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Utilization of a 1,2-Dioxine for the Synthesis of the Four Possible Stereoisomers of Oak Lactone

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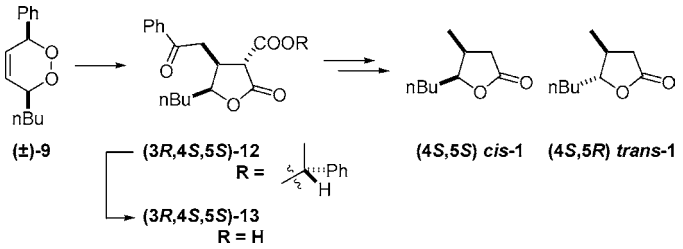
ABSTRACT



The natural products *cis*- and *trans*-oak lactone (1) have been prepared, along with their enantiomeric counterparts, from furanone 12, which was itself prepared from racemic 1,2-dioxine 9 and a chiral malonate diester. The key steps in the synthesis of 1 are the use of the malonate diester as a chromatographic resolving agent and the decarboxylation of 13, which can be directed to give either the *cis*- or *trans*-product. This leads to all four possible oak lactone stereoisomers from a common intermediate.

The (4*S*,5*S*) *cis*- and (4*S*,5*R*) *trans*-isomers of 5-*n*-butyl-4-methyl-4,5-dihydro-2(3*H*)-furanone (**1**), also known as either the "whiskey" or "oak lactones", are the most important oak-derived compounds extracted from wood into alcoholic beverages during fermentation and/or maturation. Of the two, the *cis*-isomer is considered to be of greater sensory importance, imparting characters that are variously described as "coconut", "citrus", and "vanilla".[1] Recently, as part of our ongoing studies into the chemistry of these compounds and their generation in vivo, Wilkinson et al. prepared all four possible β-D-glucopyranosides of the ring-opened analogue of **1**, 3-methyl-4-hydroxyoctanoic acid.[2] Those studies yielded the four stereoisomers of **1** enantiomerically enriched, but from a sensory point of view, the greater potency of the *cis*-isomer relative to that of the *trans*-isomer[3] meant that small quantities of the former in samples of the latter rendered them unsuitable for accurate sensory analysis.

Previously, syntheses of these compounds have usually been conducted separately, with the (4*S*,5*R*) *trans*-isomer **2** generally prepared by conjugate addition of methyl cuprates (Scheme 1, eq 1) to suitably substituted α,β-unsaturated enones.[4,5] Suzuki et al. (Scheme 1, eq 2) prepared the (4*S*,5*S*) *cis*-isomer by a route involving synthesis of the furan unit, with manipulation of the side chain leading to *cis*-**1**.[6]

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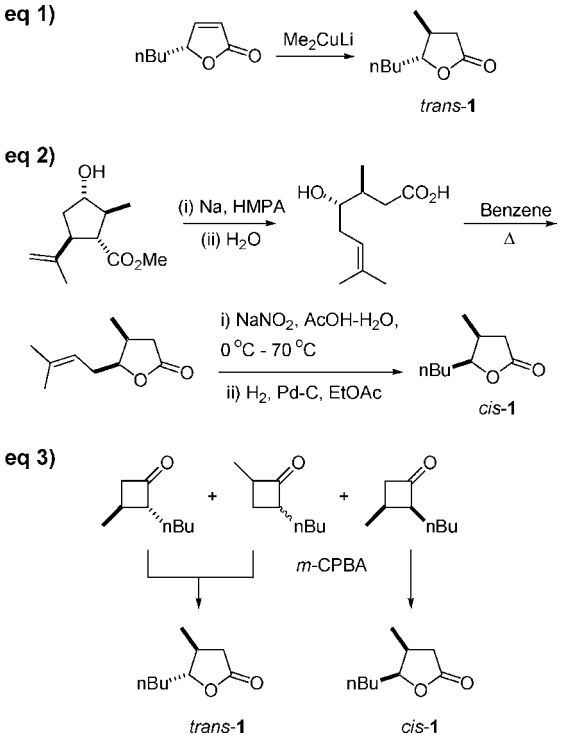
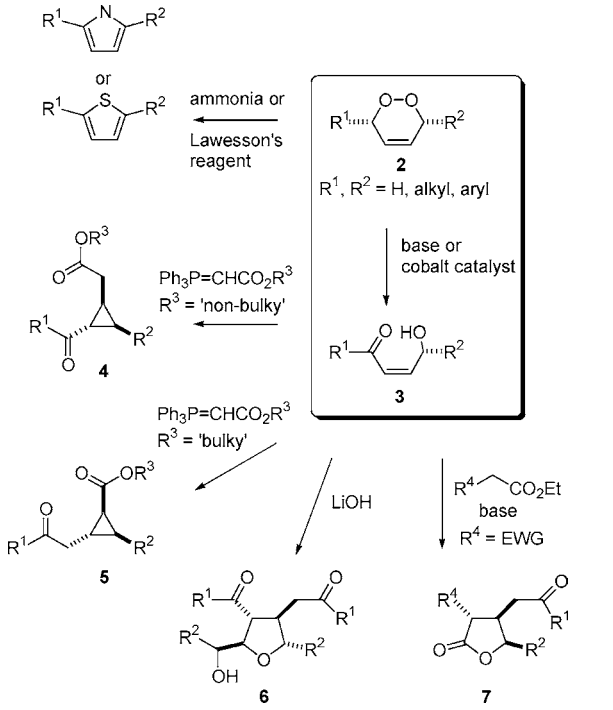
Scheme 1



