

# Synthetic approaches towards huperzine A and B

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## Abstract

Huperzine A and B are potent acetylcholinesterase inhibitors and promising against Alzheimer's disease. Completed and formal total syntheses of these medically relevant alkaloids are presented and discussed.

**Keywords:** Huperzine A, huperzine B, total synthesis, alkaloids, Alzheimer's disease

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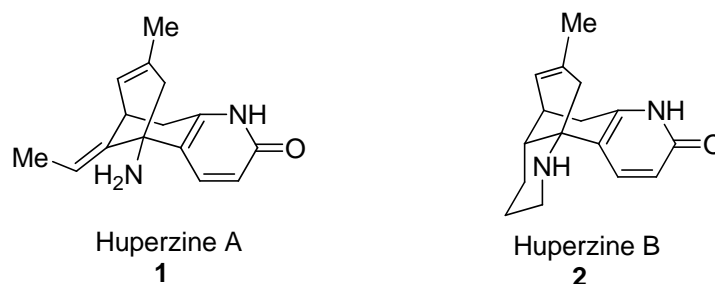
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## 1. Introduction

The lycopodium alkaloids are a structurally diverse and extensively studied alkaloid family containing quinolizine, pyridine or  $\alpha$ -pyridone moieties.<sup>1-2</sup> These naturally occurring nitrogen containing molecules are known to possess a wide range of biological activities. Some lycopodium alkaloids exert potent inhibition of acetylcholinesterase<sup>3-4</sup> and exhibit neuroprotective properties.<sup>5-9</sup> It has been documented that huperzine A increases the efficiency of learning as well as memory in animals, and it shows promise in the treatment of Alzheimer's disease (AD).<sup>10-11</sup> Because of its unparalleled biological profile to combat AD, it has recently gained considerable attention as a therapeutic agent against dementia<sup>12-15</sup> and is being used as clinical drug in China.<sup>16</sup> A number of clinical reports reveal huperzine A to be capable of facilitating cholinergic neurotransmission by increasing the levels of acetylcholine in the central nervous system.<sup>17</sup> Interestingly, its pharmacological profile is found to be superior to that of tetrahydroaminoacridine (Tacrine), an FDA-approved drug for the treatment of AD.<sup>18</sup> Its

superiority over other drugs can be partly attributed to its lower toxicity.<sup>18</sup> Huperzine B possesses an even higher therapeutic index than huperzine A which is in agreement with its longer duration of action.<sup>19</sup> Both huperzine A and huperzine B were isolated from the Chinese club moss *Huperzia serrata*<sup>20</sup> which has a long history of use as Chinese folk medicine against various ailments like contusions, strains, swellings, and schizophrenia. Later on, huperzine A was also isolated from the New Zealand club moss *Lycopodium varium*.<sup>21</sup>

Although numerous strategies for the total syntheses of huperzines and analogues thereof have been reported, a systematic review of this topic is lacking. The present review addresses this gap and aims to give the readers an up to date overview of the synthetic routes to the huperzines with a special emphasis on the strategies for the construction of the bicyclo[3.3.1] ring system. We will focus on completed and formal total syntheses of huperzine A and B while partial syntheses and incomplete or unsuccessful synthetic approaches will remain out of scope because of space constraints.

