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

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-dimethylfurman. 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.

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 endolexo selectivities and enantioselectivities. Recently, we have found that the Diels–Alder reaction of furans with cationic chiral oxazaborolidium catalyst provides 7-oxabicyclo[2.2.1]hept-5-ens with high endo-selectivity and excellent enantioselectivity. At that time, we found that 2,2,2-trifluoroethyl acrylate was the best dienophile. The catalyst, 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 endolexo 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 in 65% yield over two steps. Wittig reaction with methylphosphonium salt using NaHMDS introduced the vinyl group in 70% yield. Pyridinium chlorochromate (PCC) oxidation with celite 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 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, followed by pyridinium chlorochromate oxidation of alcohol 12, gave

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

Scheme 2

aldehyde 13 in 84% yield over the two steps. Finally, Pinnick oxidation\textsuperscript{15} and basic hydrolysis of aldehyde 13 were efficiently carried out to release \((\pm)\text{-cis}-\text{nemorensic acid} 1\) (Scheme 4). Spectral data for the synthetic acid were in accord with those of the natural isolate.\textsuperscript{14b} Comparison of the optical rotation determined the absolute stereochemistry to be as shown in 1 \([\alpha]_D^{20} = +47\) (EtOH, \(c\ 0.50\) [lit.\textsuperscript{14c} \([\alpha]_D^{20} = +49 \pm 4\) (EtOH, \(c\ 0.76\)]). As we predicted, the mechanistic model of the cationic oxazaborolidium catalyst 5 was supported (Fig. 1).\textsuperscript{9}

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

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Notes and references


