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Novel efficient synthesis of an enantiomeric pair of tricycloillicinone

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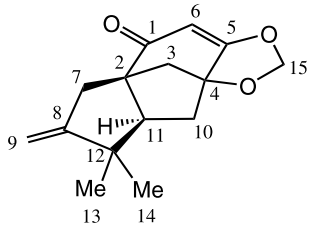
Abstract—The title synthesis was achieved starting with 3-ethoxy-2-cyclohexenone by a method featuring Davis' asymmetric hydroxylation and Pauson–Khand reaction as the key steps.

(−)-Tricycloillicinone (**1**) is a novel neurotrophic substance isolated from the wood of *Illicium tashiroi* by Fukuyama et al. in 1995,[1] and bears a tetracyclic framework characterized by three quaternary carbons, highly substituted 2-cyclohexenone system, and 2-unsubstituted 1,3-dioxolane ring[1] (Fig. 1). The structure of **1** including its absolute stereochemistry was assigned as shown by spectral studies as well as by taking into account its possible biosynthetic process.[1]

It has been reported that **1** enhances the activity of choline acetyl transferase (ChAT) which can catalyze the synthesis of acetylcholine (ACh) from its precursors, choline and acetyl-CoA.[1,2] It is well known that senile dimentia associated with Alzheimer's disease is directly correlated with reduced levels of synaptic ACh in the cortical and hippocampal areas of the brain.[2,3]



(–)-tricycloillicinone(**1**)(*ent*-**1**)

Figure 1. Structure of natural (−)-tricycloillicinone (**1**).

Keywords: natural products; asymmetric hydroxylation; Pauson–Khand reaction; choline acetyl transferase.
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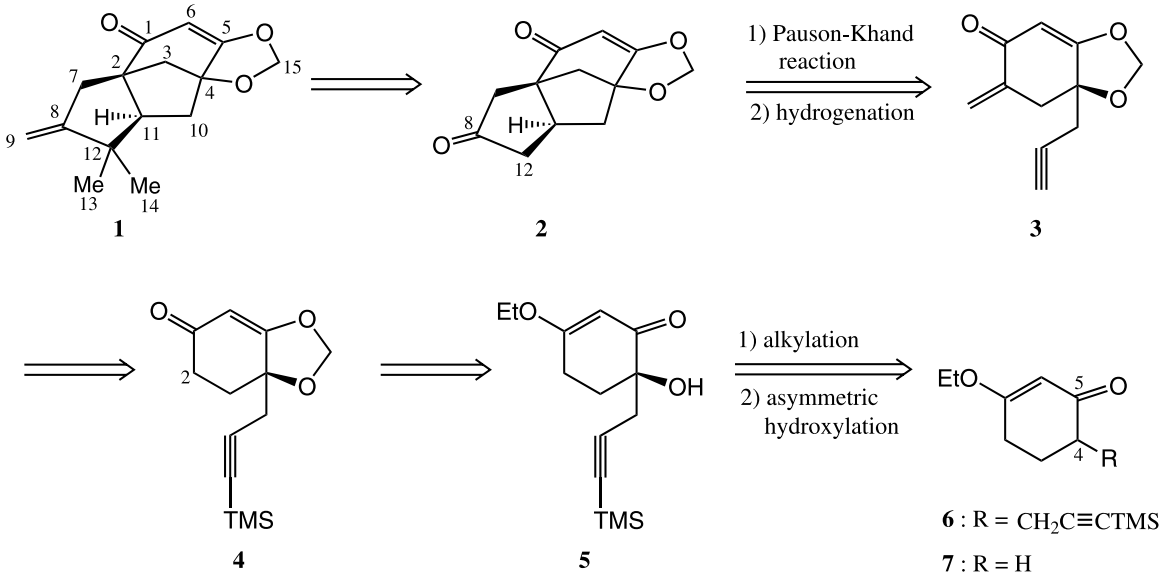
Since the current forms of therapy focus on this issue based on the cholinergic hypothesis of memory dysfunction,[3] **1** is considered to have potential as a lead for developing a novel medicine for Alzheimer's disease. Accordingly, **1** has attracted much interest among medicinal and synthetic organic chemists. While Danishefsky et al. achieved the first total synthesis of a racemic sample of **1** by employing two types of Claisen rearrangement and intramolecular radical cyclization as the key steps,[4] the synthesis of an optically pure sample of **1** has not been accomplished yet.

