Journal Pre-Proof

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PII: S0040-4039(19)30724-5
DOI: https://doi.org/10.1016/j.tetlet.2019.150973
Reference: TETL 150973

To appear in: *Tetrahedron Letters*

Received Date: 25 June 2019
Revised Date: 21 July 2019
Accepted Date: 23 July 2019

Please cite this article as: Wei, H., Zhang, H., Han, S., Mu, S., Huang, K., Chen, G., Xie, W., Concise Syntheses of (+)-austrodoral and (+)-austrodoric acid Based on H_2O_2 Mediated Oxidative Ring Contraction, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.150973

Graphical Abstract

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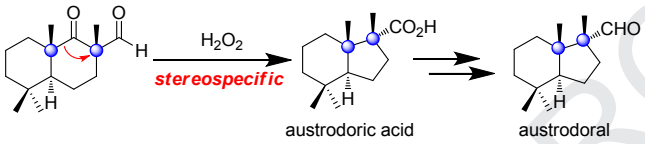

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Concise Syntheses of (+)-austrodoral and (+)-austrodoric acid Based on H_2O_2 Mediated Oxidative Ring Contraction

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ARTICLE INFO

ABSTRACT

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Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
sesquiterpene
sustrodorane
asymmetric synthesis
oxidative ring contraction

Asymmetric synthesis of the marine nor-sesquiterpenoid (+)-austrodoric acid and (+)-austrodoral in seven and nine steps respectively from Wieland-Miescher ketone was described herein. The synthesis featured an oxidative ring contraction of α-formyl cyclic ketone mediated by H_2O_2 to forge the hydrindane scaffold together with the contiguous quaternary carbon centers simultaneously.

The sesquiterpenoids are an important class of natural products with diverse structural types, which exhibit a wide variety of biological properties,[1] including significant cytotoxic,[2] anticancer,[3] insect antifeedant[4] and potent anti-HIV activity.[5] Austrodoral (**1**) and austrodoric acid (**2**) are two *nor*-sesquiterpenoid recently isolated from the skin of the marine dorid *Austrodoris kerguelenensis* collected in Antarctica by Gavagnin and co-workers (Figure 1).[6] These two compounds possess a rearranged perhydroindane moiety named 'austrodorane' and contiguous quaternary all-carbon centers, which may be biogenetically derived from drimane-type framework via ring contraction. Additionally, austrodoral (**1**) was proposed to be a stress-metabolite generated by mollusk and austrodoric acid (**2**) was a work-up product presumably by air oxidation. However, the exact biological role of austrodoral (**1**) has not been fully elucidated.

Austrodorane has received considerable attention from chemical community owing to the intriguing structural features and its potential role for chemical defending against predator. Notable is the chiral contiguous quaternary all-carbon centers, which constitutes a formidable challenge in natural products synthesis because of the severe steric repulsion between the substituents. In 2004, Gavagnin reported the first enantioselective

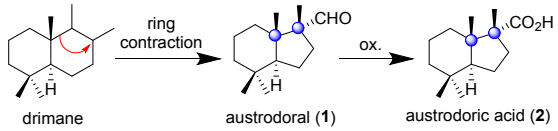
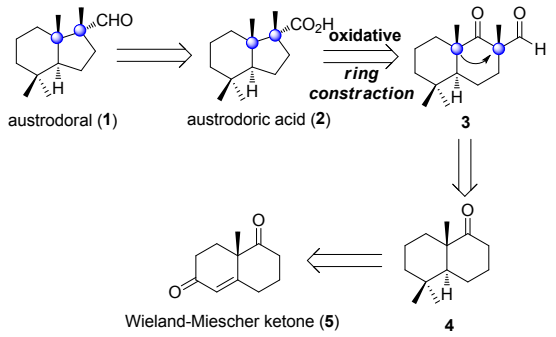


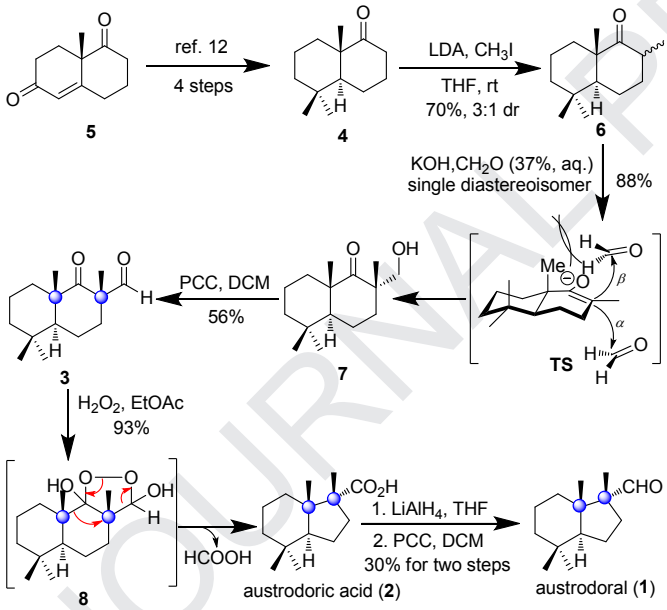
Figure 1. Structure of austrodorane and possible biosynthetic pathway

