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A Stereoselective Total Synthesis of (-)-Rishitin

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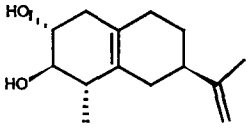
Abstract: A new synthesis of (-)-rishitin (**1**) is reported, starting with chiral pool molecules. The crucial step is a stereoselective vinyl radical cyclization, which gives a 10:1 ratio of **21** to **22**.

A short and stereoselective synthesis of (-)-rishitin, **1**, an important sesquiterpene phytoalexin, is reported here. Rishitin was isolated from potato tubers infested with *Phytophora infestans* and is a defensive agent (phytoalexin) against further damage by the invading microorganism.[1] Only one synthesis of **1** has been reported.[2] That approach used the eudesmane sesquiterpene, (-)-α-santonin, **2**, as starting material and required 22 steps. It utilized an ingenious fragmentation scheme to remove the unwanted angular methyl group. However, the step to introduce the diol system, reduction of an α-hydroxy ketone, occurred in a totally stereorandom manner.



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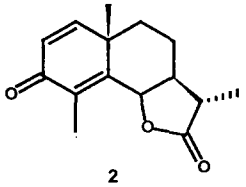

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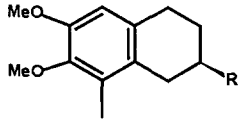


3

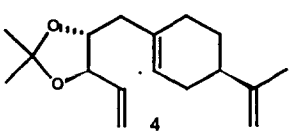
R = $C(CH_3)=CH_2$
$COO^- NH_4^+$
CH_2OH
$CH(CH_3)CH_2OH$

The ring system of rishitin, containing the double bond between the two rings, is conformationally flexible, and thus a major challenge to any synthesis is to provide stereocontrol for the steps to form the three contiguous chiral centers.

Our first approach to this system utilized a Birch reduction of a highly substituted aromatic system **3**, with the hope that pseudo-axial protonation of the anionic intermediates, controlled by directing ability of a side chain hydroxyl group or similar acidic substituent, would provide the necessary control, as has been observed in somewhat similar cases.[3] However, although the reaction was chemically successful, there was very little stereocontrol and the approach was abandoned.

The current synthesis was designed to test the feasibility of introducing stereocontrol via a cyclization of the vinyl radical **4** to form the acetonide of **1**. Vinyl radical cyclization to alkenes, which was pioneered by Stork,[4] has been used several times in natural products synthesis, but no examples with similar stereochemical features could be found in the

literature. This cyclization was expected to be diastereoselective in favor of forming the pseudo-equatorial methyl group at the chiral center, as judged by inspection of molecular models. Also, a semi-empirical calculation by the AM1 program on a close model, structure **5**, predicted that the ratio of the two diastereomers **6** and **7** might be about 7:1, in favor of the desired isomer **6**.[5]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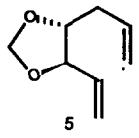
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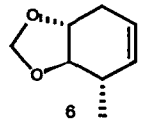
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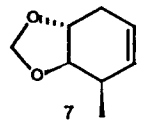
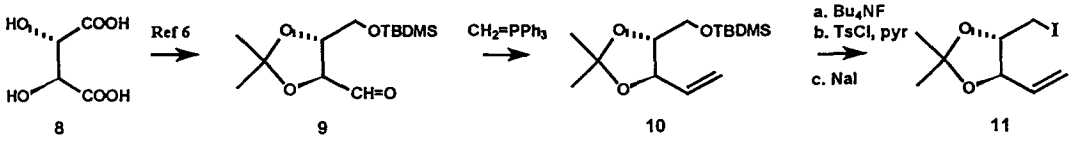
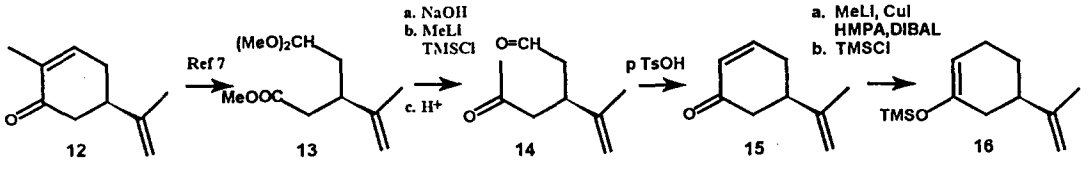

