Asymmetric synthesis of (+)-*cis*-nemorensic acid from a chiral Diels–Alder adduct of 2,5-dimethylfuran†

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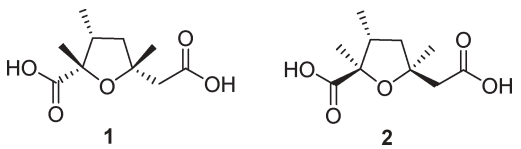
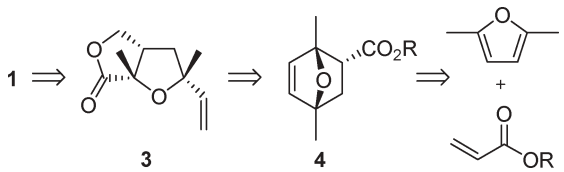
(+)-*cis*-Nemorensic acid (1) was synthesized from a chiral Diels–Alder adduct (4) prepared by a catalytic enantioselective Diels–Alder reaction with 2,5-dimethylfuran and 2,2,2-trifluoroethyl acrylate.

(+)-*cis*-Nemorensic acid **1** and (+)-nemorensic acid **2** are the necic acid components of macropyrrolizidine alkaloids retroisosenine, mulgediifoline[1] and nemorensine,[2] which show diverse biological activities such as hepatotoxicity and antitumor activity.[3] These highly substituted tetrahydrofurans are synthetically challenging because they contain two chiral quaternary carbons. Asymmetric synthesis of (+)-nemorensic acid **2**, obtained from nemorensine, has been accomplished by a number of approaches.[4] However, asymmetric synthesis of (+)-*cis*-nemorensic acid **1** has not been reported. The racemic synthesis of **1** has been disclosed by the Hodgson group[5] and the low enantioselectivity (45% ee) synthesis of the key intermediate for the synthesis of **1** was also reported.[6]



In this paper, we would like to report the first asymmetric synthesis of (+)-*cis*-nemorensic acid **1** from a chiral Diels–Alder adduct of 2,5-dimethylfuran. In connection with our interest in enantioselective Diels–Alder reactions of furans, we considered that a selective oxidative cleavage of the 1,4-dimethyl-7-oxabicyclo[2.2.1]hept-5-ene **4** could provide the key intermediate **3**, which has all functional groups of (+)-*cis*-nemorensic acid **1** (Scheme 1). Also, we envisaged that the enantioselective Diels–Alder reaction between 2,5-dimethylfuran and an acrylate derivative would provide chiral *endo*-Diels–Alder adduct **4**, which has the correct relative stereochemistry and all three chiral stereocenters for (+)-*cis*-nemorensic acid synthesis.

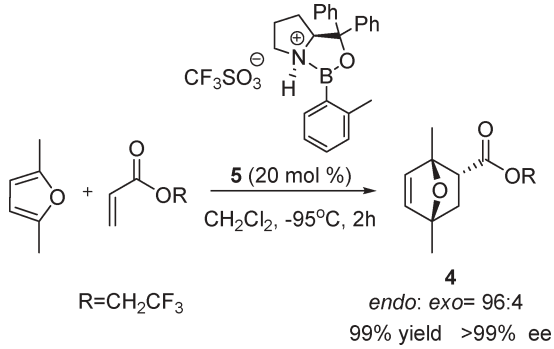


Scheme 1 Retrosynthetic analysis of (+)-*cis*-nemorensic acid **1**.

Although there were a number of methods for the enantioselective Diels–Alder reaction of furans, few of these were synthetically useful in terms of high *endo*/*exo* selectivities and enantioselectivities.[7] Recently we have found that the Diels–Alder reaction of furans with cationic chiral oxazaborolidium catalyst **5**[8] provides 7-oxabicyclo[2.2.1]hept-5-enes with high *endo*-selectivity and excellent enantioselectivity.[9] At that time, we found that 2,2,2-trifluoroethyl acrylate was the best dienophile. The catalyst **5**, which mediates the Diels–Alder reaction of 2,5-dimethylfuran and 2,2,2-trifluoroethyl acrylate, was employed at −95 °C to afford chiral adduct **4** in 99% yield with high *endo*/*exo* ratio (96 : 4) and in >99% ee (*endo*) (Scheme 2).

The next stage was the preparation of the key intermediate **3** from chiral Diels–Alder *endo*-adduct **4**, which was easily separated from the minor *exo*-product by silica gel column chromatography. After the reduction of adduct **4** using lithium aluminium hydride, alcohol **6** was subjected to osmylation and subsequent diol cleavage to give the 5-*exo* cyclized product[10] **7** in 65% yield over two steps. Wittig reaction with methylphosphonium salt using NaHMDS[11] introduced the vinyl group in 70% yield. Pyridinium chlorochromate (PCC) oxidation with celite[12] afforded the key intermediate **3** in 97% yield (Scheme 3). The structure of **3** was unambiguously determined from NOESY spectra.

