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Regioselectivity of the Claisen Rearrangement in *meta*-Allyloxy Aryl Ketones: An Experimental and Computational Study, and Application in the Synthesis of (*R*)-(−)-Pestalotheol D

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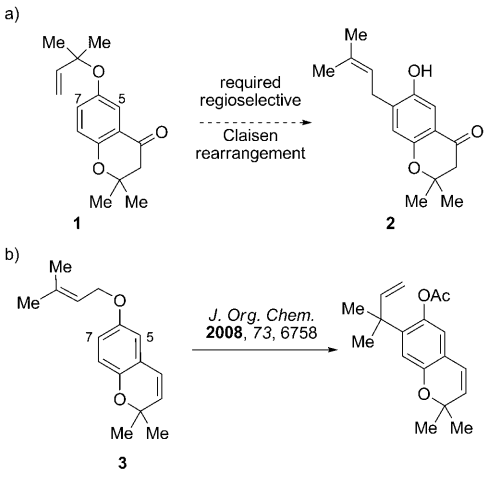
Abstract: A study of the regioselectivity of the Claisen rearrangement of *meta*-allyloxy aryl ketones showed that the electron-withdrawing carbonyl group has a major influence and strongly directs rearrangement to the more hindered *ortho* position. However, when the ketone is part of a ring structure, its electronic effect can be negated by conversion into its triisopropylsilyl enol ether, which dramatically reverses the regiochemistry of the Claisen rearrangement. DFT calculations suggest that the effect is electronic although there is also a steric effect of the bulky silyl group. This strategy for influencing the regiochemical outcome of the Claisen rearrangement was then employed in a short synthesis of the furo[2,3-*g*]chromene, (−)-pestalotheol D, that confirms the absolute stereochemistry of the natural product.

Keywords: Claisen rearrangement · heterocycles · natural product · total synthesis

Introduction

In the century since its discovery,[1] the thermal rearrangement of aryl allyl ethers, universally known as the Claisen rearrangement, has been the subject of numerous studies and has found wide application in organic synthesis.[2] Nevertheless there are still some features of this well known reaction that are poorly understood. For example, the alkene geometry resulting from rearrangement of α,α-disubstituted allyl ethers seems difficult to predict or control, whilst the regioselectivity in the rearrangement of *meta*-substituted aryl allyl ethers remains unreliably predictable in spite of experimental and computational studies.[3–6]

In connection with a planned synthesis of the furo[2,3-*g*]chromene pestalotheol D (see below), it was reasoned that the dihydrofuran ring of the natural product could be accessed using the Claisen rearrangement methodology previously used by us in the synthesis of other natural products,[7–15] with the requirement for a regioselective sigmatropic rearrangement to C7 rather than C5 in the Claisen precursor **1** (Scheme 1). We had previously observed good regioselectivity in the related Claisen rearrangement of dimethyl allyl ether **3**,[12] and we now describe a detailed experimental and computational study of the Claisen rearrangement of 3-allyloxy aryl ketones leading to a successful



Scheme 1. Regioselective Claisen rearrangements: a) required for a synthesis of pestalotheol D; b) previously observed regioselectivity in a related rearrangement.

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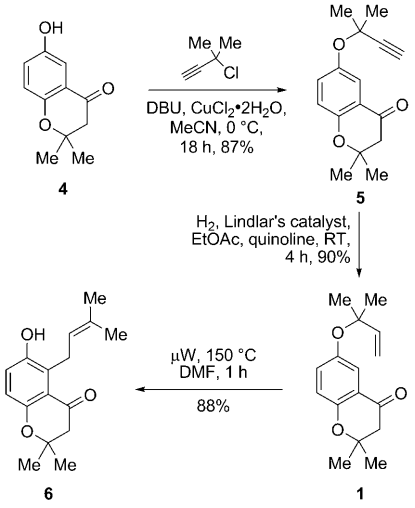
synthesis of pestalotheol D, confirming both its structure and absolute stereochemistry.