7

A convergent approach, using chiral pool starting materials, was adopted. D-tartaric acid, **8**, was converted into the known intermediate **9** as described.[6] Treatment of this with triphenylphosphonium methylide in DMSO gave **10** (85%). Deprotection of the alcohol (80%), tosylation (90%), and iodide displacement (90%) then gave the iodo derivative **11**.



8 9 10 11

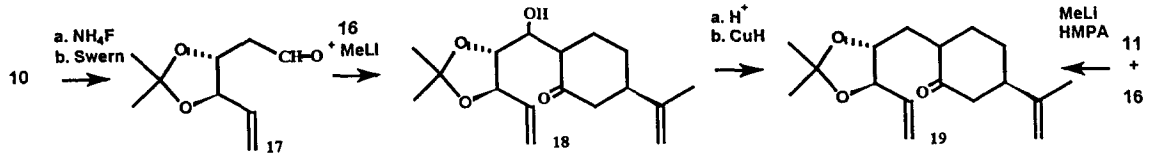
R-(-)-carvone, **12**, was converted into the cleavage product **13** by the literature method.[7] Saponification of the ester (90%) and treatment of the resultant acid with MeLi at 25° with TMSCl trapping[8] gave the enol trimethylsilyl ether, which gave the keto aldehyde **14** (70%) upon aqueous acidic hydrolysis. Smooth aldol cyclization using p-toluenesulfonic acid in toluene gave the enone **15** (70% after vacuum distillation), previously made by another route in racemic form.[9] Addition of cupric hydride via a 1,4-reduction step and trapping of the enolate with TMSCl gave the enol silyl ether **16** (80%). Stereochemical integrity was maintained, since symmetrical intermediates were avoided in the sequence.



12 13 14 15 16

Coupling of **11** and **16** gave the desired ketone **19**, but only in a very disappointing yield (7%) under the best conditions found. The product was formed reproducibly and was readily purified by column chromatography. The major pathway

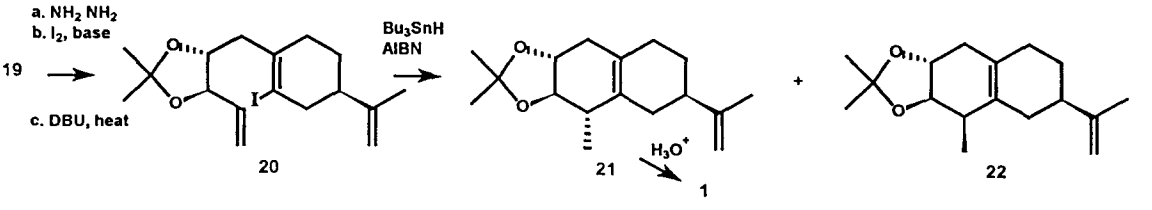
was elimination of HI from **11**. Some alkylation at the α′ position on the ketone was also observed.



Production of **19** was substantially improved by converting **10** into the corresponding aldehyde **17** via fluoride promoted deprotection and Swern oxidation. Condensation of **17** and the enolate derived from **16** gave the aldol product, which was dehydrated and reduced via copper hydride. The over-all yield for this longer sequence was 37%.

With a reasonable route to the coupled product **19** in hand, its conversion to the vinyl iodide **20** was investigated. Following the Barton method,[10] the hydrazone was formed and treated with I_2 and tetramethylguanidine, to give a mixture of geminal and vinyl iodides, as expected. Heating this mixture at 40° with DBU gave the desired tetrasubstituted vinyl iodide **20**, contaminated with the isomeric trisubstituted vinyl iodide (50% yield, 3:1 ratio). However, conducting the reaction at ca. 90° gave only the desired vinyl iodide **20**. Under these conditions, the isomeric iodide was destroyed or isomerized. Chromatography on silica gel readily gave a pure sample (40%).