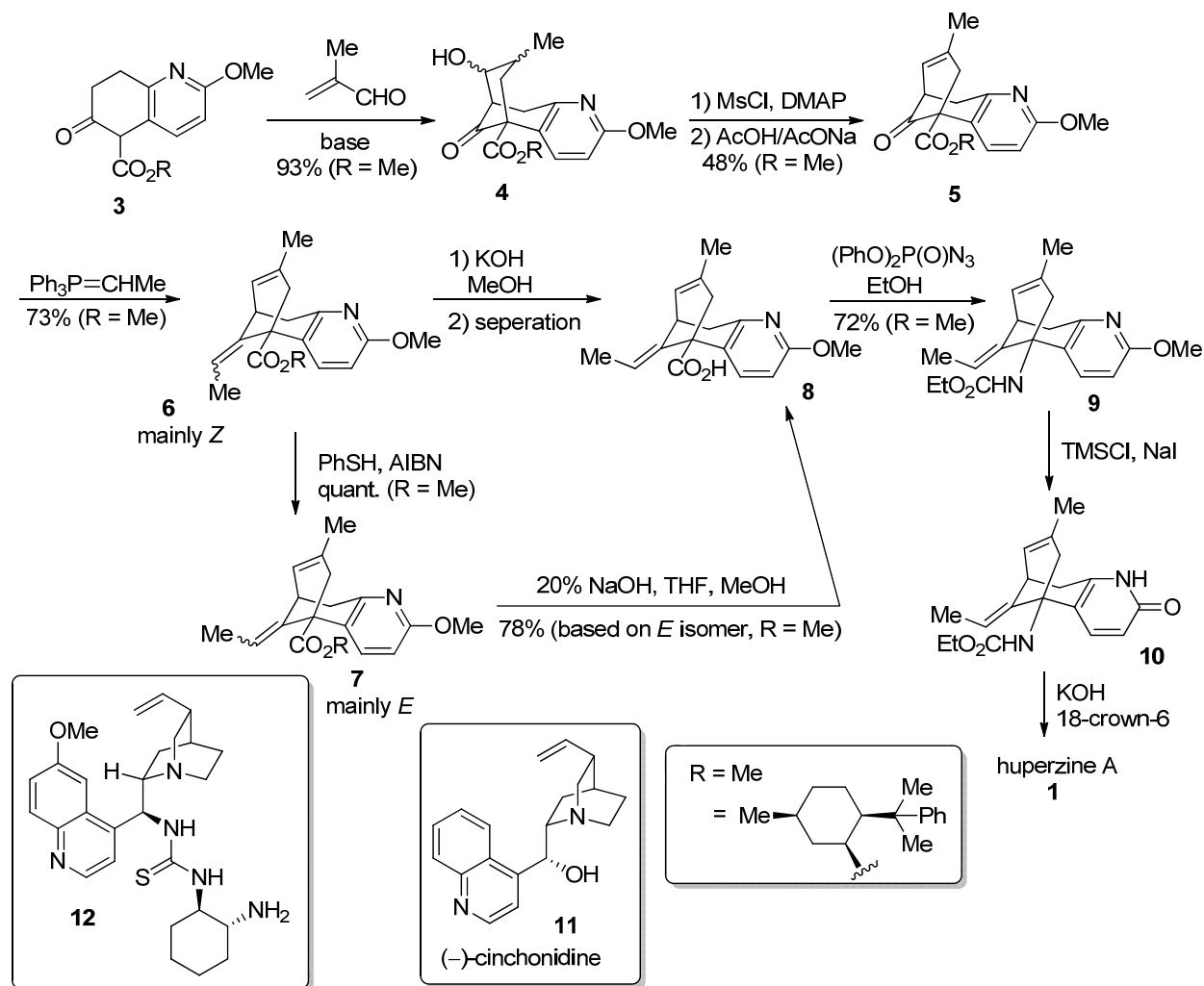


**Figure 1.** Structure of the huperzines.

## 2. Huperzine A

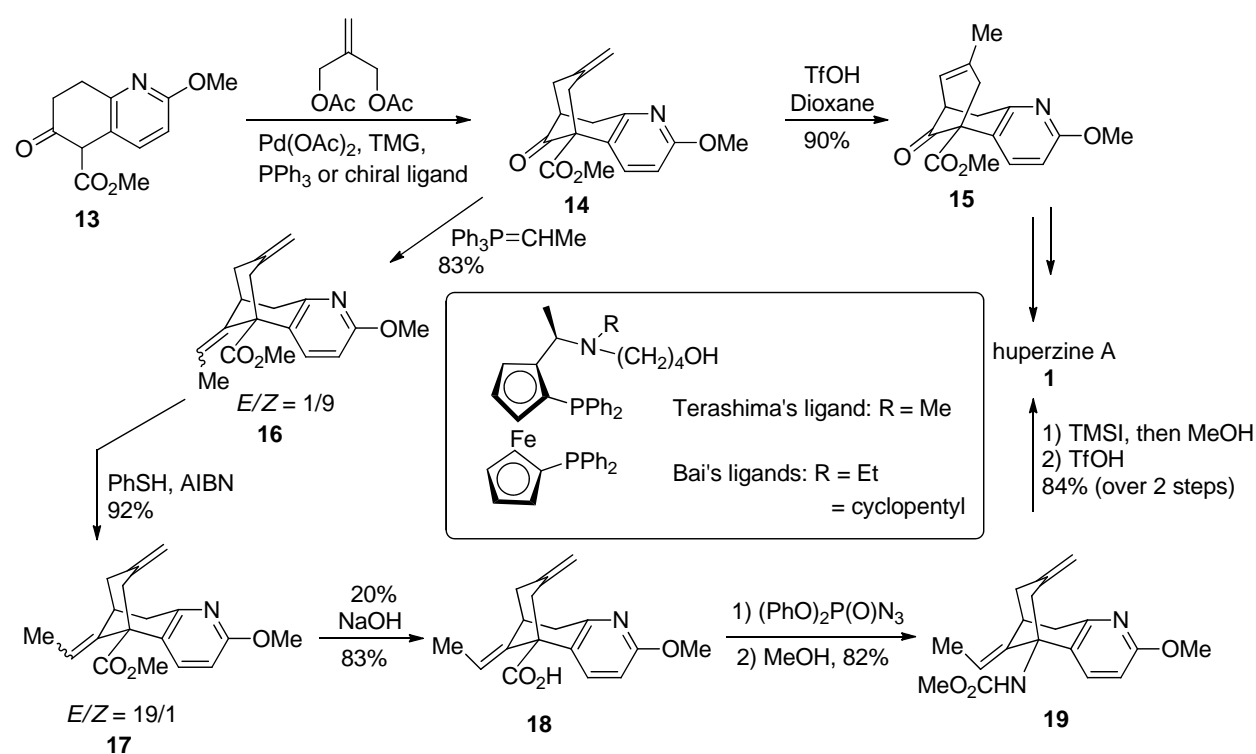
Huperzine A (**1**) presents a fascinating bicyclo[3.3.1]nonane unit fused to a 2-pyridone moiety. The bicyclo[3.3.1]skeleton is embellished with an ethylidene group and a free primary amine at the bridgehead carbon (Fig 1). The impressive biological profile in conjunction with its limited access from natural sources has stimulated many synthetic efforts towards huperzine A and resulted in a number of successful total syntheses of this alkaloid. The first of its kind produced the racemic material and were independently accomplished by Kozikowsky<sup>22-23</sup> and Qian & Ji.<sup>24</sup> In both approaches, the same  $\beta$ -keto ester **3** was reacted with methacrolein in a domino Michael-aldol addition to set up the bicyclo[3.3.1] framework (Scheme 1). The alcohol **4** thus obtained was converted into olefin **5** through mesylation and subsequent  $\beta$ -elimination. However the elimination step gave only a moderate yield (~50%) because the precursor alcohol **4** was a mixture of diastereomers of which only the isomer with an axial OH group and an equatorial methyl substituent reacted. The exocyclic double bond was installed by a Wittig olefination which produced an *E/Z*-mixture in favor of the the undesired (*Z*) isomer. At this point Kozikowsky's route differed from Qian and Ji's approach. In the former, the double bond was

isomerized in a radical reaction using thiophenol and azobisisobutyronitrile (AIBN) producing predominantly the (*E*) isomer. Subsequent saponification resulted in selective hydrolysis of the (*E*) isomer. The (*Z*) isomer was reluctant to undergo hydrolysis as its ester functionality was sterically more congested. In contrast, Qian and Ji saponified the Wittig product **6** itself while the (*E*)-isomer underwent saponification preferentially and the resulted acid **8** was separated easily from the unreacted (*Z*) form of the ester. Huperzine A was obtained from acid **8** through subsequent Curtius rearrangement, O-demethylation and hydrolysis. An asymmetric version of this synthesis was also accomplished by Kozikowski *et al.* by using 8-phenylneomenthol as a chiral auxiliary which afforded the natural enantiomer (–) huperzine A.<sup>25</sup> Another asymmetric version<sup>26</sup> of the aforementioned domino Michael-aldol sequence was implemented by employing a chiral cinchona base (**11**) which converted  $\beta$ -keto ester **3** into alcohol **4** in 64% ee. This asymmetric tandem Michael-aldol reaction has also been realized recently by Yao and co-workers<sup>27</sup> under the influence of the quinine-derived chiral thiourea organocatalyst **12** to give rise to the alcohol **4** in 92% enantiomeric excess.



