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Biomimetic total synthesis of tricycloillicinone and mechanistic studies toward the rearrangement of prenyl phenyl ethers

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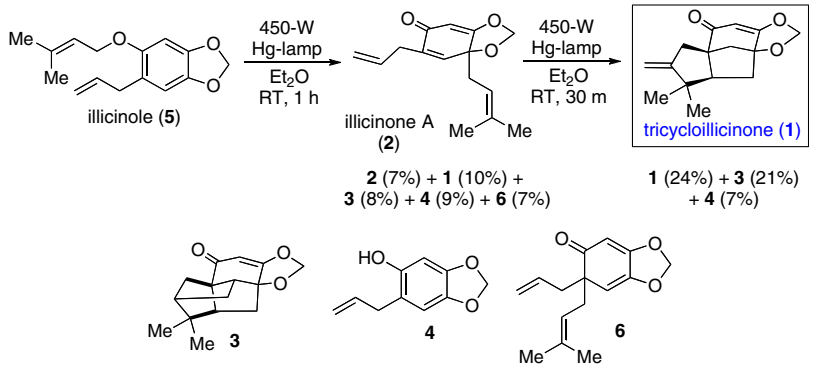
ABSTRACT

The Letter describes a short and biomimetic synthesis of tricycloillicinone, which was found to enhance the action of choline acetyltransferase (ChAT). The synthetic route has two critical reactions: bulky, oxygenophilic methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR) promoted rearrangement of prenyl phenyl ether and photochemical cyclization. Furthermore, experiments were designed to explore the process of MABR-promoted rearrangement. It was found that the stereochemistry of deuterium labeled prenyl group was only partially scrambled, which suggests that there may be two possible reaction pathways involved in this process. It also suggests that the direct migration of prenyl group to *para*-position under these conditions is slightly favored over the Claisen–Cope process. The highly efficient synthetic route also provides important new opportunities to explore the biological behavior of tricycloillicinone.

Tricycloillicinone (**1**, Scheme 1) is a member of an intriguing class of small molecule natural products that have been demonstrated to possess neurotrophic activity. Isolated from *Illicium tashiroi* by Fukuyama and coworkers in 1995,[1] tricycloillicinone was found to enhance the activity of choline acetyltransferase (ChAT), an enzyme required for the biosynthesis of the important neurotransmitter, acetylcholine.[2] Deficiencies in acetylcholine levels have been shown to be associated with the progression of neurodegenerative disorders, such as Alzheimer's disease.[3] It is therefore conceivable that a ChAT inducer, such as tricycloillicinone, could serve as a valuable lead compound in the development of novel therapeutic agents for the treatment of neurodegenerative diseases.[4]

In 1998, our laboratory disclosed the first total synthesis of **1**.[5] More recently, Terashima and coworkers reported the enantioselective total synthesis of tricycloillicinone.[6] Unfortunately, both of these synthetic routes are quite long, and the difficulties involved in gaining access to sufficient quantities of synthetic material have thus far limited our ability to perform all of the needed biological evaluations. We report herein the development



Scheme 1. Photochemical reactions of the Illicinone series.

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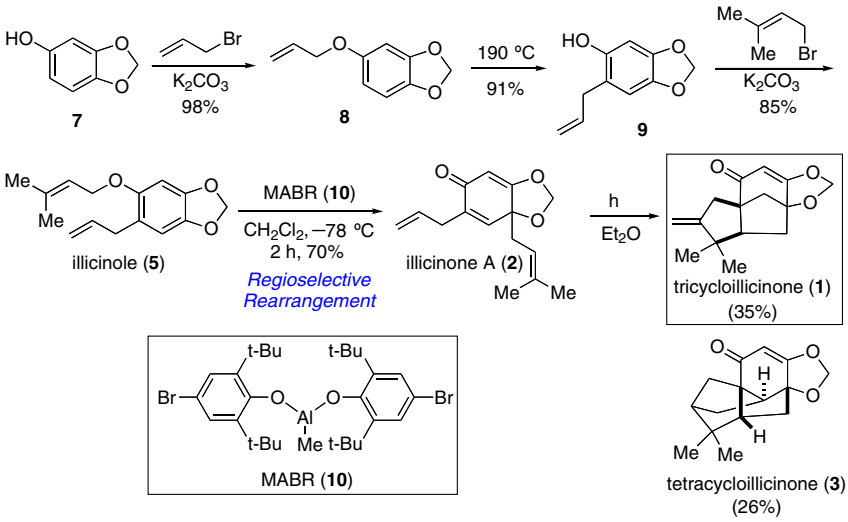


