The first enantioselective synthesis of palinurin†

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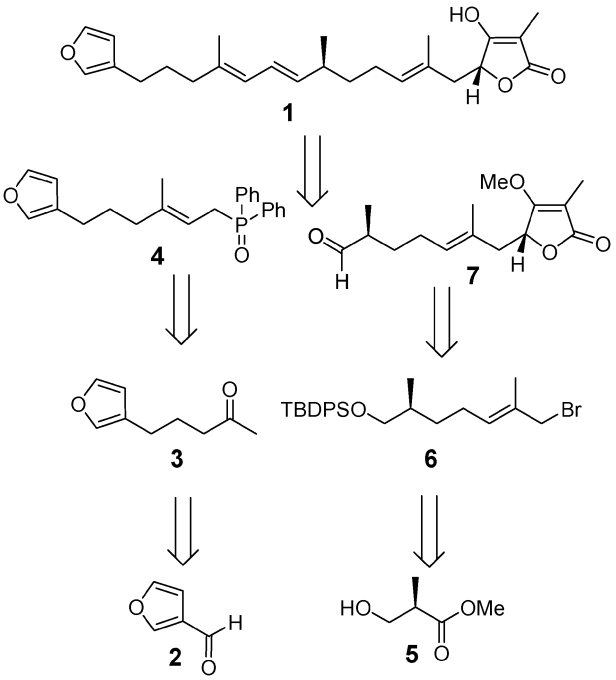
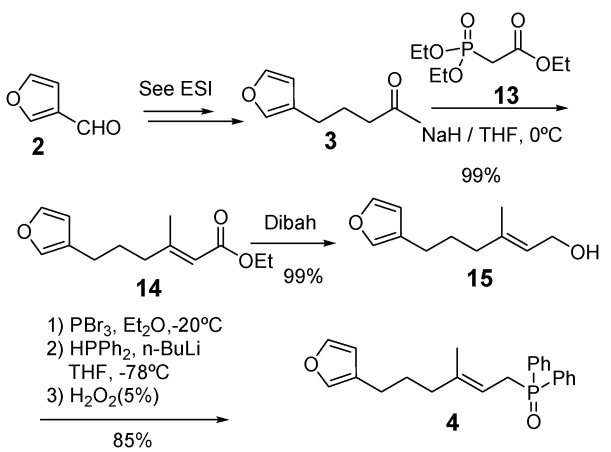
The first enantioselective synthesis of palinurin has been accomplished starting from commercially available furaldehyde and (*R*)-methyl-3-hydroxy-2-methylpropionate; the key steps of the synthesis include the use of a chiral pyrrolidine to create the chiral tetronic moiety, and Horner–Wadsworth–Emmons, Wittig and Wittig–Horner reactions to construct the alkene units.

Alzheimer's disease (AD) is characterized by intracellular disorganization (neurofibrillary tangles, NFTs) and extracellular anomalies (amyloid plaques) in the hippocampus and neocortex.[1] Amyloid plaques are composed of β amyloid [Aβ] peptides generated by cleavage of amyloid precursor protein (APP). NFTs are formed of paired helical filaments (PHFs) generated by aggregation of microtubule-associated tau protein in an abnormally hyperphosphorylated state. Several studies have implicated molecular and cell signaling cascades involving the serine-threonine kinase glycogen synthase kinase 3β (GSK-3β) in the formation of both kinds of lesion.[2] One of the strategies being pursued in the search for pharmacological therapies for AD is blockade of tau hyperphosphorylation by selective inhibitors of GSK-3β. Palinurin (**1**, Scheme 1), a linear furanosesterterpene originally found in the Mediterranean sponge *Ircinia variabilis* and later re-isolated from the Red Sea sponge *Ircinia echinata*, is a compound with anti-inflammatory and antibacterial properties.[3a,b] Related furanosesterterpenes with some cytotoxicity are known.[3c,d] Palinurin has also emerged as a non-ATP-competitive inhibitor of GSK-3β.[4] To the best of our knowledge, no synthesis of this compound has been published. Here we report the first enantioselective synthesis of palinurin, which was based on the retrosynthetic analysis indicated in Scheme 1: Wittig–Horner coupling of a phosphine oxide containing the furan ring (**4**, obtainable from commercially available furaldehyde **2**) to an aldehyde containing the tetronic moiety (**7**, obtainable from (*R*)-methyl-3-hydroxy-2-methylpropionate (**5**).



Scheme 1 Retrosynthetic analysis.