**Scheme 1.** Synthesis of huperzine A via domino Michael-aldol addition.

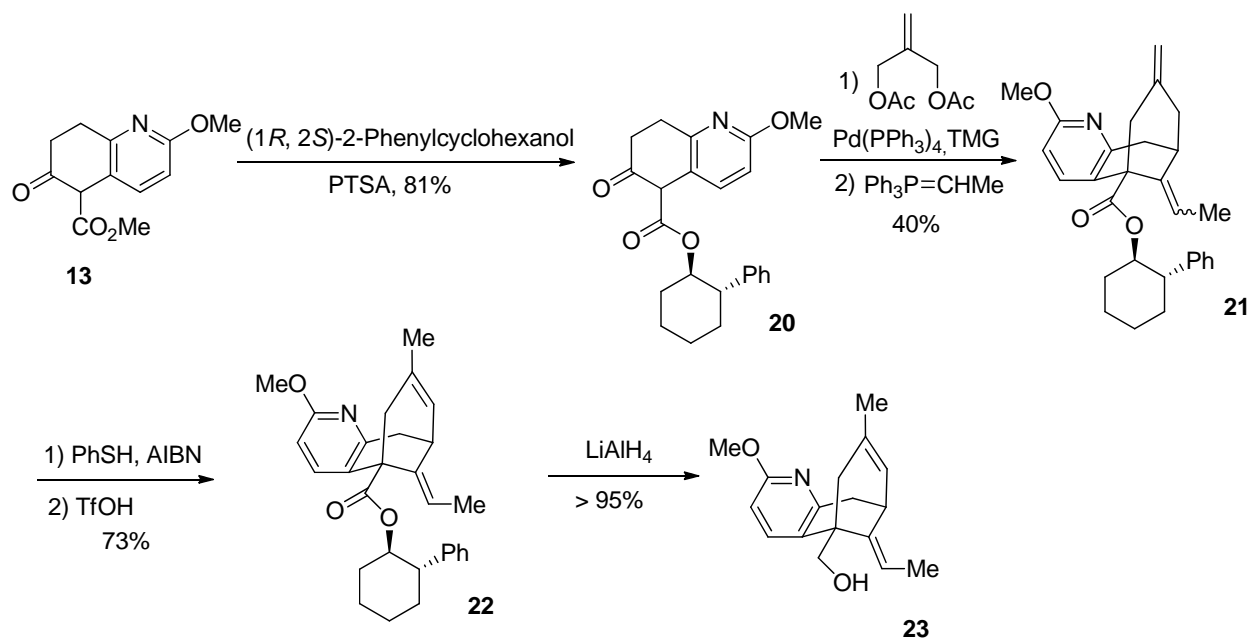
Kozikowski disclosed a second generation synthesis of huperzine A in which he exploited a palladium catalyzed annulation of  $\beta$ -keto ester **13** with 2-methylenepropane-1,3-diol diacetate (Scheme 2).<sup>28,18</sup> The exocyclic double bond in the product **14** was isomerized with triflic acid to obtain olefin **15**. Huperzine A was obtained from **15** by the same sequence as in his racemic route. An alternative route to huperzine A from the exocyclic olefin **14** has also been reported. In this synthesis, **14** was subjected to a Wittig olefination to give an *E/Z* mixture of olefin **16** rich in the undesired (*Z*) isomer. A subsequent radical isomerization led to a 95:5-mixture of olefins favoring the desired (*E*)-form. Upon saponification, the (*E*) isomer preferentially underwent hydrolysis to the corresponding acid **18** while the (*Z*)-form remained untouched. The acid was smoothly converted into carbamate **19** by Curtius rearrangement. TMSI mediated deprotection and triflic acid induced isomerization of the exocyclic double bond finally



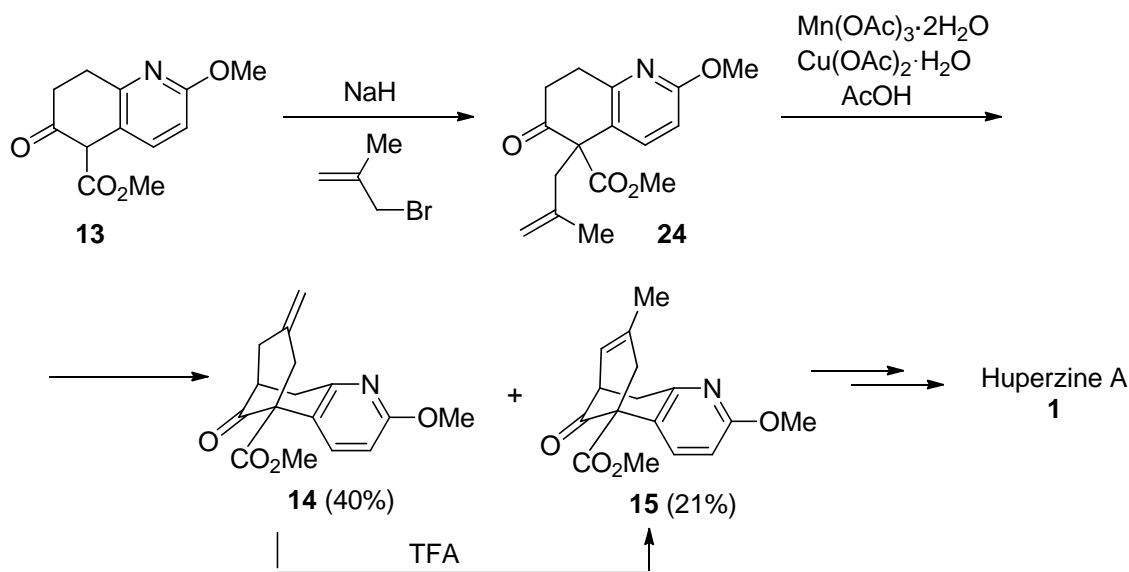
**Scheme 2.** Synthesis of huperzine A via Pd-catalyzed annulations.

furnished the natural product. These routes not only improved the overall yield of the sequence but also bypassed the low-yielding elimination step described in the previous approach. The Pd-catalyzed bicycloannulation strategy was adopted independently by Terashima and Bai to develop asymmetric routes which provided the olefin **14** in >90% ee.<sup>29-30</sup> Both groups employed ferrocene based chiral phosphine ligands for inducing asymmetry in this common key step. A chiral auxiliary based version of Kozikowski's Pd-catalyzed bicycloannulation to huperzine was demonstrated by Langlois *et al.* (Scheme 3).<sup>31-32</sup> Here, the auxiliary was attached by reacting the

$\beta$ -keto ester **13** with (1*R*,2*S*)-2-phenylcyclohexanol. After successive Pd-catalyzed bicycloannulation, Wittig olefination, *E/Z* isomerization and *exo/endo* isomerization of the olefinic double bond, the chiral handle was detached by LAH reduction. This route can be regarded as a formal synthesis of unnatural (+)-huperzine as the resulting primary alcohol **23** was an intermediate in Kozikowsky's asymmetric synthesis.<sup>25</sup>