Scheme 2. Efficient synthesis of tricycloillicinone (**1**).

of a rather more efficient, biomimetically inspired second generation total synthesis of tricycloillicinone. A key feature of this total synthesis involves rearrangement of a prenyl phenyl ether (see **5**→**2**). In addition to exploiting this reaction for our total synthesis, we conducted experiments hoping to gain a deeper understanding of the migration process. Though the results did not provide a clear-cut definitive answer to our queries, they are related herein for their intrinsic interest (see Scheme 2).

It has been shown that illicinone A (**2**) is a potential biosynthetic precursor of tricycloillicinone. Furukawa and co-workers further demonstrated that illicinole (**5**) could be converted to illicinone A (**2**) and thence to tricycloillicinone (**1**) by photo-irradiation, although the reaction yield is very low and several side products (**3**, **4**, and **6**) are also generated (Scheme 1).[7]

In order to achieve a more efficient biomimetic total synthesis of tricycloillicinone, we would first need to develop a concise route to the key precursor, illicinone **2**. Accordingly, our route to **2** began with alkylation of commercially available sesamol **7**, thus affording allyl ether **8**. Claisen rearrangement of **8** under thermal conditions smoothly provided **9** in 91% yield. Prenylation of phenol **9** afforded illicinole **5**. Initial attempts to generate illicinone **2** under thermal conditions were unsuccessful. We, therefore, decided to investigate a Lewis acid-catalyzed rearrangement of **5**. Upon screening a number of different catalysts, we were pleased to find that the bulky Lewis acid MABR (**10**), developed by Yamamoto and coworkers,[8] showed the most promising results. As shown, treatment of illicinole **5** with MABR at −78 °C for 2 h cleanly afforded illicinone **2** in 70% yield. With intermediate **2** in hand, we were able to investigate the key photochemical reaction. Upon optimization of the photochemistry conditions, we were able to obtain tricycloillicinone **1** in 35% yield, along with tetracycloillicinone **3** in 26% yield.

We next hoped to answer some questions regarding the mechanism of the key MABR-mediated rearrangement. As outlined in Figure 1, two possible reaction pathways can readily be envisioned: in the first (path a), substrate **5** would undergo Claisen rearrangement (to generate **6**), followed by Cope rearrangement, to afford product **2**. Alternatively, the transformation might involve direct prenyl group migration to the *para*-position to generate illicinone **2** (path b).

We hoped that the mechanistic nature of this key rearrangement step could be probed through a well-designed deuterium isotope study. Along these lines, we prepared the deuterium-labeled illicinole **12**, as shown in Scheme 3. Thus, the treatment of phenol **9** with alcohol **14**[9] under Mitsunobu conditions afforded vinyl iodide **13** in 86% yield. Cuprate coupling[10] of vinyl iodide **13** using CD_3Li cleanly provided the desired deuterium labeled illicinole **12**. Importantly, compound **12** has a well-defined *cis*-olefin geometry. Our thinking was that, if rearrangement path a were to predominate, then the rearranged product would be produced as a 1:1 mixture of *cis*:*trans* isomers. By contrast, if path b were operational, the product could well retain the *cis*-geometry of its rearrangement precursor.