Phosphine oxide **4** was prepared as shown in Scheme 2 (see also ESI†). Wittig reaction of **2**, followed by reduction with $LiAlH_4$ and catalytic hydrogenation, afforded alcohol **10** in excellent yield (92% from **2**). Alcohol **10** was easily converted into iodide **11** in 99% yield, and treatment of **11** with sodium cyanide gave nitrile **12**, likewise in 99% yield. Reaction of **12** with methyllithium then afforded an 80% yield of ketone **3**, which was subjected to a Horner–Wadsworth–Emmons reaction[5] with phosphonate **13** to obtain the α,β-unsaturated ester **14** in 99% yield. Finally, reduction of **14** with DIBALH gave allylic alcohol **15**, which was uneventfully converted into phosphine oxide **4** in 85% yield.[6]



Scheme 2 Synthesis of phosphine oxide **4**.

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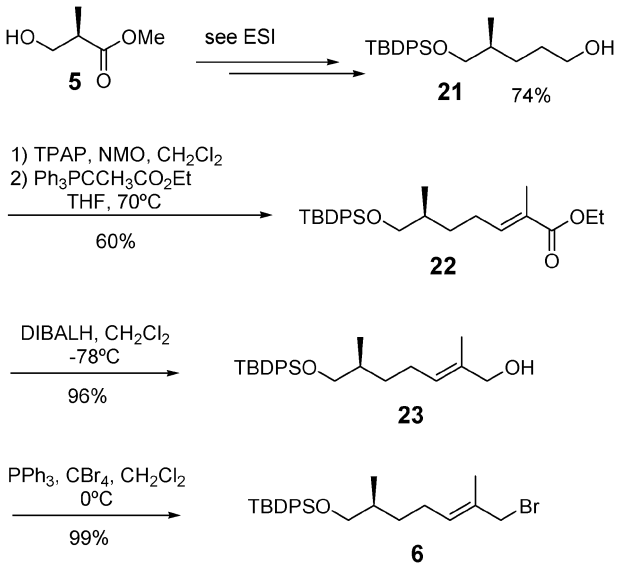
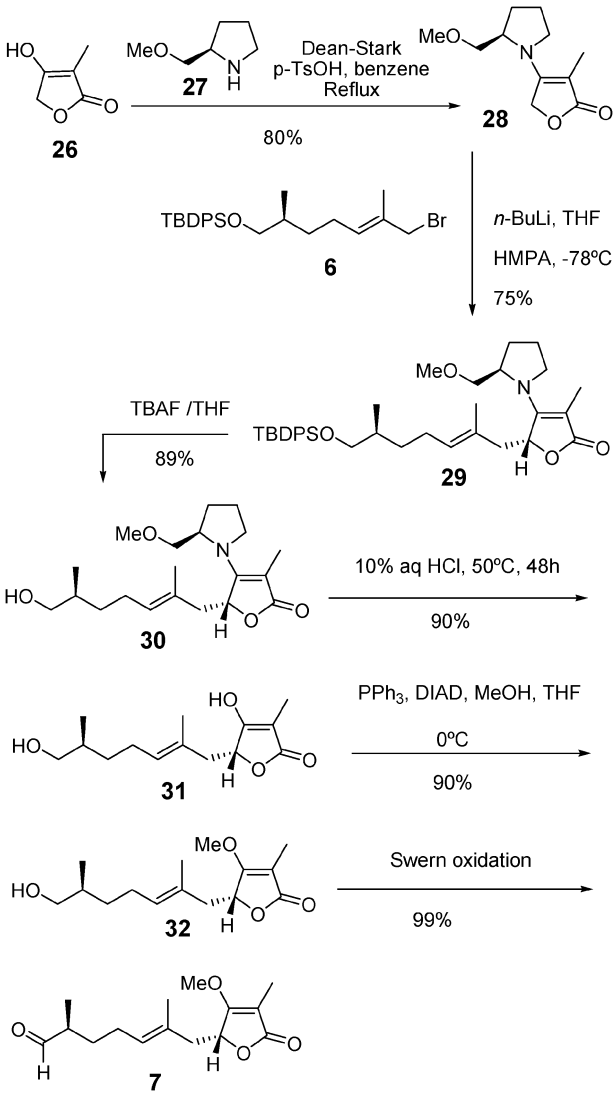


Scheme 3 Synthesis of allylic bromide **6**.