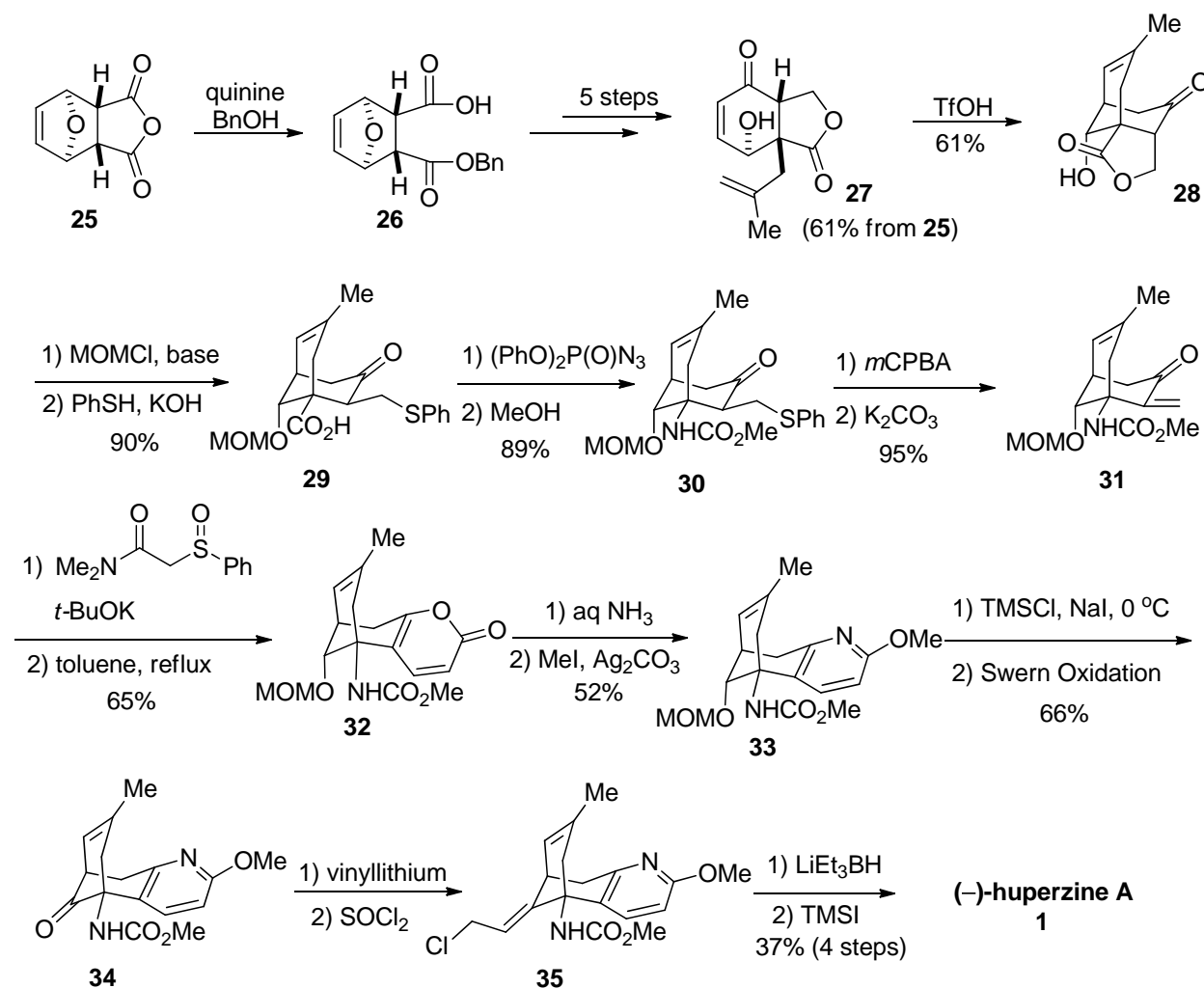


**Scheme 3.** Langlois formal synthesis of (+)-huperzine A via Pd-catalyzed annulations.



**Scheme 4.** Lee's radical cyclization for the synthesis of huperzine A.

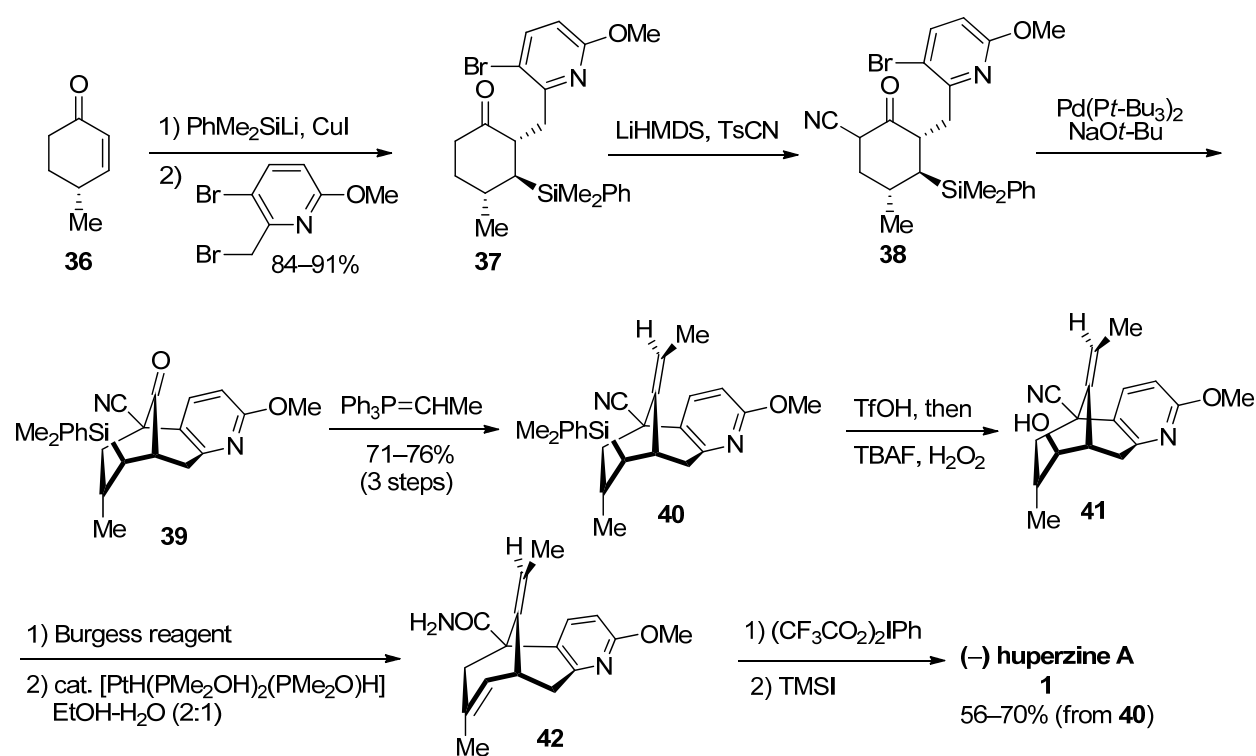
Lee<sup>33</sup> formulated a synthesis of huperzine A which relies on a Mn(III) mediated oxidative radical cyclization on the suitably substituted  $\beta$ -keto ester **24** to give the desired bicyclic product as a regioisomeric mixture (Scheme 4). Again, the undesired *exo* isomer **14** was easily converted into the *endo* isomer **15** by treatment with TFA. The precursor for the radical cyclization was readily derived from  $\beta$ -keto ester **13** by a simple methallylation reaction.