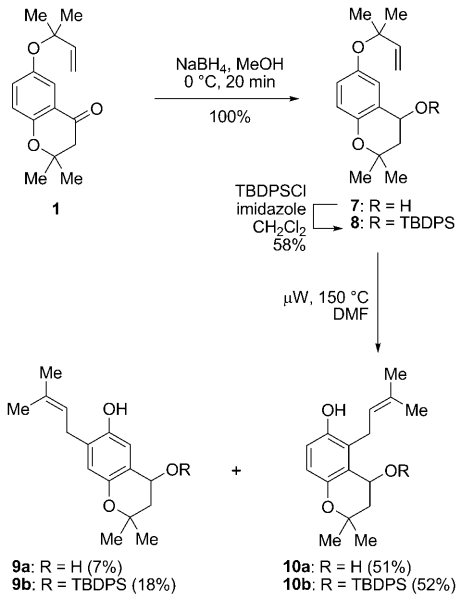
Results and Discussion

Regioselectivity in the Claisen rearrangement of 3-allyloxy aryl ketones: Starting from the known chromanone **4**, a natural product isolated from *Calea cuneifolia*,[16] and readily prepared from 2′,5′-dihydroxyacetophenone using a literature procedure,[17] the dimethylallyl moiety was then incorporated via a copper-mediated alkylation[18,19] to give the intermediate alkyne **5**, followed by hydrogenation over Lindlar's catalyst to give the intermediate dimethyl allyl ether **1** in 78% over the two steps. Claisen rearrangement of **1** under microwave irradiation occurred with complete regioselectivity, but unfortunately to the undesired 5-position rather than the 7-position of the chromanone ring, giving compound **6** in good yield (Scheme 2).



Scheme 2.

Clearly the rearrangement of the chromanone derivative **1** (Scheme 2) is very different to that of chromene **3** previously studied in our laboratory (Scheme 1),[12] and presumably reflects the electronic effect of the chromanone carbonyl group. Although the regiochemistry of the Claisen rearrangement of *meta*-substituted phenyl allyl ethers is not easy to predict, there is limited evidence that, generally, electron-withdrawing *meta*-substituents favored rearrangement to the more hindered *ortho*-position, with electron-releasing *meta*-substituents favoring rearrangement to the *para*-position.[3,4] In order to negate the apparently detrimental effect of the chromanone carbonyl group, two strategies were considered. The first involved reduction of the ketone in chromanone **1** to the corresponding chromanol **7** with sodium borohydride, subsequently protected as its bulky *tert*-butyldiphenylsilyl (TBDPS) ether **8**. The subsequent Claisen rearrangements of these two substrates, carried out under microwave heating in DMF, gave a mixture of regioisomeric products **9** and **10**, easily separable and distinguishable by ^{1}H NMR spectroscopy, with the 5-prenyl isomer **10** predominating for both the alcohol and silyl ether substrates (Scheme 3). Although this strategy does influence the outcome of the Claisen rearrangement and produce some of the desired regioisomer **9**, the selectivity remains poor, and, significantly, it involves an unattractive and avoidable change of oxidation state in the substrate.