In order to pave the way to preparing an optically pure sample of **1**, to disclose novel aspects of the structure–activity of **1**, and, moreover, to explore novel congeners of **1** which may show more promising activity than **1**, an efficient synthetic route to optically pure **1** was sought which is more efficient and flexible than that reported for the racemic compound.[4] Here, we wish to report the first total synthesis of an enantiomeric pair of **1** in optically pure forms accomplished by featuring Davis' asymmetric hydroxylation[5] and Pauson–Khand reaction[6] as the key steps.

Our synthetic design of optically pure **1** is outlined in Scheme 1 in which asymmetric hydroxylation of the 6-substituted-2-cyclohexenone **6** with the Davis reagent[5] and Pauson–Khand reaction[6] of eneyne **3** are employed as the key steps. The diketone **2** produced by hydrogenation of the Pauson–Khand product will afford **1** by sequential introduction of two methyl groups into the C-12 position and methylenation of the C-8 carbonyl group (tricycloillicinone numbering). The Pauson–Khand precursor **3** can be prepared from acetal **4** by methylenation of the C-2 position (tricycloillicinone



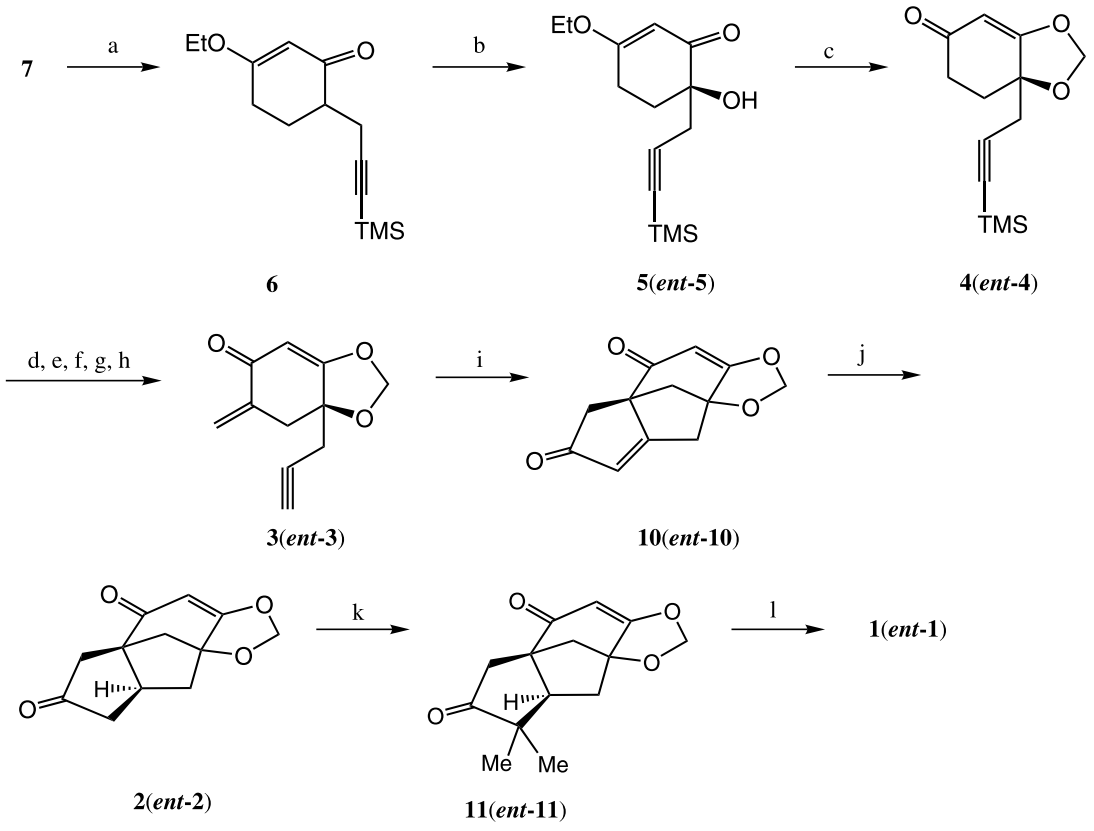
Scheme 1. Synthetic design of natural (−)-tricycloillicinone (**1**).

numbering). We planned to construct **4** by acetalization of chiral alcohol **5**. It was expected that, following the Davis protocol, the chiral center of **5** can be introduced with high optical integrity by means of asymmetric hydroxylation of **6** derived from commercially available 3-ethoxy-2-cyclohexenone (**7**).