**Scheme 5.** Fukuyama's synthesis of (-)-huperzine A.

An ingenious approach to optically pure (-)-huperzine was reported by Fukuyama *et al.* who introduced the ethylidene and pyridone moieties in the molecule in a very unique manner.<sup>34</sup> As illustrated in Scheme 5, their synthesis commenced with the *meso*-anhydride **25** which, upon desymmetrization, gave the acid **26** with 99% ee. Allylated lactone **27** was obtained from compound **26** in only five steps. Treatment of **27** with triflic acid led to cation-olefin cyclization establishing the required bicyclo[3.3.1] skeleton. The next tasks were to install the ethylidene and pyridone moieties. Protection of hydroxyl group of **28** followed by thiolysis of the lactone

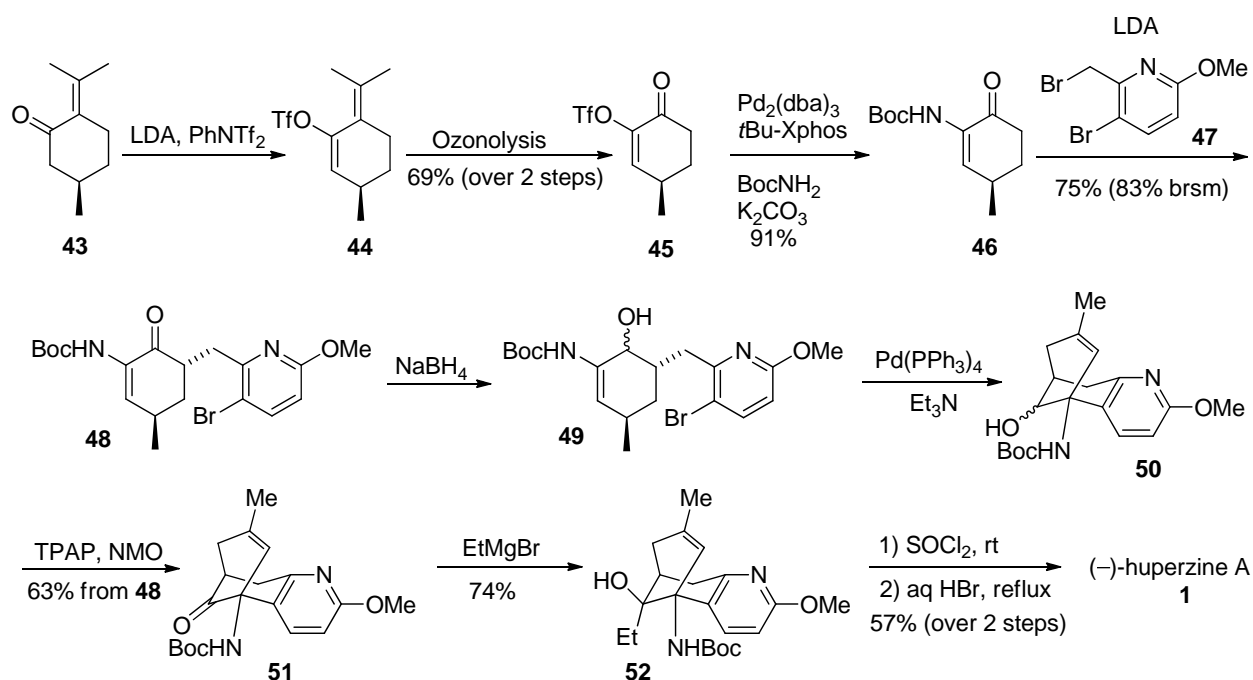
gave carboxylic acid **29** which was rearranged with diphenylphosphoryl azide (DPPA) to give carbamate **30**. Oxidation of the thioether to the sulfoxide and subsequent elimination furnished enone **31**. Michael addition of a sulfynylamide anion to enone **31** occurred smoothly to afford a  $\delta$ -ketoamide which was subjected to a cyclization/desulfination sequence in refluxing toluene. The pyrone **32** thus obtained was treated with ammonia to give rise to 2-pyridone which was further protected as the 2-methoxypyridine (**33**). Selective deprotection of the MOM group, Swern oxidation and treatment of the resulting ketone **34** with vinyl lithium led to formation of an allylic carbinol which was subjected to an  $S_N2'$  reaction with chloride to give allyl chloride **35**. In this compound, the *E*-geometry is preferred over *Z*-geometry to avoid the steric encumbrance with the preinstalled carbamate functionality at the bridgehead. Hydride reduction of the allylic chloride **35** and TMSI mediated deprotection afforded (–)-huperzine in 1.8% overall yield.



**Scheme 6.** Herzon's route to (–)-huperzine A.

Herzon *et al*<sup>35</sup> have developed a scalable synthesis of (–)-huperzine (Scheme 6). In this chiral pool approach, the (+)-pulegone derived enone **36** was chosen as the starting material. It underwent Michael addition of lithium dimethylphenylsilylcuprate to give an enolate which was quenched with 3-bromo-2-(bromomethyl)-6-methoxypyridine to afford ketone **37** as a single diastereomer. Electrophilic cyanation was effected after kinetically controlled deprotonation and the obtained  $\alpha$ -cyanoketone **38** was made to undergo a Pd-catalyzed intramolecular enolate heteroarylation to establish the bicyclo[3.3.1] framework. Subsequent Wittig olefination and

oxidative desilylation provided homoallylic alcohol **41** which was dehydrated with the Burgess reagent. Although the olefination reaction led to an *E/Z* mixture of products, the desired (*E*)-form was the major product. A platinum-catalyzed hydration of the bridgehead cyano group under Ghaffar-Parkins conditions<sup>36-37</sup> gave the amide **42**. Hofmann rearrangement of this compound under the influence of PIFA gave the precursor to (-)-huperzine. Methyl deprotection under standard conditions afforded (-)-huperzine in 35–45% overall yield.



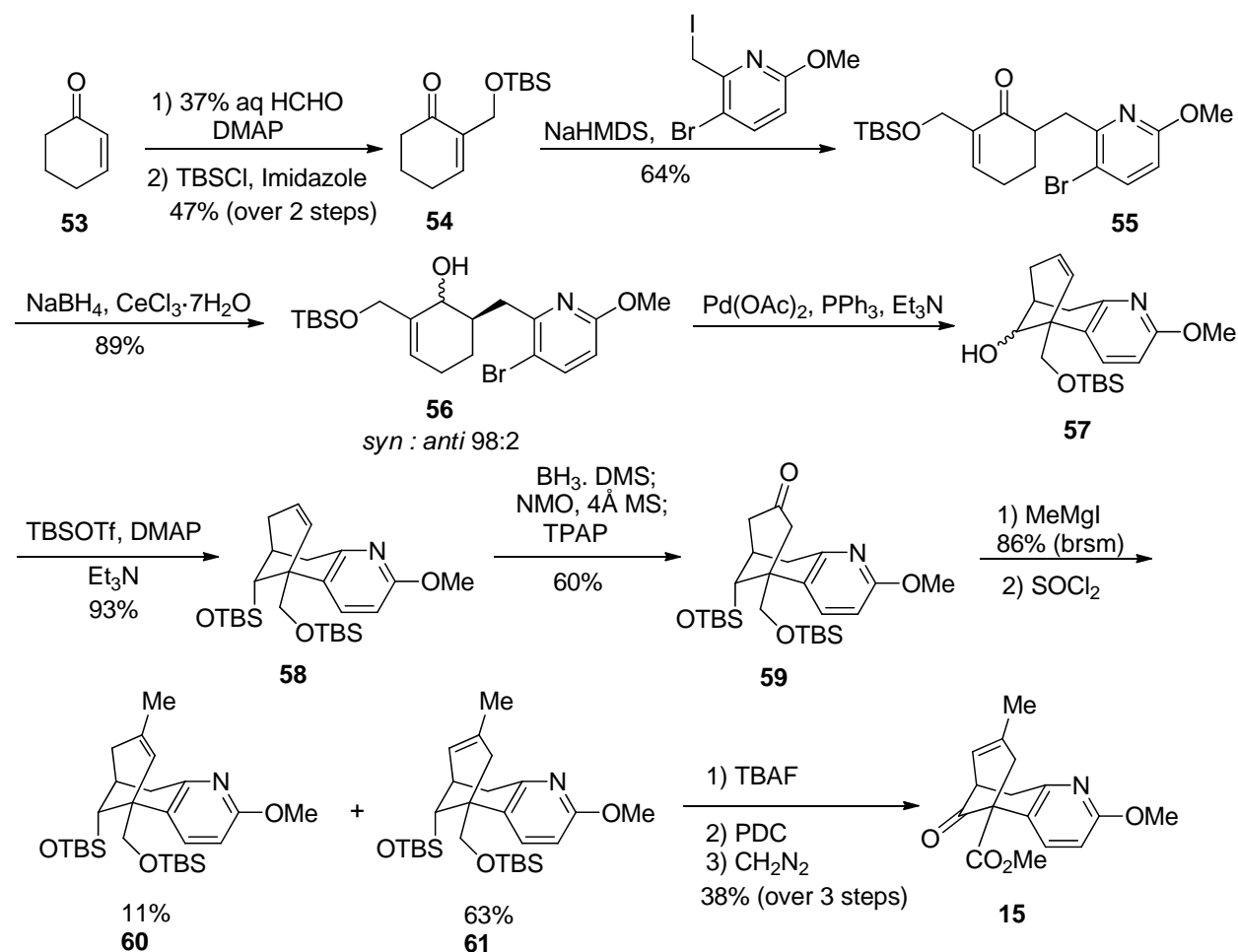
**Scheme 7.** Sun and Lin's route to (-)-huperzine A.