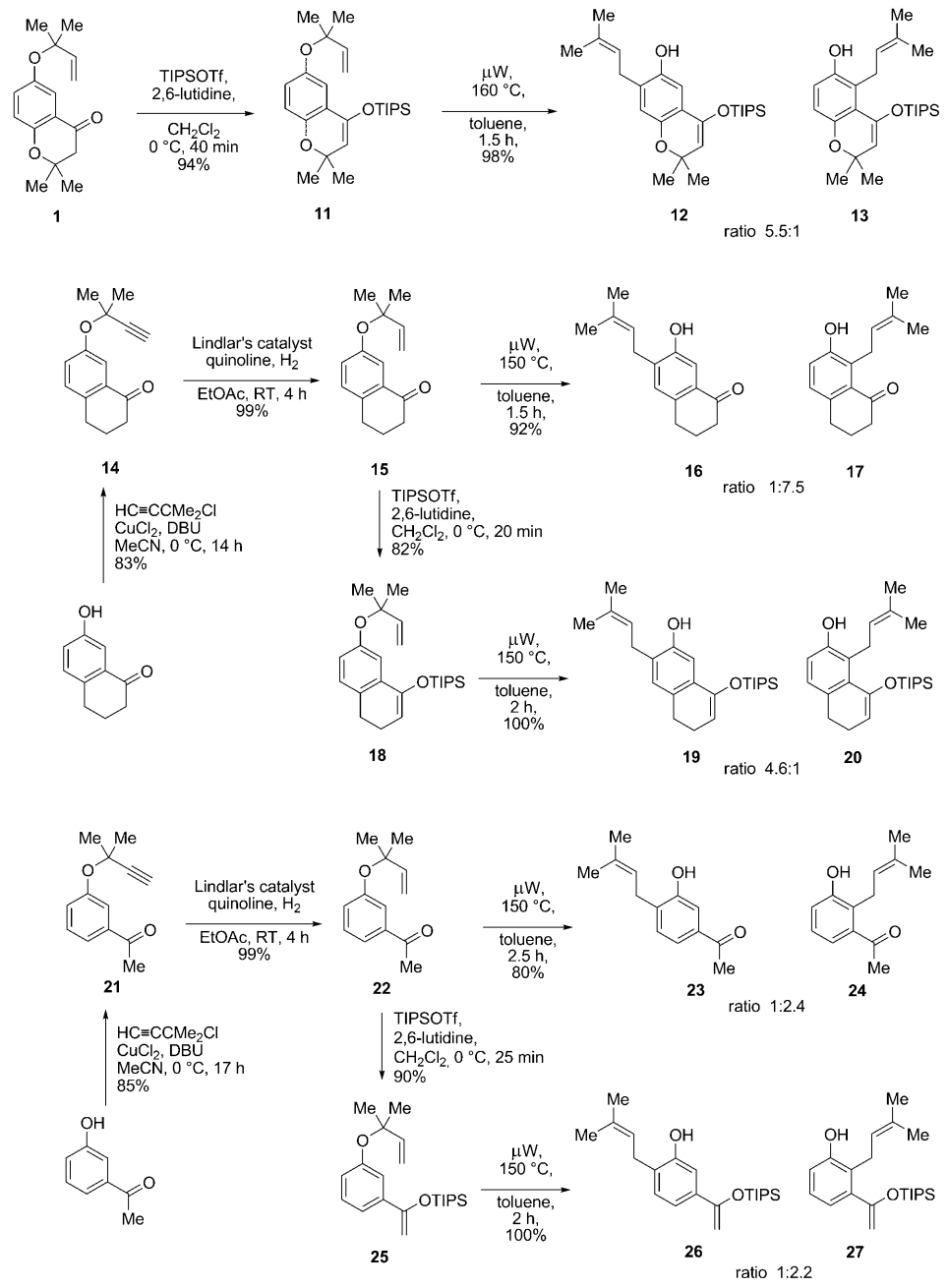
Scheme 3.

We therefore adopted an alternative strategy that involved temporary masking of the chromanone carbonyl as its triisopropylsilyl (TIPS) enol ether **11**, readily prepared from chromanone **1** in excellent yield. This silyl enol ether **11** was then subjected to microwave irradiation in DMF to give a mixture of 7- and 5-prenyl chromenes **12** and **13** in a 1:1 ratio, albeit in poor 26% yield. Pleasingly, however, both the yield and selectivity were vastly improved by switching to toluene as solvent, and this gave an excellent yield (98%) of separable regioisomers in 5.5:1 ratio in favor of the desired 7-prenyl isomer **12** (Scheme 4).

Notwithstanding the aforementioned general effect of *meta* electron-withdrawing versus electron-releasing groups, this tactic of temporary removal of the electron-withdrawing properties of a carbonyl substituent on an aromatic ring in order to influence the regiochemical outcome of the Claisen rearrangement has apparently not been employed previously, and therefore we briefly explored its generality, both experimentally and by computation. Thus, 7-hydroxy-1-tetralone was converted into the propargyl ether **14** and hence the allyl ether **15**. Heating ether **15** in toluene under microwave irradiation resulted in a highly regioselective Claisen rearrangement in favor of the 8-prenyl isomer **17** in excellent yield (92%; ratio **16**/**17** 1:7.5). On the other hand, the

readily prepared TIPS enol ether **18** underwent regioselective Claisen rearrangement in the opposite sense, with the 6-prenyl isomer **19** predominating (100% yield; ratio **19**/**20** 4.6:1) (Scheme 4). Hence in the related chromanone and tetralone series of compounds, a very similar pattern of reactivity is observed, and on switching the π-acceptor properties of a carbonyl substituent to the π-donating enol ether, the regioselectivity of the Claisen rearrangement is inverted.

