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Anodic oxidation reactions: the total synthesis of (+)-nemorensic acid

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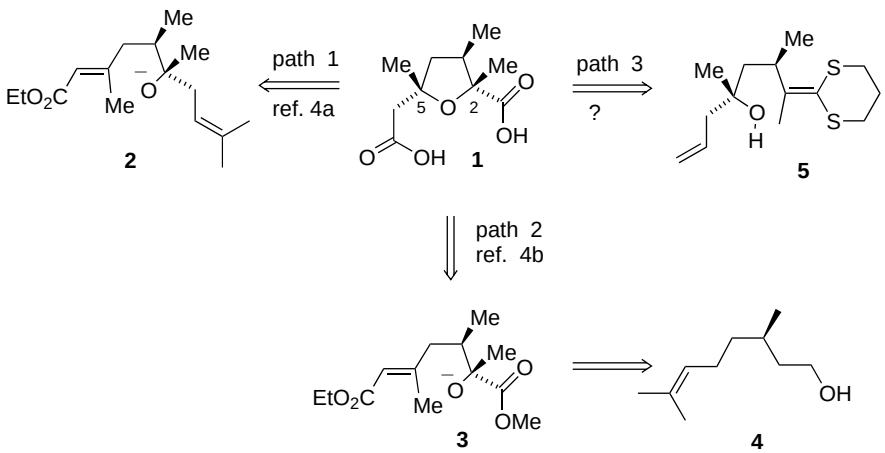
Abstract—The anodic coupling of an enol ether to an oxygen nucleophile has been used as a key step in the total synthesis of (+)-nemorensic acid. The anodic cyclization reaction allows for a reversal in the way the tetrahydrofuran ring of the natural product is normally assembled and thus enables construction of the ring in a highly stereoselective fashion.

The trapping of enol ether and ketene dithioacetal derived radical cations by oxygen nucleophiles can provide a convenient means for synthesizing both tetrahydrofuran and tetrahydropyran rings.[1,2] These reactions are intriguing because they lead to the formation of products where the nucleophilic oxygen has been added to the normally nucleophilic carbon alpha to a carbonyl. The result is an umpolong reaction that can dramatically alter the manner in which the synthesis of a desired product is approached. For example, consider the synthetic approaches to (+)-nemorensic acid outlined in Scheme 1. (+)-Nemorensic acid is the necic acid component of the macropyrrolizidine alkaloid nemorensine.[3] It has twice been made in an asymmetric fashion.[4,5] Both of the previous syntheses (paths one and two) used an intramolecular Michael reaction to construct the tetrahydrofuran ring of (+)-nemorensic acid. While the cyclization reaction in both cases worked well, both reactions led to a mixture of stereoisomers where the minor product had the correct configuration for the natural product. The cyclization of **2** led to a 1:3.8 ratio of isomers favoring an isomer with the opposite configuration at C_5.[4a] The cyclization of **3** led to a 1:4.5 ratio of isomers.[4b] In addition, both routes to (+)-nemorensic acid lost efficiency because completing the synthesis required the removal of carbons from the initial starting materials. For path one the allyl group masking the acid at C_2 of the natural



Scheme 1.

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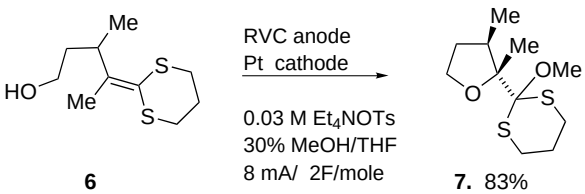
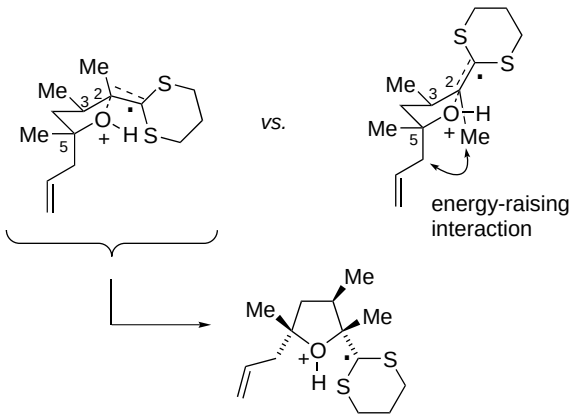
product had to be shortened before the synthesis could be completed, while for the synthesis proceeding through **3**, compound **4** was initially degraded and then rebuilt to form the substrate for the Michael reaction.