Sun and Lin's synthesis<sup>38</sup> of (-)-huperzine A which exploits an intramolecular Heck coupling as the key step emanated from commercially available (*R*)-pulegone (Scheme 7). It was triflylated first and the resulting enol triflate **44** was subsequently ozonolyzed to give ketone **45** which underwent a smooth Buchwald-Hartwig coupling to provide carbamate **46**. Deprotonation and reaction of the resulting dianion with bromide **47** led to enone **48** with a > 20:1 diastereomeric ratio. Subsequent NaBH<sub>4</sub> reduction and Pd-catalyzed intramolecular Heck coupling of the diastereomeric alcohols established the bicyclic framework under formation of the secondary alcohol **50**. Ley oxidation and Grignard addition of the product ketone **51** produced the tertiary alcohol **52**. Finally, a one pot sequence comprising the treatment of **52** with SOCl<sub>2</sub> followed by exposure to aqueous HBr led to the formation of (-)-huperzine A through demethylation, double bond transposition and Boc-removal. This ten step route provided the natural product in 17% overall yield.

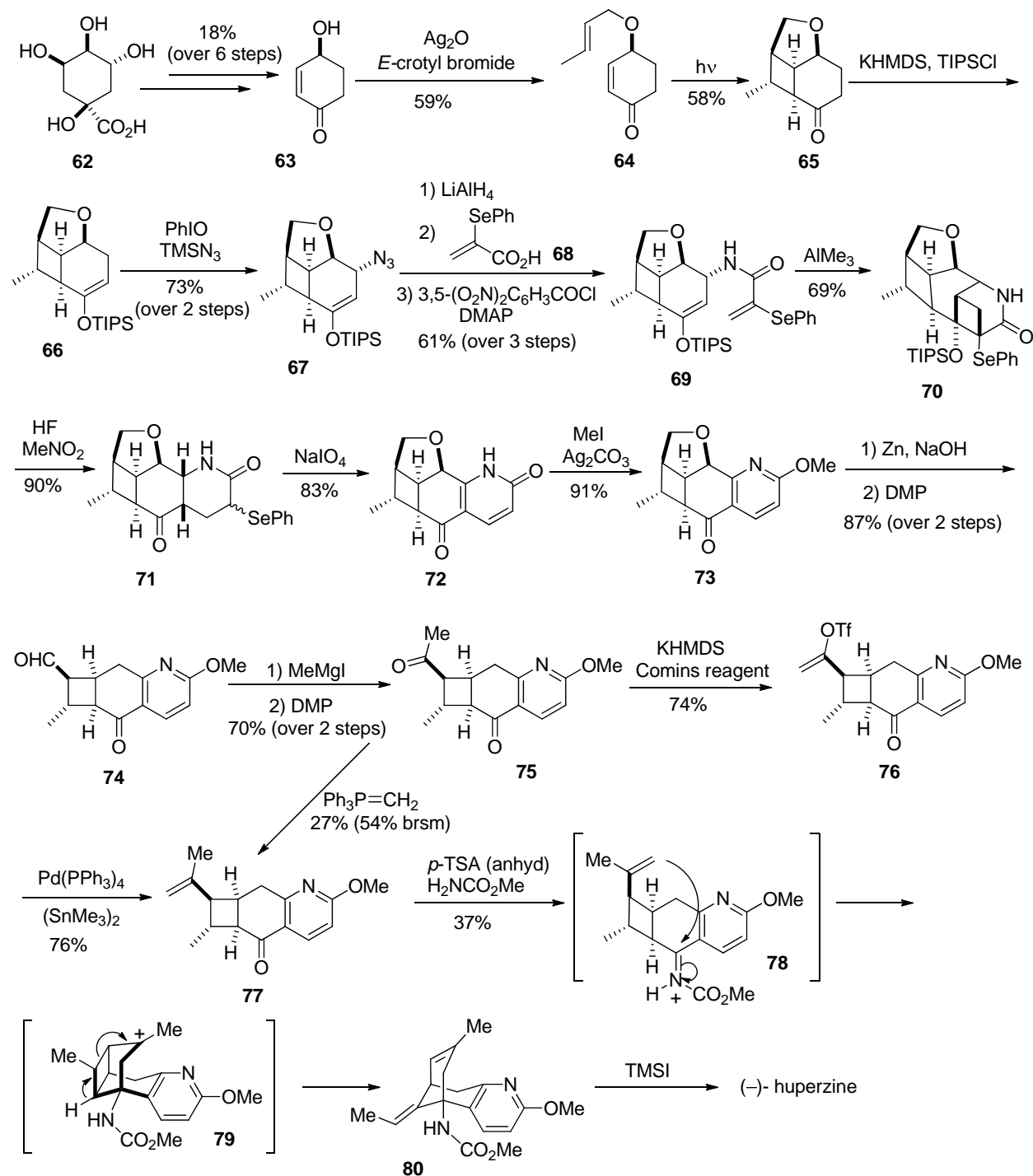
A very similar approach was disclosed by Mann and colleagues<sup>39</sup> who accomplished a formal total synthesis of huperzine A. As depicted in scheme 8, this route also uses intramolecular Heck



coupling as the pivotal step in the synthetic sequence which commences with 2-cyclohexenone as the starting material. Baylis-Hillman reaction of 2-cyclohexenone followed by TBS protection and alkylation provided the enone **55** which was subjected to Luche reduction to prepare the alcohol **56** as a *syn/anti* mixture. Heck coupling on this diastereomeric alcohol substrates was successfully implemented to establish the requisite bicyclo[3.3.1] skeleton. The major *syn* isomer of **57** was first TBS protected before subjecting it to a one pot hydroboration-oxidation sequence. Ketone **59** thus obtained was reacted with methylmagnesium iodide and the resulting tertiary alcohol was dehydrated to furnish olefin **61** as the major regioisomer along with the undesired regioisomer **60**. Desilylation and oxidation of the product 1,3-diol led to the formation of a  $\beta$ -keto acid which was subsequently esterified with diazomethane to produce the  $\beta$ -keto ester **15**. This route constitutes a formal total synthesis of the natural product since  $\beta$ -keto ester **15** was a pivotal intermediate *en route* to huperzine A.<sup>28</sup>