Since it was not clear whether the observed change in regioselectivity was entirely electronic (π-acceptor vs π-donor) in nature, or whether steric[1] effects are also involved, additional examples were sought. Consequently, the rearrangement of the simplest possible *meta*-acyl aryl dimethyl allyl ether was investigated. 3-Hydroxyacetophenone was converted into the allyl ether **22** by way of the propargyl derivative **21**. Heating in toluene gave a mixture (80%) of Claisen rearrangement products **23** and **24** with, as expected, the 2-prenyl isomer predominating (ratio **23**/**24** 1:2.4). Conversion of ketone **22** into the corresponding TIPS enol ether **25** followed by heating in toluene gave a very similar mixture of regioisomeric Claisen rearrangement products **26** and **27** in the ratio 1:2.2 (Scheme 4). Hence in this case, the conversion of the methyl ketone into its silyl enol ether has little effect on the regioselectivity of the Claisen rearrangement. This suggests that steric factors do play a role, since the conformational constraints provided by the chromanone or tetralone rings ensure that the steric effect of the bulky silyl group in enol ethers **11** and **18** is more pronounced than in the enol ether **25** where it can rotate out of the way.



Scheme 4.

Computational Study

In an attempt to distinguish steric and electronic factors for the observed changes in regioselectivity, we performed a series of DFT transition-state calculations in which we compared the effects of an electron-withdrawing ketone substituent with the corresponding enol and silyl enol ethers (Table 1). This study was performed using B3LYP/6-31G*, as previous studies on the Claisen rearrangement of allyl phenyl ethers have indicated that this method gives consistent results,[20,21] and because computation using a larger

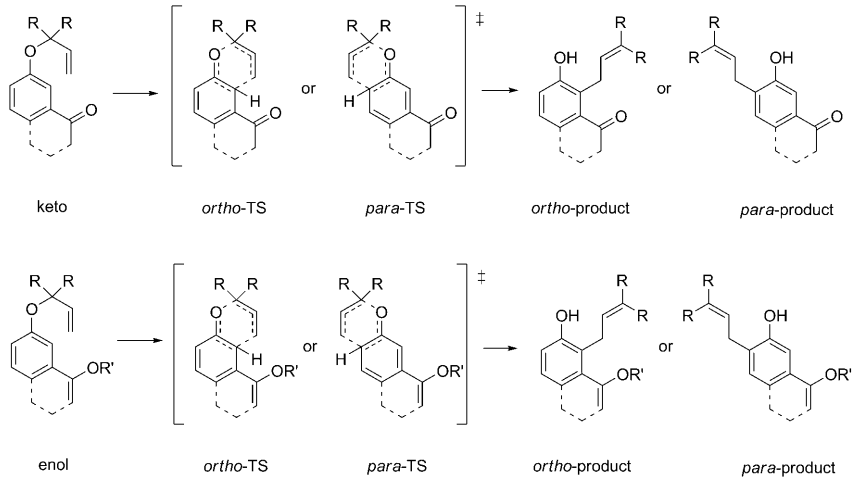
[1] Although the difference in regioselectivity in the Claisen rearrangements of the alcohol **7** and its TBDPS-ether **8** suggests that steric factors may play a role, the substituents are at an sp^3 center and therefore geometrically distinct from the examples in question (**1** vs **11**, **15** vs **18**) that involve substituents on an sp^2 center.

basis set (B3LYP/6-311++G**) on selected examples (Table 1, entries 1–3, 6) gave near identical results. The predicted relative energies of the chair-transition states for the two rearrangement pathways for a series of related 3-allyloxy aryl ketones and their enol derivatives, including substrates **1**, **15**, **18**, **22** and **25** that had been studied experimentally as described above, are shown in Table 1.