It appeared that an anodic cyclization route to (+)-nemorensic acid might address both of these issues (path 3). First, the anodic cyclization would reverse the direction in which the ring was constructed, and hence the allyl group would be used to protect the acetic acid chain at C_5 of the ring. The required acid group would be generated with the use of a simple ozonolysis reaction. Second, previous model studies indicated that the proposed anodic cyclization reaction would afford the tetrahydrofuran ring with the proper stereochemistry (Scheme 2).[6] In this experiment, a ketene dithioacetal group was oxidized in order to determine if the subsequent cyclization reaction would be compatible with the formation of a quaternary carbon. The reaction generated the quaternary carbon and a tetrahydrofuran ring in high yield. In addition, only a single isomer having the two methyl groups *cis* to each other was obtained.

The presence of the quaternary center in the proposed substrate (**5**) for the synthesis of (+)-nemorenisic acid was not expected to interfere with the stereoselectivity observed for **6**. For the analogous Michael reaction arising from **3**, it was argued that the stereochemical outcome of the reaction was determined by an interaction in one of two possible 'chair-like' transition states between the allylic methyl group of the enone and the methyl group on the quaternary carbon bearing the oxygen nucleophile.[4a] In the transition states for the reaction, the methyl group on the quaternary carbon occupied a psuedoaxial position due to its relationship with the vicinal methyl group that controlled coiling of the chain. The interaction between the two methyl groups disfavored the transition state in which it arose and, hence, favored a product where these two methyl groups wound up on opposite sides of the ring. For the proposed cyclization of **5**, the opposite scenario would arise. Since the quaternary carbon would have a 1,3-relationship to the methyl group that controls coiling of the chain, the allyl substituent would occupy the pseudoaxial position (Scheme 3). If the same interaction arose between the axial substituent and the allylic methyl group, then the allylic methyl group would wind up *trans* to the allylic group and *cis* to both the methyl group on the quaternary carbon and the vicinal methyl group. Hence, the presence of the quaternary carbon would favor the same stereochemistry observed for the cyclization of **6**.



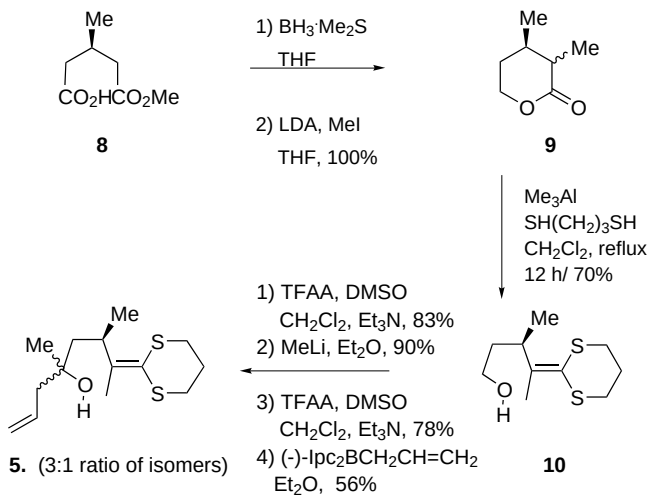
Scheme 2.