**Scheme 8.** Mann's formal synthesis of huperzine A.



**Scheme 9.** White's asymmetric synthesis of (-)-huperzine A.

White's recent approach which hinges on a domino aza-Prins reaction/cyclobutane fragmentation has recently culminated in a new synthesis of (-)-huperzine A.<sup>40</sup> As depicted in Scheme 9, White's synthesis starts with (*S*)-4-hydroxycyclohex-2-enone (**63**) which is readily

synthesized from (–)-quinic acid (**62**). Enone **63** was alkylated first with *E*-crotyl bromide and the resulting ether was subjected to a photochemical [2+2] cycloaddition to establish the tricyclic framework in intermediate **65**. This was converted into allylic azide **67** in two steps via silyl enol ether **66**. Azide **67** was subsequently converted into amide **69** via reduction to the amine and reaction with acid **68** in the presence of 3,5-dinitrobenzoyl chloride. Amide **69** underwent a smooth [2+2] cycloaddition on exposure to AlMe<sub>3</sub> to furnish **70** which on treatment with HF led to a desilylation/retro-aldol fragmentation to form the  $\alpha$ -selenyl  $\delta$ -lactam **71** as a mixture of diastereomers.  $\alpha$ -Pyridone **72** was obtained from selenide **71** through NaIO<sub>4</sub> oxidation/elimination and subsequent O-methylation produced methoxypyridine **73**. The scission of the benzylic C–O bond was achieved by exposure of **73** to activated zinc and methanolic NaOH to give a  $\delta$ -hydroxy ketone, the subsequent Dess-Martin oxidation of which furnished aldehyde **74**. Diketone **75** was synthesized from aldehyde **74** through a two step protocol comprising Grignard addition and oxidation. The product was directly converted into olefin **77** by Wittig olefination but the yield of the latter step was only 27%. Therefore, the enolate derived from **75** was treated with Comins reagent to form the enol triflate which was subjected to Stille coupling to produce the desired olefin **77**. Reaction of **77** with methyl carbamate and anhydrous *p*-toluenesulfonic acid orchestrated a domino aza-prins/fragmentation reaction to assemble the bicyclo[3.3.1] skeleton though the intermediacy of iminium ion intermediate **78**. (–)-Huperzine A was obtained upon treatment of the resulting carbamate **80** with TMSI.

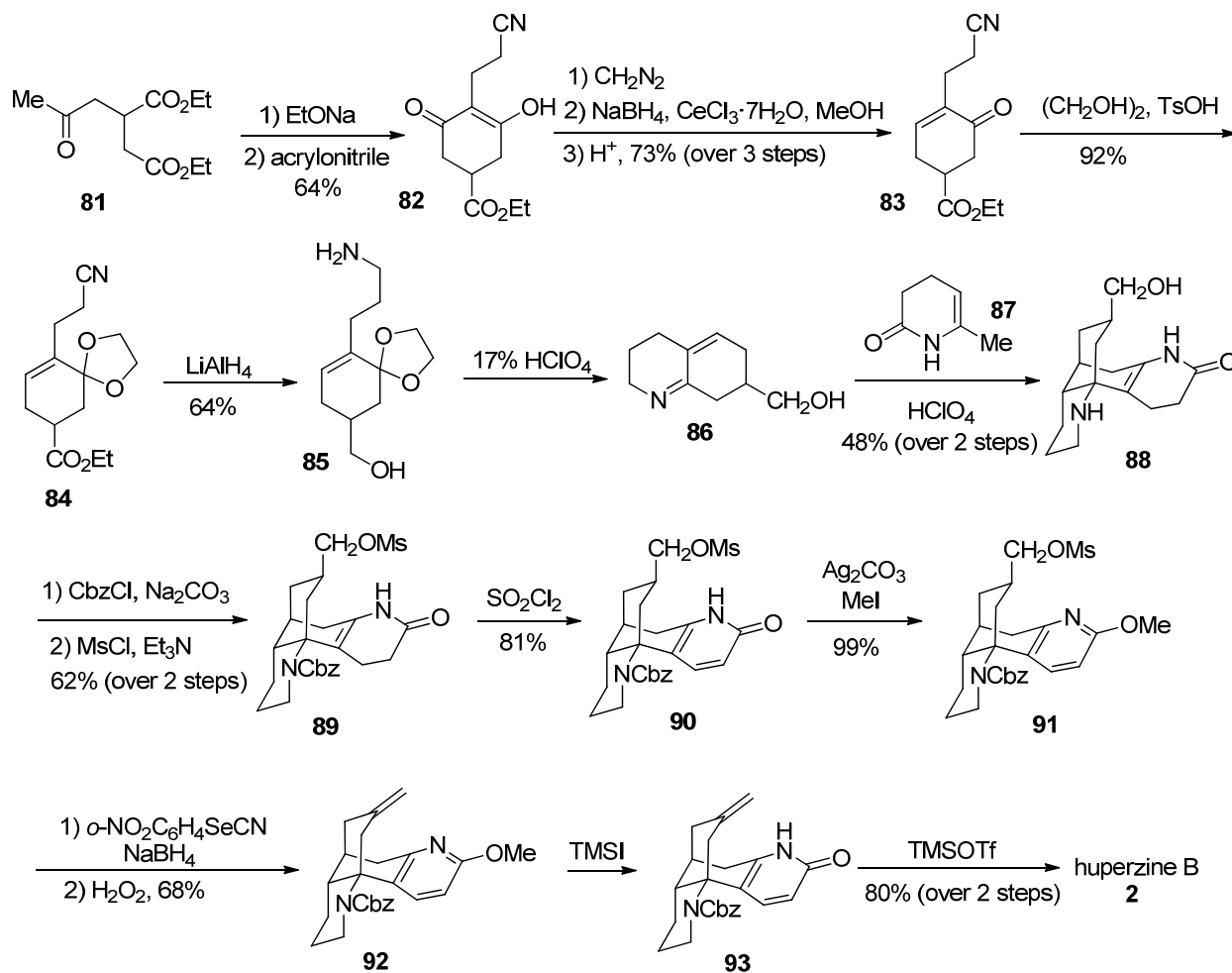
### 3. Huperzine B

Huperzine B is a structural sibling of huperzine A. Despite of its lower acetylcholinesterase inhibitory action, it is also considered an important molecule to combat AD and dementia mainly because of its higher therapeutic index and its longer duration of action.<sup>19</sup> Although there are reports concerning the synthesis of structural congeners<sup>41-42</sup> of huperzine B, the number of total syntheses of huperzine B itself remains limited. In addition to the bicyclo[3.3.1]nonane unit fused to a 2-pyridone moiety, huperzine B (**2**) bears an additional piperidine ring fused to the bicyclo[3.3.1] skeleton.