The results of these calculations are broadly consistent with the experimental results and clearly support the conclusion that both electronic and steric effects contribute to the overall regioselectivities. Specifically, the calculations suggest that:

i) The keto group has a strong directing effect favoring the *ortho*-substituted product (entry 1 vs entry 3).
ii) The *gem*-dimethyl has little influence on the regiochemistry of the rearrangement (entry 2 vs entry 3, entry 6 vs entry 7, and entry 9 vs entry 10).
iii) Switching from ketone to enol significantly reduces the preference for the *ortho*-substituted product (entry 2 vs entry 6, entry 3 vs entry 7, and entry 4 vs entry 8).
iv) A combination of the electronic effect and the steric bulk of the TIPS-group would appear to be primarily responsible for the switch in selectivity to the *para*-substituted product (entry 7 vs entry 10 vs entry 11).
v) Rotation about the Ar–C bond allows the acyclic enol ether to minimize this latter effect (entry 3 vs entry 5 and entry 11 vs entry 12).

Table 1. Relative transition-state energies leading to *ortho*- and *para*-Claisen rearrangement products.



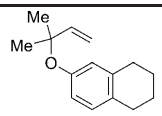
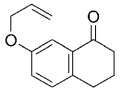
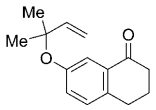
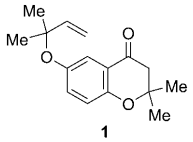
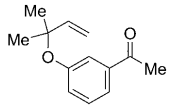
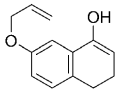
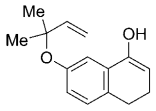
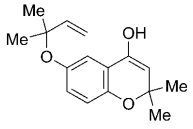
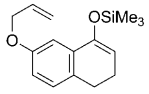
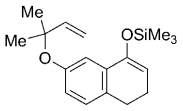
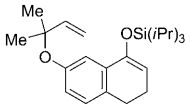
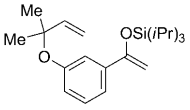
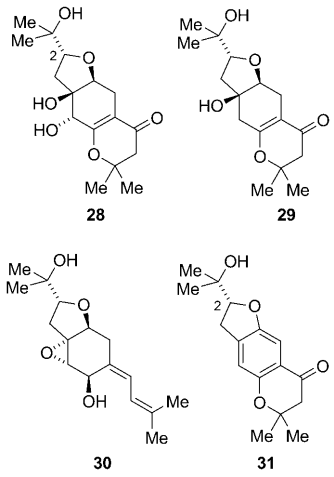
Entry	Substrate	Relative energy [kcal mol^{-1}] *ortho*-TS	*para*-TS
1		0.0	0.8
2		0.0	3.2
3	 **15**	0.0	3.1
4	 **1**	0.0	3.9
5	 **22**	0.0	2.5
6		0.0	0.3
7		0.0	0.4
8		0.0	0.8
9		0.0	0.6
10		0.0	0.4

Table 1. (Continued)

Entry	Substrate	Relative energy [kcal mol^{-1}] *ortho*-TS	*para*-TS
11	 **18**	0.5	0.0
12	 **25**	0.0	2.0

Comparison with experimental data suggests that, for the most part, the calculations predict the observed trends. However, it has previously been suggested that B3LYP/6-31G* may overestimate breaking and forming bond-lengths in the transition state of the aromatic Claisen rearrangement by ca. 0.05 Å.[21] This may result in an over-estimation of the amount of the *ortho*-product, as increased steric compression in a tighter transition state structure would be expected to impact more on the pathway leading to the *ortho*-products.