synthesis of austrodoric acid (**2**) from (+)-sclareolide, establishing the absolute configuration of austrodorane.[7a] The pivotal ring contraction of the epoxide intermediate for the stereospecific construction of the quaternary carbon centers was realized by treatment with tris(4-bromophenyl)aminium hexachloroantimonate in 45% yield, which was greatly improved by using FSO_3H as promoter on a truncated epoxide in the following paper.[7b] However, the synthesis was plagued by poor diastereoselectivity (3:1) for the construction of key epoxide intermediate. Soon after that, Alvarez-Manzaneda and coworkers described a concise synthesis of austrodorane from (-)-sclareol via a Pinacol rearrangement of a triol intermediate in the presence of $BF_3{\cdot}Et_2O$.[8] Following this work, Akita described a TFA promoted semi-Pinacol rearrangement of an unprotected epoxide intermediate for the asymmetric synthesis of austrodorane.[9] Another $BF_3{\cdot}Et_2O$-catalyzed highly regioselective Pinacol-type rearrangement of 1,2-diol for the synthesis of (+)-austrodoral (**1**) and (+)-austrodoric acid (**2**) using (+)-sclareolide as starting material was reported by Wu in 2017.[10] Recently, Fañañas and Rodríguez reported a $BF_3{\cdot}Et_2O$-catalyzed epoxide rearrangement to deliver racemic austrodoral with complete diastereoselectivity, which highlighted a cationic cyclization of dienyne to forge the decalin scaffold.[11] It should be pointed out that all above-mentioned strategies exploited a Pinacol-type rearrangement as key step to construct the contiguous quaternary carbon centers of the austrodorane, while no other strategy of has ever been attempted.



Scheme 1. Retrosynthetic analysis of austrodorane

In 2017, our group reported an oxidative ring contraction reaction of cyclic α-formyl ketones promoted by H_2O_2.[12] This novel protocol was highly regioselective and enables stereospecific construction of contiguous quaternary all-carbon centers. To further showcase the synthetic potential of this novel protocol, the asymmetric synthesis of austrodorane was thus executed. As shown in Scheme 1, we surmised that austrodoral (**1**) could be prepared from austrodoric acid (**2**) via a reduction/oxidation of the carboxylic acid moiety. Austrodoric acid (**2**) would in turn arise from α-formyl ketone **3** via oxidative ring contraction facilitated by the action of H_2O_2 to stereospecifically forge the quaternary carbon centers. Bicyclic ketone **3** could be diastereoselectively accessed via methylation followed by hydroxymethylation/oxidation of ketone **4**, which was a known compound derived from Wieland-Miescher ketone **3**.[12]



Scheme 2. Total synthesis of austrodoric acid and austrodoral

As illustrated in Scheme 2, our synthesis commenced with the preparation of bicyclic ketone **4** from Wieland-Miescher ketone **5** in four steps according to the literature procedure.[13] α-Methylation of ketone **4** mediated with LDA/MeI gave ketone **6** in 70% yield with 3:1 dr,[14] which was inconsequential for the next step. Fortunately, introduction of hydroxymethyl group was successfully realized as a single diastereoisomer by treating ketone **6** with formalin in basic medium (KOH/MeOH) at 60 °C.[15] This may be rationalized by sever steric hindrance from the axial methyl for the β attack in the transition state **TS**, which favored the approach of electrophile from the α-face to give the *cis* product **7**.[16] Oxidation of ketone **7** with PCC led to the corresponding *α*-formyl cyclic ketone **3**, which set to the stage for the critical oxidative ring contraction. To our delight, treatment of **7** with aqueous H_2O_2 smoothly afforded (+)-austrodoric acid (**2**) in 93% yield without detection of the C-C bond cleavage product. Based on our previous hypothesis, nucleophilic addition of H_2O_2 to α-formyl ketone followed by cyclization delivered 1,2-dioxolone **8**, which underwent a concert alkyl migration/C-C bond and O-O bond cleavage to give the desired product. Reduction of (+)-austrodoric acid (**1**) with $LiAlH_4$ and subsequent PCC-oxidation gave (+)-austrodoral in 30% yield for two steps. The optical rotations and the spectral data of synthetic austrodoric acid (**2**) and austrodoral (**1**) were in excellent agreement with those reported for natural product.

In conclusion, we described a concise synthesis of the marine nor-sesquiterpene (+)-austrodoral (**1**) and (+)-austrodoric acid (**2**) from Wieland-Miescher ketone. The key step featured an oxidative ring contraction of cyclic α-formyl ketones facilitated by aqueous H_2O_2 under mild conditions for the stereospecific construction of the quaternary carbon centers in high efficiency.

Acknowledgments

We gratefully acknowledge the financial support from the Natural Science Foundation of China (201702166 to H.W. and 21722206 to W.X.) and the Scientific Startup Foundation for Doctors of Northwest A&F University (No. Z109021702).

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Supplementary Material

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/ .

Highlights

- Concise syntheses of (+)-Austrodoric acid and (+)-Austrodoral was achieved
- Wieland-Miescher ketone was used as starting material
- H_2O_2-mediated oxidative ring contraction forged the hydrindane scaffold
- The contiguous quaternary carbon centers were built up via rearrangement