Lactone ring opening under basic conditions with caesium hydroxide[13] produced a carboxylate salt, which transformed into a methyl ester with trimethylsilyldiazomethane in 80% overall yield. Conversion of alcohol to iodide afforded **10** in a yield of 84%, along with *ca.* 10% of **3**. Sequential hydroboration and oxidation provided alcohol **11** in 77% yield. Removal of iodine,[14] followed by pyridinium chlorochromate oxidation of alcohol **12**, gave



Scheme 2

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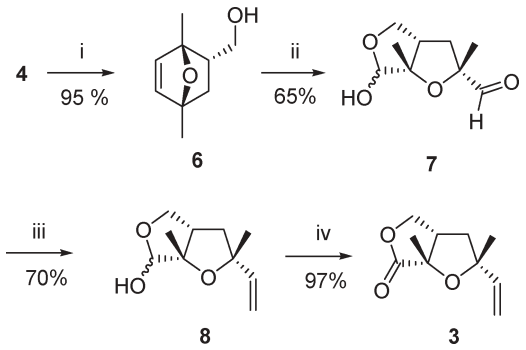
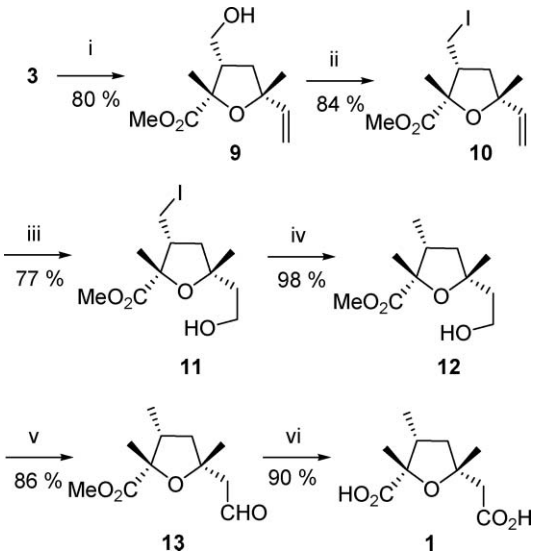


Scheme 3 *Reagents and conditions*: i, $LiAlH_4$, THF, −30 °C, 30 min; ii, OsO_4, NMO, *t*-BuOH–THF–H_2O (8 : 6 : 3), 25 °C, 12 h, then $NaIO_4$, 25 °C, 12 h; iii, PPh_3CH_3Br, NaHMDS, 0 °C, 2 h; iv, PCC, celite, CH_2Cl_2, 25 °C, 3 h.



Scheme 4 *Reagents and conditions*: i, CsOH, *t*-BuOH, 25 °C, 12 h, then 10% citric acid, pH = 4–5, $TMSCHN_2$, MeOH, 25 °C, 5 min; ii, I_2, PPh_3, THF, imidazole, 25 °C, 1 h; iii, BH_3·THF, THF, 0 °C, 3 h then, H_2O_2, 0.15 N NaOH, 0 °C, 1 h; iv, Zn, CH_3COOH, 25 °C, 6 h; v, PCC, celite, CH_2Cl_2, 25 °C, 3 h; vi, 2-methyl-2-butene, 1 M $NaClO_2$, 1 M NaH_2PO_4, *t*-BuOH–THF–H_2O (4 : 4 : 1), 25 °C, 3 h, then 2 N NaOH, 25 °C, 6 h.

aldehyde **13** in 84% yield over the two steps. Finally, Pinnick oxidation[15] and basic hydrolysis of aldehyde **13** were efficiently carried out to release (+)-*cis*-nemorensic acid **1** (Scheme 4). Spectral data for the synthetic acid were in accord with those of the natural isolate.[1a,6] Comparison of the optical rotation determined the absolute stereochemistry to be as shown in **1** $[\alpha]_D$ = +47 (EtOH, *c* 0.50) [lit.[1a,c] $[\alpha]_D$ = +49 ± 4 (EtOH, *c* 0.76)]. As we predicted, the mechanistic model of the cationic oxazaborolidium catalyst **5** was supported (Fig. 1).[9]

In conclusion, we have achieved an asymmetric synthesis of (+)-*cis*-nemorensic acid **1** from 2,5-dimethylfuran. We are now applying this strategy to the preparation of other substituted tetrahydrofurans.

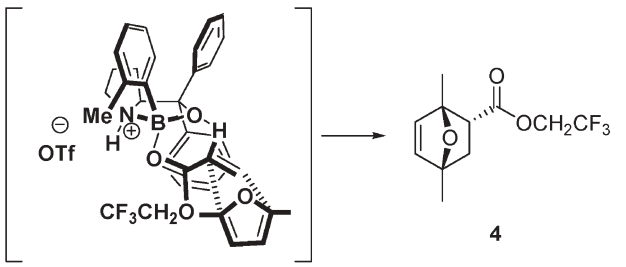


Fig. 1

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