Synthesis of the furo[2,3-*g*]chromene natural product pestalotheol D: The pestalotheols were isolated in 2008 from *Pestalotiopsis theae* fungal spores growing on an unidentified tree on a mountain in Hainan Province in China,[22] and assigned the unusual highly oxygenated structures **28**–**31** (Scheme 5), three of which contain the furo[2,3-*g*]chromene nucleus. The structure of pestalotheol A **28** was confirmed by X-ray crystallographic analysis, and the absolute configurations of the secondary alcohols in both pestalotheols A and C were determined as (*R*) by the use of the modified Mosher method, thereby allowing assignment of the stereochemistry of the other chiral centers in the compounds by NMR spectroscopy. Although the absolute stereochemistry of pestalotheol D (**31**) was not reported,[22] we assumed that it would also have the (*R*)-configuration at C2, and in continuation of our interest in other naturally occurring chromenes,[14,23] we set out to confirm the structure and stereochemistry of pestalotheol D by synthesis using the regioselective Claisen rearrangement strategy developed in the above studies.



Scheme 5. Structures of pestalotheols A–D; although the stereochemistry of pestalotheol D (**31**) was not reported,[22] we propose it to have the (*R*)-configuration at C2 as shown.

With the 7-prenylchromene derivative **12** now available, silyl deprotection using tetra-*n*-butylammonium fluoride in the presence of water restored the ketone **2**, poised for the introduction of the dihydrofuran ring (Scheme 6). Initially this was carried out to give racemic pestalotheol D by epoxidation (64%) using *m*CPBA, followed by treatment of the epoxide **32** under basic conditions to effect ring closure. The structure of (±)-epoxide **32** was confirmed by X-ray crystallography (Figure 1). Alternatively, direct treatment of the crude product from the epoxidation reaction with base obviates the need for isolation of epoxide **32**, and gives racemic pestalotheol D (±)-**31** in 88% yield over the two steps (Scheme 6). The compound had identical ^{1}H and ^{13}C NMR spectra to those reported in the literature.[22]

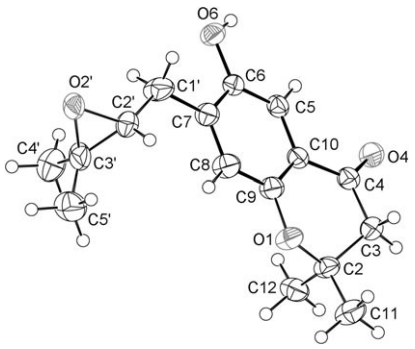
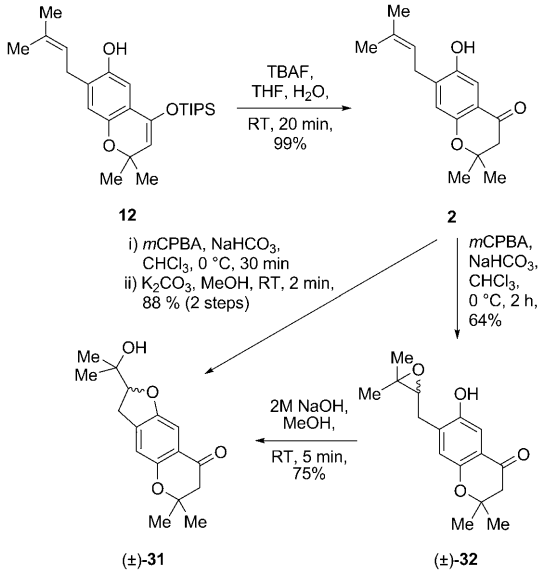


