Enantioselective total synthesis of (−)-ericanone

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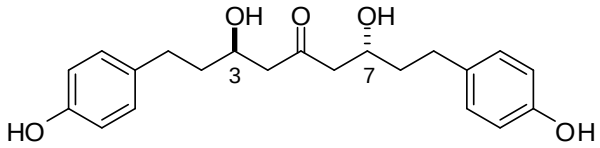
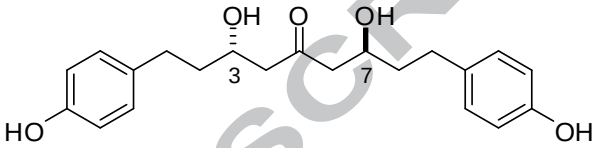


rel-(3*R*,7*R*)-**1**
structure proposed by Chulia's group



(3*S*,7*S*)-**1**
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Enantioselective total synthesis of (−)-ericanone

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ABSTRACT

The first total synthesis of (−)-ericanone was achieved in 10 steps with a 16% overall yield from *p*-hydroxybenzaldehyde. Notable features of this stereocontrolled approach include a Keck allylation to install the stereocenter at C3 and a 1,5-*anti* aldol reaction to install the hydroxyl group at C7.

In 2011, the Chulia group reported the structure of (−)-ericanone (**1**), a diarylnonanoid aglycone isolated in small amounts from the aerial parts of *Erica cinerea* (48 mg from 4.5 kg of *E. cinerea*) (Figure 1).[1] The structure of (−)-ericanone was determined to be rel-(3*R*,7*R*)-1,9-bis-(*p*-hydroxyphenyl)-3,7-dihydroxynonan-5-one using NMR analyses. The 1,5-*anti* relationship between C3 and C7 was determined on the basis of its levorotatory nature ($[\alpha]_D^{27}$ –14 (*c* 0.042, MeOH)).[1,2]

Figure 1: Proposed and assigned structures of (−)-ericanone.

We describe herein our efforts toward the total synthesis of ericanone (**1**) for the purposes of confirming Chulia's structural assignment, determining the absolute stereochemistry, obtaining material for further biological evaluation and gaining access to novel analogues.

The synthesis began with protection of *p*-hydroxybenzaldehyde (**2**) using TBSCl and imidazole[3] followed by a Wittig reaction with known phosphorane **3** providing α,β−unsaturated ester **4** in 83% yield for the two step sequence (Scheme 1).[4] Hydrogenation of **4** (94% yield) followed by reduction of the ester functional group using DIBAL-H led to the formation of aldehyde **5** (82% yield).[5]

Scheme 1: Preparation of aldehyde **5**.

With aldehyde **5** in hand, we turned our attention to the preparation of methylketone **9** (Scheme 2). First, asymmetric Keck allylation of aldehyde **5** provided the homoallylic alcohol **7** in an 81% yield with an excellent enantiomeric excess (*ee* 96%).[6,7] Then, the treatment of **7** with the 2,2,2-trichloroacetimidate of *p*-methoxybenzyl (PMB-TCA) in the presence of a catalytic amount of CSA gave olefin **8** in 60% yield. Finally, Wacker oxidation of the terminal olefin of **8** led to the formation of methylketone **9** in 87% yield.[8]

Scheme 2: Preparation of methylketone **9**.

Next, we performed the key aldol reaction between the boron enolate generated from methylketone **9** with aldehyde **5** to provide aldol adduct **10**. This reaction favored the 1,5-*anti* isomer (*dr* 94:06) (Scheme 3).[9,10,11,12]

Scheme 3: Completion of the synthesis of (−)-ericanone (**1**).