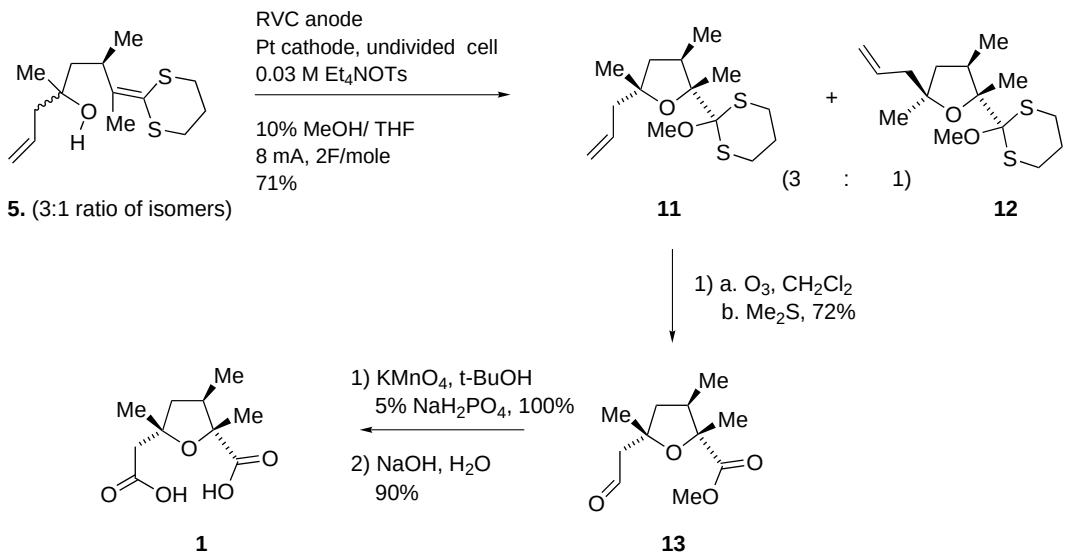
Scheme 3.

With this in mind, the total synthesis of (+)-nemorensic acid was initiated with the asymmetric preparation of substrate **5** (Scheme 4). This was accomplished by first reducing methyl (*R*)-(+)-3-methylglutarate with $BH_3{\cdot}Me_2S$ according to the known procedure,[7] and then alkylating the resulting lactone to form **9**. The lactone was then treated with 1,3-propane thiol and trimethylaluminum in order to form the ketene dithioacetal moiety needed for the cyclization. Oxidation of the alcohol followed by treatment with methyllithium and a second oxidation afforded a methyl ketone that was then treated with allyl-β-isopinocampheny-9-borabicyclo[3.3.1]nonane[8] in order to assemble the quaternary carbon and complete the synthesis of **5**. The quaternary center was obtained as a 3:1 mixture of isomers that could not be separated until after the subsequent electrochemical cyclization reaction. Alternatively, the ketone could be treated with allylmagnesium bromide to afford **5** in near quantitative yield as a 1:1 ratio of isomers. Again, the isomers were separated following the cyclization reaction.

Substrate **5** was oxidized at a reticulated vitreous carbon (RVC) anode (100 ppi, 1 cm×0.8 cm×0.8 cm) in an undivided cell using a Pt cathode, a 0.03 M Et_4NOTs in



Scheme 4.



Scheme 5.

30% MeOH/THF electrolyte solution, and a constant current of 8 mA (Scheme 5).[9] The oxidation was continued until 2 F/mol of charge had been passed and led to the formation of a 71% isolated yield of product. At this point, the two isomers originally formed from allyl addition to the ketone were separated by HPLC (250× 4.6 mm silica gel column using 98:2 hexane/ether as eluant). Both isomers were shown to have a *cis* relationship between the vicinal methyl groups at C_2 and C_3 with the use of a NOESY experiment. In each case the assignment was made using an NOE signal between the two methyl groups and signals between the methyl group at C_2 and the methyl group at C_3 with the same methylene proton at C_4. Clearly, the presence of the quaternary carbon had no effect on the stereochemistry of the anodic cyclization reaction. As in the earlier model study, the electrolysis afforded a single stereoisomer having the correct stereochemistry for (+)-nemorensic acid.

The major product (**11**) was then converted into (+)-nemorensic acid, as outlined in Scheme 5. The olefin was cleaved and the orthoester converted to the methyl ester with the use of an ozonolysis reaction. The aldehyde was then oxidized to an acid and the methyl ester saponified to complete the synthesis.

In conclusion, an anodic cyclization reaction has been used as a key step in the total synthesis of (+)-nemorensic acid. In contrast to earlier Michael reaction based strategies, the cyclization reaction afforded the tetrahydrofuran core of the molecule in a highly stereoselective manner that favored the stereochemistry required for the natural product. In addition, the use of the anodic oxidation strategy reversed the direction of the synthesis and enabled the use of an allyl group to mask the two-carbon acid side chain at C_5 of the natural product instead of the shorter acid side chain at C_2. The result of obtaining the correct stereochemistry in the cyclization and eliminating the need to remove carbons from the starting materials was an efficient 11-step synthesis (compared to 17[4b] and 20[4a] steps for the previous syntheses).

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