Scheme 2



Chevtchouk et al. (Scheme 1, eq 3) prepared both (4*S*,5*S*) and (4*S*,5*R*) isomers of **1** with the key step being the Baeyer−Villiger ring expansion of dialkyl-substituted cyclobutanones.[7]

1,2-Dioxines **2** have proven to be extremely versatile starting materials (Scheme 2). They behave as if they are, in effect, masked *cis*-γ-hydroxy enones **3** into which they are converted by treatment with either base or a cobalt-based catalyst.[8] The ring-opened form, **3**, can be converted into cyclopropanes **4** in a highly diastereoselective manner by reaction with stabilized phosphorus ylides.[9] Subsequently, it was discovered that the use of sterically hindered ylides altered the regiochemistry and gave rise to a different class of cyclopropanes **5**.[10] 1,2-Dioxines can be converted into disubstituted pyrroles or thiophenes,[11] or the γ-hydroxy enone equivalent can be transformed into more complex substituted tetrahydrofurans **6**[12] or furanones **7**.[13] It was the last of these conversions that we wished to exploit for the purposes of synthesizing the oak lactones (**1**).

Thus we explored the possibility of preparing both *cis*- and *trans*-**1** enantiomerically pure, from a common dioxine. All four isomers were sought for a full sensory evaluation of their impact on beverages. This has surprisingly been lacking from the literature given the known importance of these compounds to the perceived aroma of beverages fermented and/or stored in oak barrels. Therefore, the strategy used for the syntheses of **1** was devised so that both the naturally occurring isomers of **1**, as well as their corresponding enantiomers, could be prepared in an enantiomerically pure manner. To facilitate resolution of diastereomers by chromatography, a chiral ester group was introduced that did not feature in the final products.

The synthesis of dioxine **9** (Scheme 3) was accomplished by the [4 + 2] cycloaddition reaction between 1-phenylocta-1,3-diene (**8**) and singlet oxygen. Diene **8** was prepared in 82% yield by a Wittig reaction between the ylide derived from 1-iodopentane and cinnamaldehyde. This reaction actually produced a 3:1 mixture of the (*E*,*E*)- and (*E*,*Z*)-isomers of **8**; however, the latter was observed to isomerize into the former under the conditions of photolysis, obviating the separation of the two stereoisomers. The photolysis was conducted in dichloromethane, with illumination from two tungsten halogen lamps (500 W) and with Rose Bengal present as a photosensitizer,[14] to give the desired dioxine **9** as a racemate in 79% yield.

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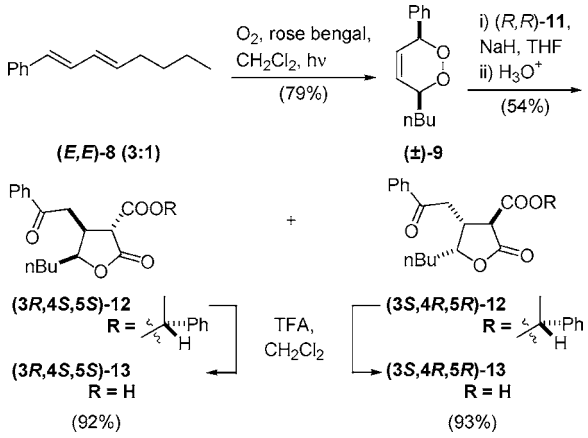
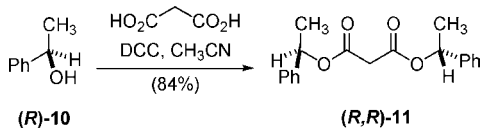
Scheme 3