The tetronic intermediate **7** was prepared *via* allylic bromide **6**, which was obtained from commercially available hydroxyester **5** as shown in Scheme 3. Silylation of **5** with TBDPSCl and subsequent reduction of the methyl ester group provided an excellent yield of alcohol **17**, which was easily converted into iodide **18** in 90% yield. Reaction of **18** with dimethyl malonate anion afforded diester **19** in 91% yield, and Krapcho decarboxylation[7] of **19**, followed by DIBALH reduction, gave a mixture of diol **20** (16%) and the desired alcohol **21** (74%) (see ESI†). TPAP oxidation of alcohol **21** and Wittig reaction of the resulting aldehyde then afforded α,β-unsaturated ester **22**, which upon reduction with DIBALH provided allylic alcohol **23** (96%). Finally, reaction of **23** with PPh_3 and CBr_4 gave allylic bromide **6** in nearly quantitative yield.

With allylic bromide **6** in hand, we turned our attention to the tetronic moiety **7** (see Scheme 4). First, tetronic acid derivative **26** was obtained by protection of glycolic acid with cyclohexanone[8] in 73% yield, followed by reaction of the resulting lactone, **25**, with methyl propanoate anion.[9] (see ESI†). Reaction of **26** with commercially available pyrrolidine **27** then gave an 80% yield of the chiral enaminofuranone **28**,[10] coupling of which with compound **6** afforded, as expected,[11] the chiral furanone **29** (75%). Removal of the silyl protecting group of **29** with TBAF provided an 89% yield of alcohol **30**; removal of the chiral auxiliary from **30** with 10% aqueous HCl in THF[12a] gave a 90% yield of diol **31**; and reaction of **31** with methanol under Mitsunobu conditions[12] supplied a 90% yield of alcohol **32**, which contains the desired methyl tetronate moiety. Finally, Swern oxidation of alcohol **32** gave the target aldehyde **7** in nearly quantitative yield.

The synthesis of compound **1** was completed according to plan by Wittig–Horner reaction[13] of aldehyde **7** with phosphine oxide **4** (Scheme 5): reaction of **4** with *n*-Buli in THF at −78 °C afforded a deep red anion that was coupled to aldehyde **7**, providing compound **33** in 40% yield with an 8:1 *E*/*Z* ratio at the newly formed double bond. Finally, demethylation of **33** with *n*-C_3H_7SLi in HMPA[14] (r.t., 2 h)



Scheme 4 Synthesis of aldehyde **7**.

afforded **1** in 90% yield. The spectroscopic data of **1** were in good agreement with those reported for natural palinurin.[3a] The difference in the α_D value measured by us at room temperature (+28.8 degrees) and the published value measured at 0 °C (+45.3 degrees) might be explained by the instability of palinurin at room temperature.

In conclusion, we have achieved the first enantioselective total synthesis of palinurin from commercially available starting material. The key steps of the synthesis include the use of a chiral pyrrolidine to create the chiral tetronic moiety, and Horner–Wadsworth–Emmons, Wittig and Wittig–Horner reactions to construct the alkene units. Biological evaluations of the final target as well as all the intermediate compounds are currently being carried out and will offer a platform from which to design a QSAR model in the search for inhibitors of glycogen synthase kinase 3β (GSK-3β). This is a highly convergent and flexible synthetic strategy which may be used to prepare palinurin analogues and other structures predicted by the QSAR studies.

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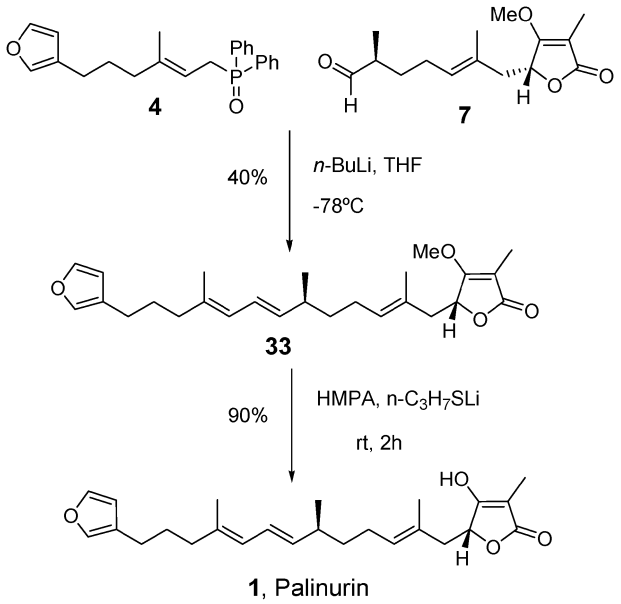

Scheme 5 Completion of the synthesis of palinurin.

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