In the event, following exposure to MABR, as shown, illicinole isotope **12** rearranged to afford adduct **15** as a 3:1 mixture of *cis* and *trans* isomers (Fig. 2). This result suggests that, in fact, both reaction pathways may be involved; however, the direct prenyl

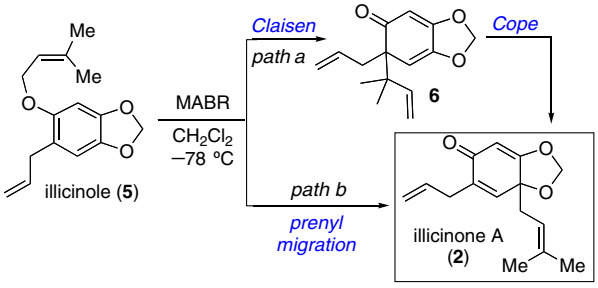
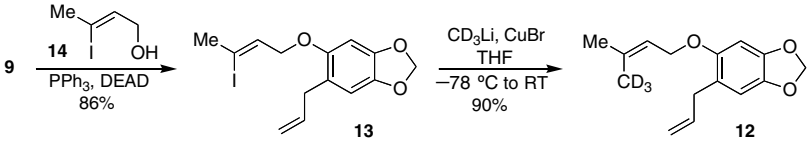


Figure 1. Possible reaction pathways for the MABR-mediated rearrangement.



Scheme 3. Synthesis of deuterium labeled illicinole **12**.

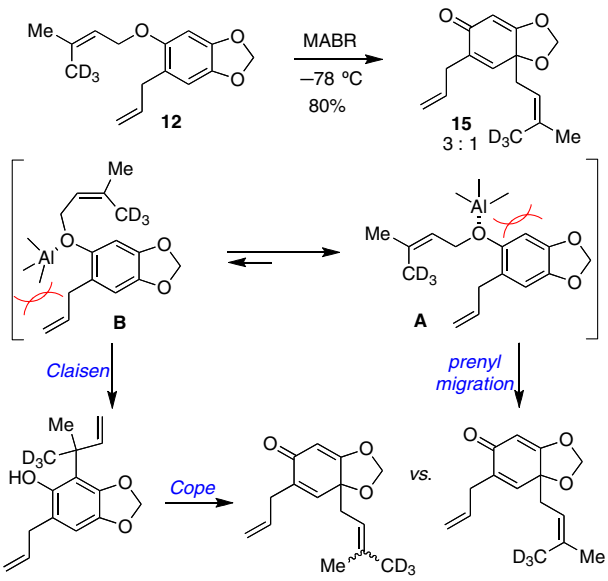


Figure 2. MABR-mediated rearrangement.

migration is apparently favored. Yamamoto and coworkers have proposed a transition state for this Lewis acid-mediated rearrangement process.[8b] As shown in Figure 2, the experimental results imply that the initial coordination of bulky aluminum catalyst (MABR) to prenyl ether **12** generates the sterically more favored complex **A** rather than the alternate complex **B**. This presumably favored conformation of the complex would indeed tend to rationalize the observed preference for the direct prenyl migration pathway. Unfortunately, our data do not definitively speak to the question as to whether there may be some erosion in the stereointegrity of the prenyl double bond, even in a direct prenyl migration pathway. If some scrambling occurred in such a 'direct' walkover, there would be no need to invoke any level of participation from the two-stage Claisen–Cope scenario (see compound **6**) to account for the loss of geometric 'memory'. Of course, avoidance of formation of an intermediate of the type **6** would explain the absence of competing allyl migration. However, it is not at all unlikely that the migration aptitude of the dimethylallyl group in the hypothetical **6** would be far greater than the allyl group in the migration of the allyl. Hence, the question of the intermediacy of **6** as a competing process is not fully answered.

In summary, an efficient biomimetic total synthesis of the neurotrophic agent tricycloillicinone has been accomplished from commercially available sesamol in only six steps. The synthesis relies on a key MABR-promoted rearrangement of prenyl phenyl ether and a subsequent photochemical cyclization sequence. Preliminary mechanistic studies toward the rearrangement process suggest that two different reaction pathways (Claisen–Cope and direct prenyl migration) may be operational in the key rearrangement step. With the development of this concise and scalable route, we are now able to readily access large quantities of synthetic tricycloillicinone, and its analogs, for further biological and SAR studies.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.184.

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