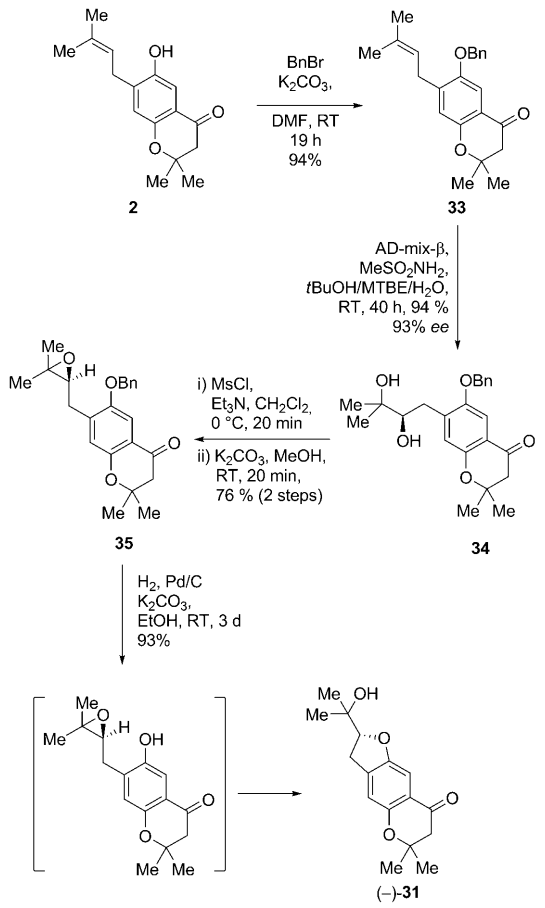
Figure 1. X-ray crystal structure of (±)-7-((3′,3′-dimethyloxiran-2′-yl)-methyl)-6-hydroxy-2,2-dimethylchroman-4-one (**32**).

It remained to perform an asymmetric functionalization of the prenyl double bond, and we elected to use the reliable Sharpless asymmetric dihydroxylation methodology.[24] Initial studies into the dihydroxylation of phenol **2** were unsuccessful, and we had to resort to its protection as the benzyl ether **33**. Thereafter, dihydroxylation in the presence of AD-mix-β proceeded smoothly, though owing to the insolubility of benzyl ether **33**, some *tert*-butyl methyl ether (MTBE) was added as a substitute for some of the *tert*-butanol component of the usual solvent mixture.[25] This deliv-



Scheme 6. Synthesis of racemic pestalotheol D.

ered the (*R*)-diol **34** in excellent yield and 93% *ee* (by HPLC comparison with the racemate), the stereochemistry being assigned on the ample precedent when using AD-mix-β, and confirmed by X-ray crystallography of the final product (Figure 2). With the desired chirality installed, the secondary hydroxyl was converted into the corresponding mesylate (used without purification), and hence the (*S*)-epoxide **35** (Scheme 7). Finally the chiral epoxide **35** was hydrogenolyzed under basic conditions to effect the required 5-*exo-tet* ring closure of the resulting phenolic epoxide in situ to provide (*R*)-pestalotheol D in excellent yield. Comparison with the racemic sample by HPLC on a chiral stationary phase suggested that the material had an enantiomeric excess of 87%, and its optical rotation $[\alpha]_D^{23}$ −7.16 (c = 0.2, MeOH) is close to that reported.[22] Although the natural product was described as a gum, we were able to recrystallize it, and hence confirm the absolute configuration of our synthetic material as (*R*) by X-ray crystallography (Flack parameter = 0.05; Figure 2).



Scheme 7. Synthesis of (*R*)-pestalotheol D.

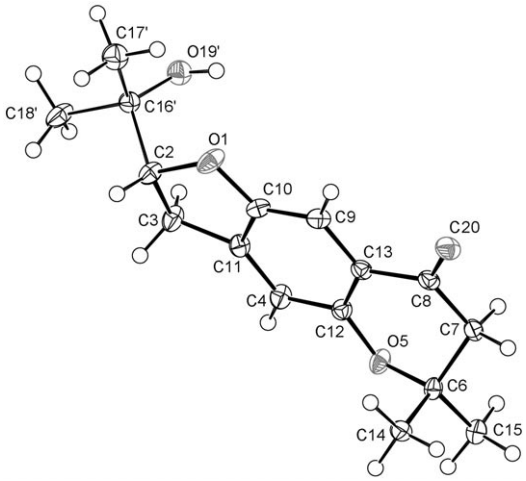


Figure 2. X-ray crystal structure of (*R*)-pestalotheol D (**31**).

The successful synthesis described herein not only confirms the absolute stereochemistry of the natural product, but also features a new strategy for influencing the regiochemical outcome of the Claisen rearrangement of *meta*-allyloxy aryl ketones.

Experimental Section

Full experimental details are given in the Supporting Information.

Acknowledgements

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