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Removal of the PMB ether using H_2 and $Pd(OH)_2/C$[13] followed by treatment with HF/MeCN[14] gave (–)-ericanone (**1**) in 60% yield for the three step sequence. Spectral data (^1H and ^{13}C NMR, IR, and HRMS) from the synthetic sample were in excellent agreement with those reported in the literature for the natural product.[1] Furthermore, the specific rotation of the synthetic material matched both the sign and magnitude reported for natural ericanone (*lit*: $[\alpha]_D^{27}$ −14 (*c* 0.042, MeOH)[1], *observed*: $[\alpha]_D^{20}$ −17 (*c* 0.04, MeOH)). These results indicate that compound **1** has been prepared as the naturally occurring antipode. Based on the known absolute stereochemistry of homoallylic alcohol **7**,[6] ultimately generated by Keck allylation, the absolute stereochemistry of (–)-ericanone (**1**) can now be assigned as 3*S*,7*S*.

In conclusion, we have accomplished the first total synthesis of (–)-ericanone (**1**) in 10 steps with a 16% overall yield starting from *p*-hydroxybenzaldehyde. The key step in this approach is the 1,5-*anti* aldol coupling between the boron enolate generated from methylketone **9** with aldehyde **5**. Based on these results we were able to determine the absolute stereochemistry of (–)-ericanone (**1**) to be 3*S*,7*S*.

Acknowledgements

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Supplementary data

Experimental procedures and spectral data for the prepared compounds associated with this article can be found, in the online version, at

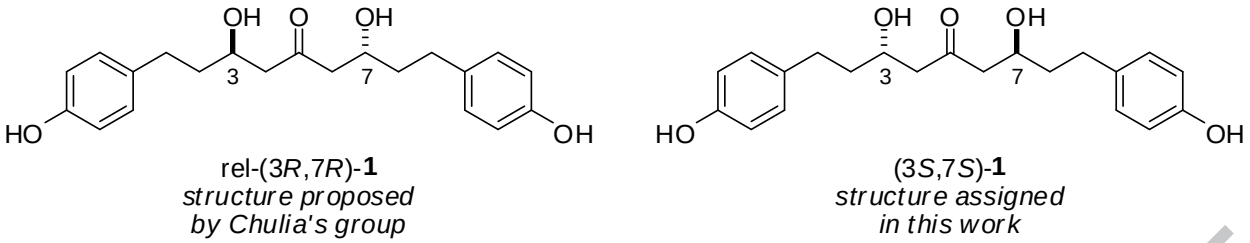
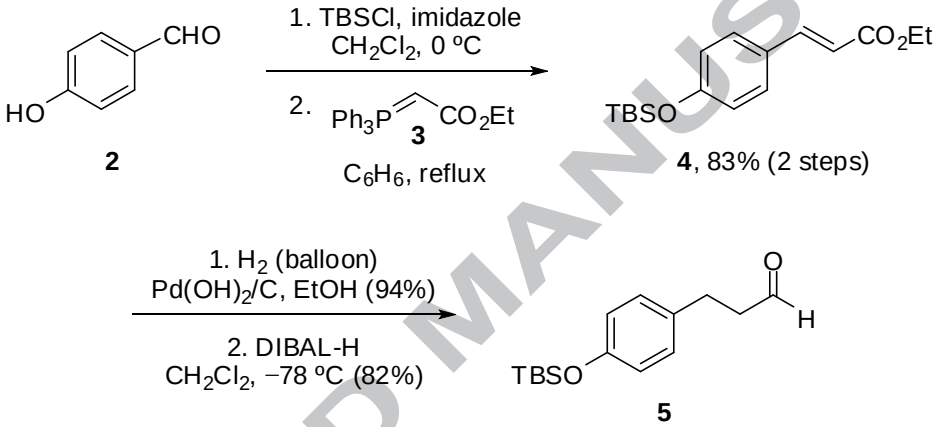
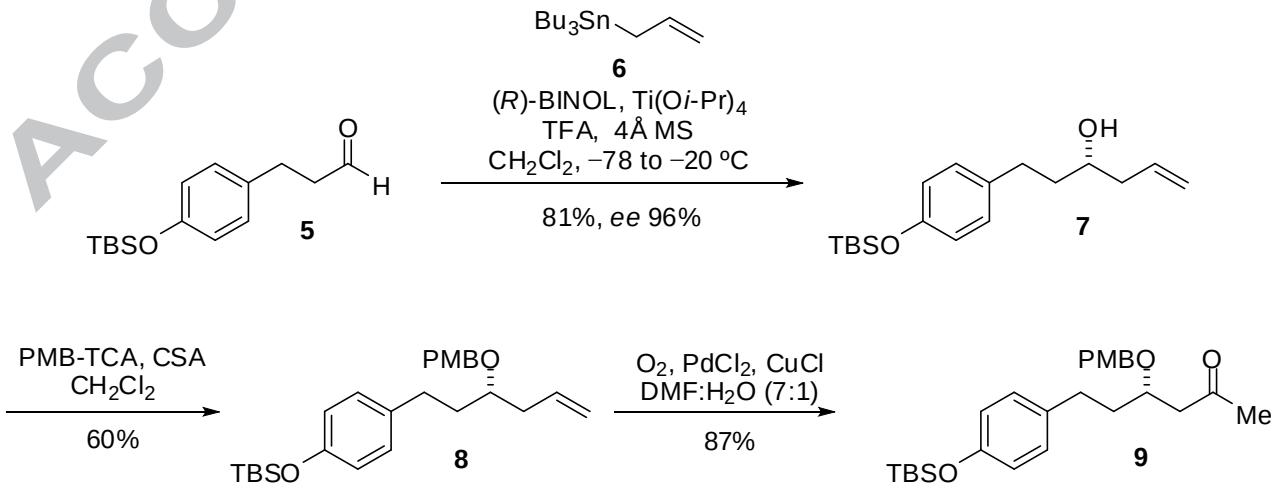


