use of commercial

vinegar, *i.e.*, dilute acetic acid, is suitable for the reduction and that the use of steel wool instead of iron powder enhances the reaction by increasing surface contact of the metal with the mixture.[17] This inexpensive, relatively fast (30 minutes), environmentally benign protocol followed by a neutralization work-up afforded talampanel in 60% isolated yield.

Conclusions

In summary, (-)-talampanel(**1**) was synthesized in 8 steps from safrole with 13% overall yield. Although this overall yield is lower than that of Anderson´s route, several aspects in the presented route were improved with respect to green principles, including greater energy efficiency (use of microwaves, sonication), less hazardous and renewable reagents (*Daucuscarota* as the biocatalyst, sassafras oil as the starting material and vinegar as a solvent) and shorter reaction times. However, further optimization of the reactions, for example, with respect to the low yields for reduction of the nitro group, is necessary.

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