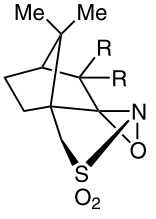
Following the designed synthetic scheme, our approach to optically pure **1** commenced with alkylation of **7**.[7] As shown in Scheme 2, alkylation of **7** with 3-bromo-1-(trimethylsilyl)-1-propyne took place smoothly, providing **6** in 89% yield. With **6** in hand, asymmetric hydroxylation of **6** was next attempted. At first, taking into account the results accumulated by Davis et al. for asymmetric hydroxylation of the α-position of ketone,[5] the lithium enolate of **6** was treated with (−)-(camphorylsulfonyl)oxaziridine (*ent*-**8**) in THF at −78°C[8] (Fig. 2). Unexpectedly, this reaction was found to afford *ent*-**5**,[8] 16% *ee*,[9] in 48% yield. The absolute stereochemistry of *ent*-**5** was definitely determined by the successful synthesis of unnatural (+)-tricycloillicinone (*ent*-**1**) from *ent*-**5** (vide infra). In order to improve the optical yield, the asymmetric hydroxylation was further examined using (−)-[(8,8-dicholorocamphoryl)sulfonyl]oxaziridine (*ent*-**9**),[10] giving rise to *ent*-**5**, 57% *ee*,[9] in 29% yield. After experimentation, it was finally found that the optical and chemical yield of *ent*-**5** can be dramatically improved by carrying out the reaction with *ent*-**9** in a mixture of THF and DMF (7:3), affording *ent*-**5**, 77% *ee*,[9] in 44% yield. At present, the remarkable effect of DMF can not be explained. Since the racemic alcohol *dl*-**5** was found to be more prone to crystallize than *ent*-**5**, removal of *dl*-**5** by recrystallization from pentane gave *ent*-**5** of 88% *ee*[9] in 77% yield based on *ent*-**5** of 77% *ee*. In the same manner, **5**, 76% *ee*,[9] was prepared from **6** in 46% yield by employing **9** as a chiral oxidant. Recrystallization of this sample from pentane similarly afforded **5** of 91% *ee*[9] in 74% yield based on **5** of 76% *ee*. The absolute stereochemistry of **5** was rigorously established as shown by the successful synthesis of natural (−)-tricycloillicinone (**1**) (vide infra).[11,12]

With completion of the asymmetric synthesis of **5**, acetalization with simultaneous cleavage of an enol ether system was next attempted. After experimentation, it was found that treatment of **5** with paraformaldehyde in the presence of a catalytic amount of *dl*-camphorsulfonic acid in cyclohexane afforded **4** in 17% yield with 56% recovery of **5**. The recovered chiral alcohol was again treated under the same acetalization conditions as described above, producing **4** in 34% yield along with 18% recovery of **5**. The rather lower yield of **4** might reflect the possibility that the difference in thermodynamic stability between **5** and **4** is small. Being different from **5**, optically active **4** was found to more readily crystallize than *dl*-**4**. Thus, recrystallization of **4** of 91% *ee* from hexane–ether cleanly gave an optically pure sample of **4**, mp 112.5–113°C and $[\alpha]_D^{21} = -156°$ (*c* 1.05, EtOH), >99% *ee*,[13] in 66% yield based on **4** of 91% *ee*. Methylenation of **4** following the protocol reported by Danishefsky et al.[14] consisting of silyl enol formation, alkylation with the Eschenmoser reagent, dimethyl(methylene)ammonium iodide, quarternization, and base-promoted elimination, furnished the Pauson–Khand precursor **3** after desilylation. The chemical yield of **3** was 45% over five operations.