The first total synthesis of huperzine B appeared in 1997 while Wu and Bai constructed the skeleton via tandem Michael-Mannich reaction.<sup>43</sup> As outlined in Scheme 10, the key intermediate **86** was synthesized in eight steps from ketoester **81**. This starting material was first subjected to a Dieckmann cyclization in the presence of sodium ethoxide and the resulting sodium enolate was further reacted with acrylonitrile to prepare  $\beta$ -diketone **82**. The latter compound was protected first as the methyl enol ether and subsequent ketone reduction followed by acid treatment led to the formation of unsaturated ketone **83**. This intermediate was converted into amine **85** in two steps via protection of the keto group and LAH reduction. Cyclic imine **86** was formed spontaneously when the ketal in **85** was cleaved upon exposure to perchloric acid.

Imine **86** reacted smoothly with 1,2,3,4-tetrahydro-6-methyl-2-oxopyridine **87** in the presence of perchloric acid to form secondary amine **88** which was protected as a carbamate.

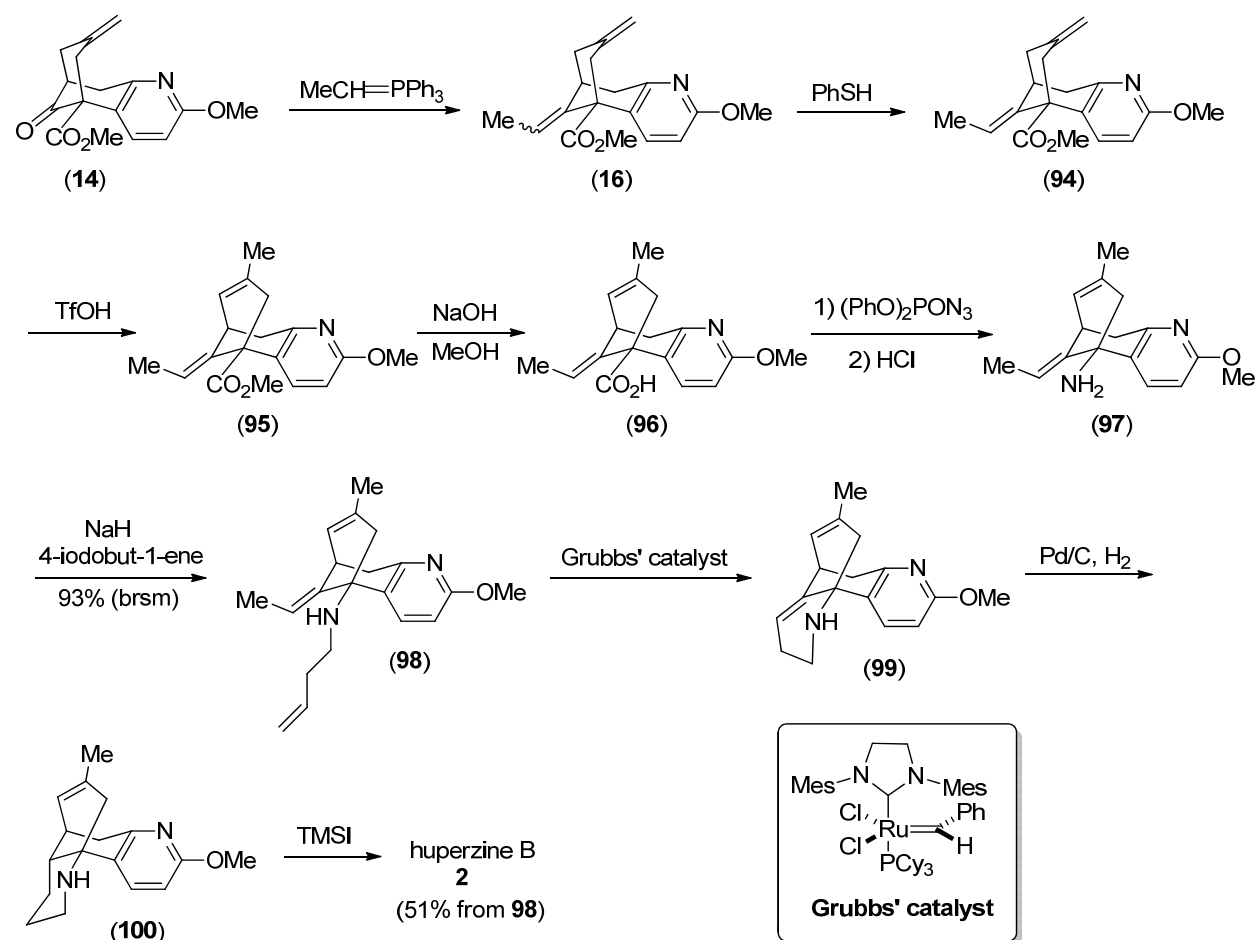
Subsequent mesylation gave dihydropyridone **89** which was converted into pyridone **90** by the action of sulfuryl chloride followed by the elimination of HCl from the resulting chloride. The pyridone moiety was protected by O-methylation before inducing a selenoxide elimination. Once the exocyclic double bond was installed, the pyridone moiety was revealed upon demethylation. Finally, the exocyclic double bond in **93** was isomerized by TMSOTf to afford racemic huperzine B in 6.6% overall yield.



**Scheme 10.** Bai's synthesis of huperzine B.

A ring-closing metathesis based synthesis of huperzine B was demonstrated by Lee *et al.*<sup>44</sup>  $\beta$ -Keto ester **14** on Wittig olefination followed by isomerisation of the obtained *E/Z* mixture provided olefin **94** with the required (*E*) geometry (Scheme 11). Isomerization of the exocyclic double bond, saponification, Curtius rearrangement and subsequent treatment of the resulting isocyanate with HCl gave amine **97**. This compound was N-alkylated with 4-iodobut-1-ene to produce secondary amine **98** which underwent smooth ring closing metathesis to the cyclized

product **99**. Huperzine B was obtained from intermediate **99** through hydrogenation and O-demethylation.



**Scheme 11.** Lee's synthesis of huperzine B.

In summary, we have presented an overview of the strategies for the total synthesis of huperzine A and B. Complete total syntheses, asymmetric approaches and formal total syntheses of these two alkaloids have been covered. In view of the attractive molecular architecture of these natural products and their strong biological activity, newer strategies will continue to emerge and may well pave the way for the development of new drug candidates to combat Alzheimer's disease and dementia.

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