The stage was now set for the crucial radical cyclization reaction of **20**. Treatment of **20** with tributyltin hydride with a catalytic amount of AIBN in refluxing toluene proceeded smoothly (95%) to only a mixture of **21** and **22**. We were pleased to find that the ratio of **21** to **22** was ca. 10:1 (PMR methyl doublets at δ 1.15 vs. 1.06). All spectral parameters of the synthetic material (65% after chromatography) of **21** and of rishitin, **1**, obtainable via simple acid hydrolysis of **21**, matched the literature values.[2,11] Thus, the stereoselectivity of such radical cyclizations should offer a viable synthetic approach to other natural products.



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5) The work was carried out on the model compound **5** by locating the transition states of the two possible pathways and calculating the energies of them. For the AM1 program, see Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. P. *J. Amer. Chem. Soc.* **1985**, *107*, 3902.

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11) PMR data (200 MHz, $CDCl_3$) of selected compounds: **11**: 1.44 (s, 3H), 1.48 (s, 3H), 3.23 (dd, J=10.7, 5.1, 1H), 3.35 (dd, J=10.7, 4.6, 1H), 3.64 (m, 1H), 4.17 (dd, J=7.2, 7.1, 1H), 5.31 (ddd, J=10.2, 1.8, 1.4, 1H), 5.42 (ddd, J=16.9, 1.8, 1.4, 1H), 5.87 (ddd, J=16.9, 10.2, 7.2, 1H)). 16: 0.18 (s, 9H), 1.2 - 1.45 (m, 1H), 1.55 - 1.85 (m, 1H), 1.73 (br s, 3H), 1.90 - 2.15 (m, 4H), 2.15 - 2.25 (m, 1H), 4.72 (br s, 2H), 4.8 (br s, 1H). **19**: 1.15 - 1.50 (m, 2H), 1.37 (s, 3H), 1.40 (s, 3H), 1.50 - 1.80 (m, 1H), 1.74 (br s, 3H), 1.85 - 2.05 (m, 1H), 2.05 - 2.50 (m, 5H), 2.50 - 2.65 (m, 1H), 3.79 (m, 1H), 3.94 (t, J=7.2, 1H), 4.73 (br s, 1H), 4.76 (br s, 1H), 5.28 (ddd, J=10.2, 1.8, 1.4, 1H), 5.42 (ddd, J=16.9, 1.8, 1.4, 1H), 5.86 (ddd, J=16.9, 10.2, 7.2, 1H). **20**: 1.41 (s, 3H), 1.45 (s, 3H), 1.5 - 1.8 (m, 2H), 1.72 (br s, 3H), 2.2 - 2.8 (m, 7H), 3.86 m, 1H), 4.14 (m, 1H), 4.71 (br s, 1H), 4.74 (br s, 1H), 5.28 (dd, J=10.0, 1.6, 1H), 5.43 (dd, J=17.0, 1.6, 1H), 5.85 (ddd, J=17.0, 10.0, 7.0, 1H). CMR data (50 MHz) of selected compounds: **11**: 4.7, 27.2, 27.2, 79.1, 82.7, 109.5, 119.4, 134.7. **16**: 0.30, 20.7, 23.7, 27.3, 35.1, 41.8, 103.4, 108.7, 149.1, 149.8 19: 20.4, 26.9, 27.3, 30.7, 31.8, 34.2, 47.2, 47.3, 47.4, 79.2, 83.2, 108.6, 109.7, 119.0, 135.0, 147.4, 211.7. **20**: 16.4, 21.1, 26.4, 27.2, 27.2, 30.2, 30.9, 35.9, 39.2, 40.2, 76.1, 84.1, 109.0, 109.4, 125.6, 129.7, 148.7.

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