ChemComm

# The synthesis of (+)-nemorensic acid

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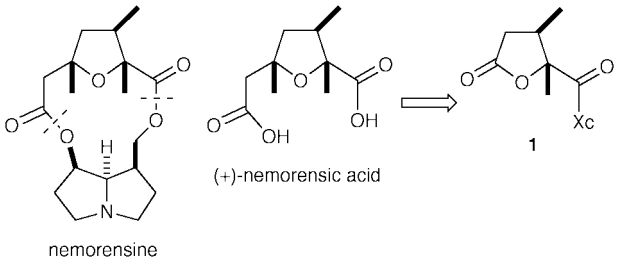
***Received (in Liverpool, UK) 19th January 2000, Accepted 8th February 2000, Published on the Web, 2nd March 2000***

**The synthesis of (+)-nemorensic acid in nine steps is described; key steps in the route were the stereoselective Birch reduction of a substituted furan, and addition of allyltrimethylsilane to an oxonium ion at C-5; an X-ray crystal structure of (−)-nemorensic acid provided proof of the relative stereochemistry of the target.**

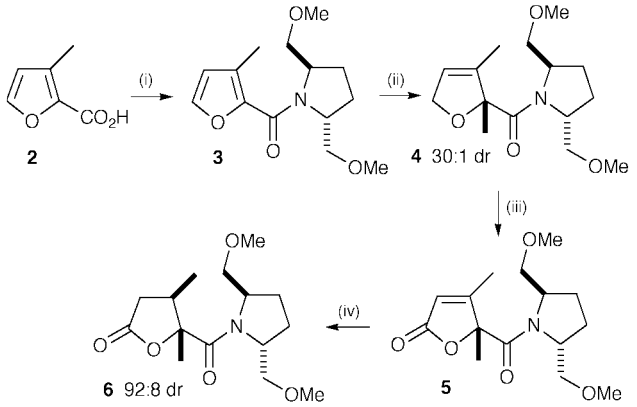
We have recently initiated a research programme aimed at synthesising the pyrrolizidine alkaloids.[1] These alkaloids are a diverse series of compounds, isolated from the *Senecio* family of plants, which display a wide range of biological activities such as hepatotoxicity and carcinogenic activity; some of these alkaloids have the ability to cross-link DNA at specific points.[2] In particular we were drawn to pyrrolizidine alkaloids containing a macrocyclic bislactone. Hydrolysis of these bislactone alkaloids yields a diol (necine base) and a diacid (necic acid). While the synthesis of necine bases is well established, the necic acid moiety has received relatively little attention; indeed it is variation in this part of the molecule that is responsible for much of the diversity of these plant alkaloids. We now report our studies on the synthesis of nemorensic acid, which is obtained from hydrolysis of nemorensine (Scheme 1).[3] A survey of the literature reveals that nemorensic acid has been synthesised by the groups of Klein (±),[4] White (+),[5] Mascareñas (±)[6] and Honda (+).[7] Our retrosynthetic analysis of nemorensic acid identified the lactone **1** as a viable precursor for the target; we know from previous studies that **1** can be prepared from the commercially available 3-methyl-2-furoic acid *via* a Birch reduction on a chiral auxiliary (Xc) laden furan.[8]

Our synthesis began with **2**, which was coupled to (*R*,*R*)-(−)-bismethoxymethylpyrrolidine in excellent yield. We have already reported that the reductive methylation of **3** proceeds in high yield and with ⩾30:1 diastereoselectivity.[8] Subsequent Jones (allylic) oxidation gave **5** and hydrogenation with palladium provided **6** in good overall yield, and with high selectivity for the isomer shown (Scheme 2).[9]

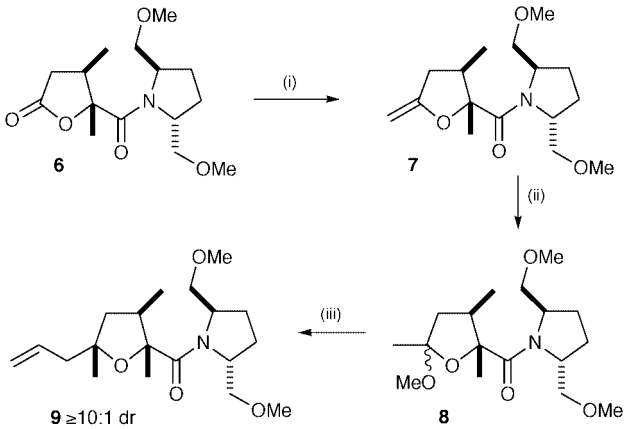
The lactone **6** (structure proven by X-ray crystallography) was treated with '$Cp_2TiMe_2$' which was freshly prepared from $Cp_2TiCl_2$ and MeLi, according to Petasis (Scheme 3).[10] The resulting enol ether **7** was rather sensitive to hydrolysis and was, therefore, converted immediately into the acetal **8** (1:1 mixture of epimers) with acidic methanol (72% overall yield). Introduction of carbon functionality at C-5 was accomplished by




**Scheme 1**




**Scheme 2** *Reagents and conditions*: i, $SOCl_2$, then (*R*,*R*)-bismethoxymethylpyrrolidine, NaOH, 95%; ii, Na, $NH_3$, THF, −78 °C then MeI, 93%; iii, $CrO_3$, $H_2SO_4$, 89%; iv, $H_2$, Pd-C, EtOH, AcOH, 87% (pure *cis*).