The Pauson–Khand reaction of **3** was next examined which constitutes another key step of our novel synthetic route to **1**. Thus, treatment of **3** with dicobalt octacarbonyl in toluene at room temperature readily produced a suspension of the cobalt complex, which on reflux smoothly produced the Pauson–Khand product **10** in 79% yield. Hydrogenation of the double bond in **8** over 5% Pd–C gave rise to the tetracyclic diketone **2**[15] in 94% yield. Dimethylation of **2** with methyl iodide in the presence of potassium *tert*-butoxide[16] took place highly regioselectively at the sterically less hindered C-12 position, affording dimethyl ketone **11** as a sole



Scheme 2. Synthesis of optically pure (−)-tricycloillicinone (**1**). *Reagents and conditions*: (a) LDA, $TMSC{\equiv}CCH_2Br$, THF, −78°C, 2 h, 98%; (b) LDA, (+)- or (−)-[(8,8-dichlorocamforyl)sulfonyl]oxazoridine, THF–DMF, −78°C, 2 h, 46%, 76% *ee*, then recrystallization from pentane, 74%, 91% *ee* for **5**; 44%, 77% *ee*, then recrystallization from pentane, 77%, 88% *ee* for *ent*-**5**; (c) $(HCHO)_n$, CSA, cyclohexane, reflux, 20 min, 34% (recovery of starting material 16%), then recrystallization from hexane–Et_2O, 66%, >99% *ee* for **4**; 26% (recovery of starting material 42%), then recrystallization from hexane–Et_2O, 51%, >99% *ee* for *ent*-**4**; (d) LHMDS, TESCl, THF, −78°C, 1 h; (e) the Eschenmoser reagent, CH_2Cl_2, rt, overnight; (f) MeI, CH_2Cl_2–Et_2O, rt, 6 h; (g) satd $NaHCO_3$ aq, rt, 1 h; (h) TBAF, THF, rt, 1 h, 45% (five steps) for **3**; 41% (five steps) for *ent*-**3**; (i) $Co_2(CO)_8$, toluene, rt, 3 h, then reflux, 3.5 h, 79% for **10**; 74% for *ent*-**10**; (j) H_2, Pd–C, EtOH, 0°C, 1.5 h, 94% for **2**; 87% for *ent*-**2**; (k) KO^{t}Bu, ^{t}BuOH, CH_3I, 30°C, 1 h, 35% for **11**; 56% for *ent*-**11**; (l) PPh_3CH_3 Br, KO^{t}Bu, THF, rt, 1 h, 56% for **1**; 59% for *ent*-**1**.



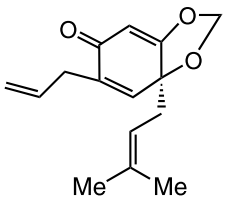
8(*ent*-**8**) : R = H
9(*ent*-**9**) : R = Cl

Figure 2. Structures of the Davis reagents.

product in 35% yield. Subsequent olefination with methylenetriphenylphosphrane[17] furnished optically pure **1**,[15] mp 95–96°C and $[\alpha]_D^{20} = -29.5°$ ($c = 1.15$, EtOH), >99% *ee*.[18] While ^1H ($CDCl_3$) and ^{13}C (C_6D_6) NMR spectra of the optically pure sample for synthetic **1** were found to be identical to those reported for natural[1] and synthetic racemic **1**,[4b] the $[\alpha]_D$ value and melting point observed for our synthetic sample of optically pure **1** were completely different from those described for the natural product, mp 78–79°C and $[\alpha]_D^{20} = -5.56°$ ($c = 1.15$, EtOH).[1,19] With the aim to exemplify the efficiency of our novel synthetic route, the enantiomer of **1** (*ent*-**1**) was prepared from *ent*-**5**, >99% *ee*, following the same reaction scheme as described for the preparation of **1**. An optically pure sample of *ent*-**1** thus obtained, showed mp 95–96°C and $[\alpha]_D^{20} = +29.1°$ ($c = 1.07$, EtOH), >99% *ee*[18] (vide supra).