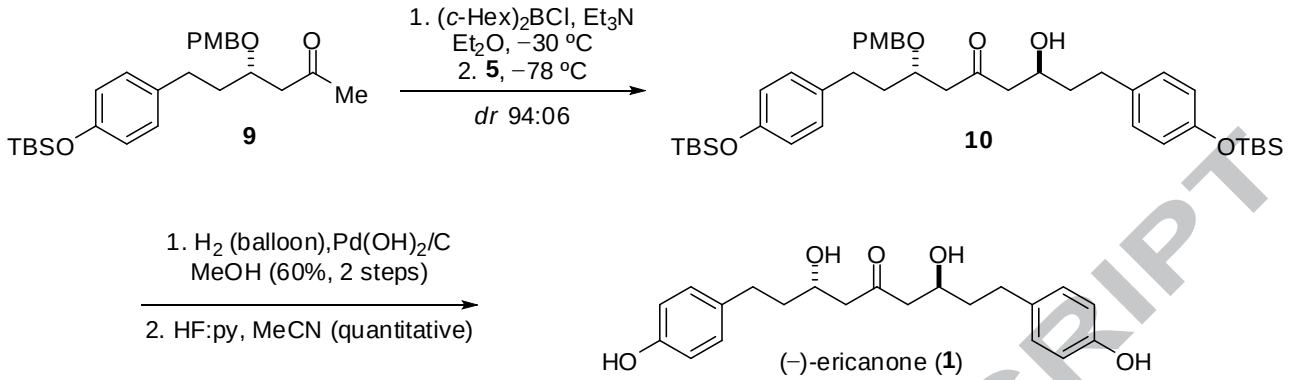
Figure 1: Proposed and assigned structures of (–)-ericanone.



Scheme 1: Preparation of aldehyde **5**.



Scheme 2: Preparation of methylketone **9**.



Scheme 3: Completion of the synthesis of (−)-ericanone (**1**).

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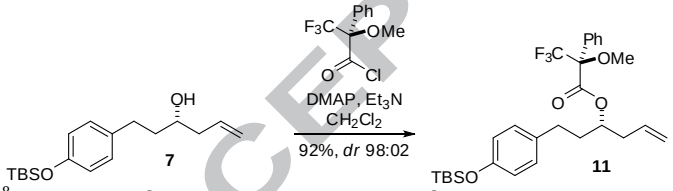

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