Treatment of **9** with the enolate derived from the chiral malonate diester **11** (synthesized as shown in Scheme 4[15])

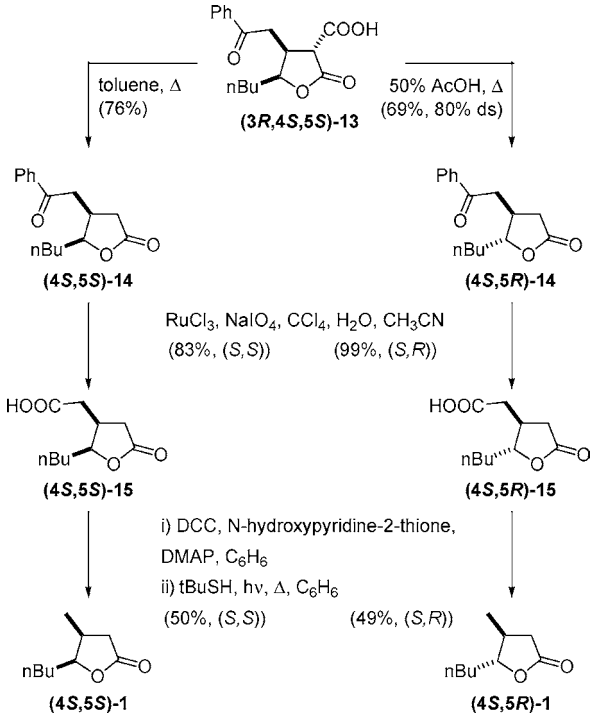
Scheme 4



gave two diastereomeric furanones **12** (Scheme 3) in 54% yield. Separation by chromatography on silica gel provided pure samples of each, with the (3*R*,4*S*,5*S*) diastereomer allowing access to the two nature-identical isomers of **1**, whereas the (3*S*,4*R*,5*R*) diasteromer leads to the formation of the non-nature-identical isomers of **1**. Small amounts (<5%) of the all-*cis* diastereomers were detected as previously reported;[13] however, separation was not considered necessary as subsequent loss of the C3 carboxyl function removes this extra stereocenter. Cleavage of the ester function to give (3*R*,4*S*,5*S*)-**13** and (3*S*,4*R*,5*R*)-**13** was easily achieved using TFA in excellent yields of 92% and 93%, respectively. Preliminary experiments had shown that saponification of esters of type **12** could lead to significant epimerization of the stereocenters but that this could be avoided by the use of a benzylic-type ester under acidic conditions.

The key step in the conversion of furanone **13** into the two isomers of oak lactone **1** was the loss of the C3 carboxyl group under thermal decarboxylation conditions (Scheme 5). When heated in toluene only, a decarboxylation of **13** proceeded cleanly to give (4*S*,5*S*)-**14**, which was free of any of the (4*S*,5*R*) epimer, in 76% yield. Under these conditions, the C3 carboxyl function is lost directly. It had previously been observed that decarboxylation could be directed to give mainly the other epimer.[13] By heating in 50% aqueous acetic

Scheme 5



acid, isomerization of (3*R*,4*S*,5*S*)-**13** occurs to give mainly (3:1) the thermodynamically favored isomer (3*R*,4*S*,5*R*)-**13**, which then undergoes loss of CO_2.

Purification of (4*S*,5*R*)-**14** was achieved on a small scale by recrystallization from carbon tetrachloride/hexanes; however, it proved to be more efficient to isolate the required isomer by silica gel chromatography in the final step of the synthetic pathway. From this point it only remained to convert the C4 substituent into the required methyl group. Oxidation of the benzoyl group into a carboxyl group was achieved by the use of ruthenium(III) and periodate[16,17] in a ternary solvent system of acetonitrile, water, and carbon tetrachloride (1/1.5/1). This reaction gave the desired acids in very good yields and in high states of purity. Finally, decarboxylation under Barton conditions[18,19] gave the two nature-identical isomers of oak lactone **1**, with NMR data virtually identical to those previously reported,[20] only differing where further splitting was observed.

Acid (3*S*,4*R*,5*R*)-**13** was subsequently carried through in an identical manner to (3*R*,4*S*,5*S*)-**13** to produce the non-nature-identical (4*R*,5*R*) and (4*R*,5*S*) isomers of **1**. Chiral GC−MS analysis[2] showed that all four stereoisomers of oak lactone **1** were obtained diastereomerically pure and that each

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was in a highly enantiopure form (98% ee), as required for sensory evaluation.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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