**Scheme 3** *Reagents and conditions*: i, $Cp_2TiCl_2$, MeLi; ii, MeOH, HCl, 72% (two steps); iii, allyltrimethylsilane, $TiCl_4$, $CH_2Cl_2$, −78 °C, 79%.

reaction of the epimeric mixture of acetals with titanium tetrachloride and allyltrimethylsilane. The allylated compound **9** that resulted from this reaction was formed as a single diastereoisomer according to $^1H$ NMR analysis of the crude reaction mixture. We could assign the stereochemistry of the product with the aid of NOE experiments which showed a strong (and reciprocal) enhancement between the allylic methylene protons and the (*cis*) methine proton at C-3 (Fig. 1).

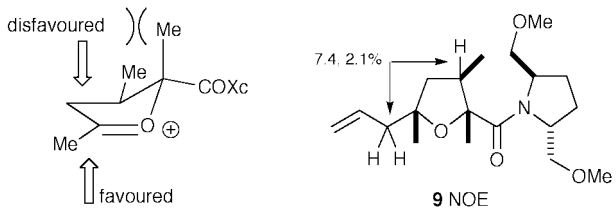



**Fig. 1**

† Author to whom correspondence on the X-ray crystal structure should be addressed.

DOI: 10.1039/b000565g



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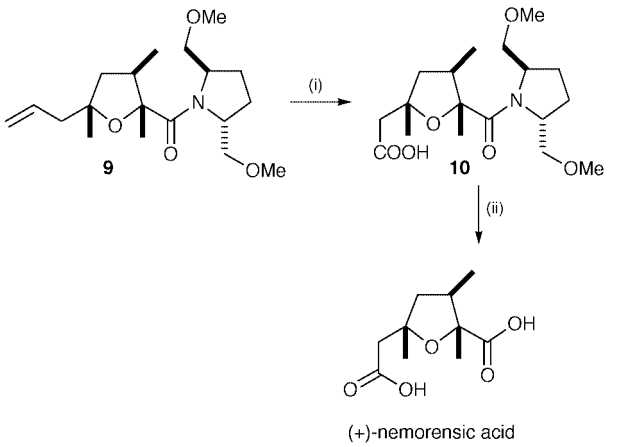


**Scheme 4** *Reagents and conditions*: i, $RuCl_3$ (cat.) $NaIO_4$; ii, 6 M HCl, Δ, 65% (two steps).

The sense of diastereoselectivity displayed during the allylsilane addition to acetal **8** is interesting and is consistent with a recent observation by Woerpel *et al.* on related systems.[11] According to this model, geminal substitution at C-2 is crucial for high levels of selectivity, and the main reason for addition to the lower face of the oxonium ion derived from **8** is steric interaction with the pseudoaxial methyl group at C-2 (Fig. 1).

The synthesis was completed by oxidative cleavage of the alkene unit with catalytic ruthenium tetroxide; the acid **10** was immediately treated with aqueous acid to cleave the auxiliary and liberate nemorensic acid, (65% yield from **9**) (Scheme 4). The relative stereochemistry of the product was confirmed by X-ray crystallographic analysis (Fig. 2).‡

Nemorensic acid produced by this sequence had spectroscopic data ($^1H$, $^{13}C$ NMR) that were identical with those reported in the literature. Its melting point was 171–173 °C (lit.[3] 174–177 °C) and its optical rotation was $[\alpha]_D$ +84 (*c* 0.18, EtOH) (lit.[3] $[\alpha]_D$ +87 (*c* 0.84, EtOH)).

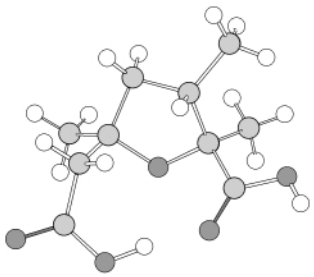

**Fig. 2** Nemorensic acid.

To conclude, we have prepared (+)-nemorensic acid in nine steps and 25% overall yield using the Birch reduction of furan as the key step. This synthesis is particularly efficient and is amenable to the preparation of ample amounts of material.

We thank the EPSRC and Roche Pharmaceuticals for financial support. Clare Stevenson is thanked for some preliminary experiments.

## Notes and references

‡ In the initial phase of our studies we prepared the unnatural (−) enantiomer of nemorensic acid and obtained X-ray crystallographic analysis on this material. *Crystal data* for (−)-nemorensic acid: $C_{10}H_{16}O_5$, $M$ = 216.23, orthorhombic, $a$ = 8.4556(2), $b$ = 11.4227(2), $c$ = 11.4637(2) Å, $U$ = 1107.23(4) Å$^3$, $T$ = 123(1) K, space group $P2_12_12_1$ (no. 19), $Z$ = 4, $D_c$ = 1.297 g cm$^{-1}$, $\mu$(Mo-Kα) = 0.104 mm$^{-1}$. Data collected on a Bruker AXS SMART CCD diffractometer, 9403 reflections measured, data truncated to 0.80 Å ($\theta_{max}$ 26.37°, 99.8% complete), 2269 reflections unique ($R_{int}$ = 0.0182). Final agreement factors for 161 parameters gave $R_1$ = 0.0274, $wR^2$ = 0.0773 and GOF = 1.001 based on all 2269 data, absolute structure not determined, final difference map +0.21 and −0.15 e Å$^{-3}$. Programs used: Bruker AXS SMART and SAINT control and integration software, SHELXTL Structure solution and refinement (G. M. Sheldrick, University of Göttingen, Germany). CCDC 182/1540. See http://www.rsc.org/suppdata/cc/b0/b000565g/ for crystallographic data in .cif format.

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*Communication b000565g*