The absolute configuration of **1** was assigned as shown by assuming that **1** is presumably biosynthesized from (+)-illicinone A (**12**) which is the main component of *I. tashiroi* affording **1**[1] (Fig. 3). On the other hand, Furukawa et al. reported that (−)-illicinone A (*ent*-**12**) was easily isolated from *Illicium arborescens*[20] belonging to the same species as that of *I. tashiroi*. Taking these facts into account, our results strongly suggest that natural **1**, which is ca. 20% *ee*, has been isolated from the natural source.[21]

In summary, we have succeeded in developing a novel synthetic route to an enantiomeric pair of optically pure tricycloillicinone (**1** and *ent*-**1**) by employing asymmetric hydroxylation and Pauson–Khand reaction as



(+)-illicinone A (**12**)

Figure 3. Structure of (+)-illicinone A (**12**).

the key steps. Considering its directness and flexibility, the explored synthetic scheme may be amenable to a large-scale preparation of **1** as well as applicable to synthesis of various structural types of novel congeners of **1**. Additionally, our first total synthesis of an enantiomerc pair of optically pure **1** disclosed an interesting feature concerning the optical purity of a natural sample of **1**.

Acknowledgements

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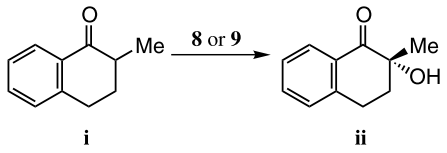
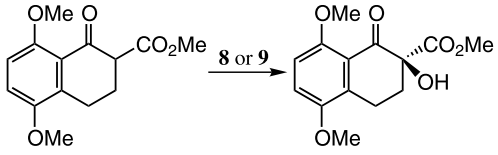
8. (−)-(Camphorylsulfonyl)oxazoridine (*ent*-**8**) was utilized as a chiral oxidant of the first choice by considering the structural similarity between **6** and 2-methyl-1-tetralone (**i**). Thus, it had been reported that oxidation of **i** with **8** or **9** gives **ii** corresponding to *ent*-**5** (Ref. 5).



i **ii**

9. The optical purity of **5** and *ent*-**5** was rigorously determined by HPLC analysis with a chiral column (Daicel Chiralcel OD-H, *i*-PrOH/hexane 90/10, flow rate 0.5 ml/min, t_R 22.8 min (**5**) and 24.2 min (*ent*-**5**), detection at 254 nm).
10. Davis et al. reported that, depending upon the structure of the ketonic substrate, (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxazoridine (**9**) sometimes gives a chiral alcohol which is more highly optically active than that produced by using **8** (Ref. 5).
11. The reaction mechanism of asymmetric hydroxylation which, for example, provides **ii** and **iv** from **i** and **iii**, respectively, has not hitherto been presented by Davis et al. (Ref. 5).
12. Summing up the results collected by our studies on asymmetric hydroxylation, it appeared that **6** should be considered structurally more close to the 2-methoxylcarbonyl-1-tetralone **iii** than to **i** since **iii** gives **iv** when oxidized with **8** or **9** (Ref. 5).



iii **iv**

13. The optical purity of **4** and *ent*-**4** was rigorously determined by HPLC analysis with a chiral column (Daicel Chiralcel OD-H, *i*-PrOH/hexane 97.5/2.5, flow rate 1.0 ml/min, t_R 25.7 min (**4**) and 26.8 min (*ent*-**4**), detection at 254 nm).
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15. The relative stereochemistry of this compound was definitely determined by single-crystal X-ray analysis. See: Furuya, S.; Ijuin, Y.; Terashima, S., to be published.
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18. The optical purity of **1** and *ent*-**1** was definitely determined by HPLC analysis with a chiral column (Daicel Chiralcel AD-H, *i*-PrOH/hexane 90/10, flow rate 0.5 ml/min, t_R 13.5 min (**1**) and 14.5 min (*ent*-**1**), detection at 254 nm).
19. The melting point of the synthetic racemic sample for **1** was not reported in Ref. 4b.
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21. Direct comparison of natural and synthetic **1** by HPLC analysis[18] could not be performed since the natural sample had been completely consumed for biological studies (personal communication from Professor Y. Fukuyama).