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Asymmetric synthesis of andavadoic acid via base-catalyzed 5-*exo*-tet cyclization of a β-hydroperoxy epoxide

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ABSTRACT

The first total synthesis of andavadoic acid, a naturally occurring five-membered ring peroxide, and its absolute configuration assignment are reported. Central to this venture was the development of an effective synthesis of a key β-hydroperoxy epoxy ester from (*R*)-epichlorohydrin via chemoselective methylenation with Nysted reagent in the presence of $Ti(Oi\text{-}Pr)_2Cl_2$ and chemo- and regioselective Mukaiyama–Isayama peroxidation. This approach also featured the construction of the 1,2-dioxolane ring system by an efficient base-promoted 5-*exo* epoxide opening by a hydroperoxy group.

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1. Introduction

Marine sponges of the family Plakinidae have been reported to be a rich source of cyclic peroxides, many of which exhibit antimicrobial, antitumor, antifungal and antiparasitic activities.[1] The majority of these natural products contain six-membered peroxide rings (1,2-dioxane). Plakortolides, one of the family of secondary metabolites found in these sponges, have for most of them, an aromatic ring connected via a methylene chain to a 4,6-dimethyl peroxylactone ring.[2] They differ in absolute configuration at C_3, C_4, C_6, the substituted pattern, the level of unsaturation and the chain length. A representative sample of plakortolides is depicted in Fig. 1.

Often isolated along with plakortolides are 1,2-dioxolane carboxylates, which belong to the large family of plakinic acids.[2b,d,g–i] Thus from the extract of the sponge *Plakortis aff simplex* were isolated plakortolide I **2** and the five-membered ring peroxide: andavadoic acid 7 (Fig. 2), which showed significant activity against 13 tumor cell lines with GI_{50} values in the sub-micromolar range.[2h] In this article, only the relative stereochemistry of andavadoic acid **7** was assigned.[2h] No total synthesis of **7** has been reported. So far, only one total synthesis of a natural product bearing a 3,5-dimethyl-1,2-dioxolane-3-acetic acid system (plakinic acid A) has been published.[3,4]

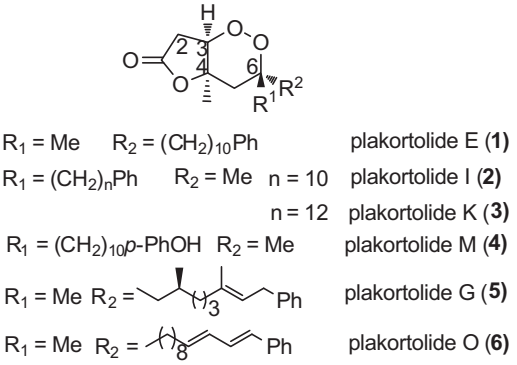

Fig. 1. Representative examples of plakortolides.

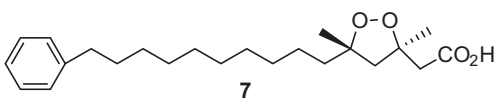

Fig. 2. Structure of andavadoic acid.

In 2002, Jung and co-workers described the first racemic total synthesis of a plakortolide: plakortolide I **2** using as key steps a [4+2] photocycloaddition of a singlet oxygen to a diene and

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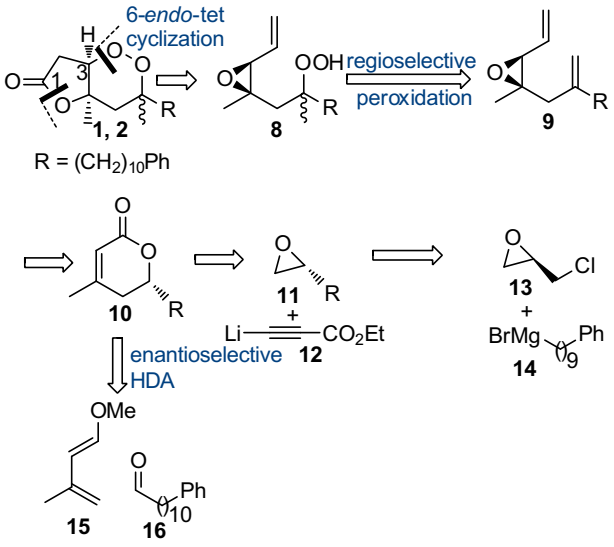
iodolactonization.[5] Later on, we reported the synthesis of (−)-*ent*-plakortolide I **2** and E **1** involving the elaboration of the 1,2-dioxane ring by intramolecular Michael addition of a hydroperoxide to a butenolide.[6]

As a part of an ongoing project devoted to the directing effect of a double bond in the regiocontrol of intramolecular opening of vinyl epoxides with nucleophiles, such as alcohols and hydroperoxides via disfavored 5- or 6-*endo* modes,[7–9] we have recently reported a study concerning the application of this concept to forge the 1,2-dioxane ring system of plakortolides I **1** and E **2** from β-hydroperoxy vinyl *cis*-trisubstituted epoxides.[8] We report here the results of this investigation and the application of some of these results to the first synthesis of andavadoic acid **7** and of its configurational assignment.

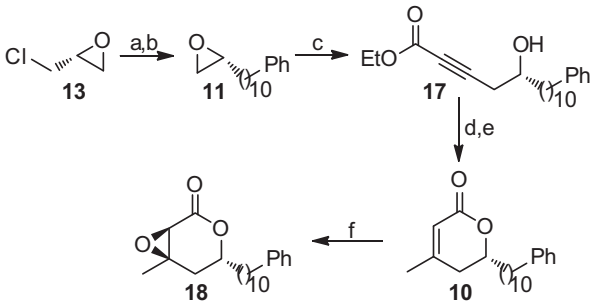
Our retrosynthetic analysis, summarized in Scheme 1, guided by our approach of 1,2-dioxane ring forming based on anti-Baldwin 6-*endo* cyclization of β-hydroperoxy vinyl epoxides, started by a disconnection of C_3—O and C_1—O bonds within **1** and **2** revealing the vinyl epoxide **8**. To introduce the hydroperoxide function, we chose the hydroperoxysilylation developed by Mukaiyama and Isayama because of its mildness and remarkable regio- and chemoselectivity.[10,11] With this method in mind, we envisioned that hydroperoxide **8** could arise from epoxy diene **9**, itself being able to originate from the unsaturated lactone **10** via diastereoselective epoxidation and standard functional manipulation. Construction of the pentenolide **10** would call upon successive addition of lithium salt of ethyl propiolate to epoxide **11**, methyl cupration of the triple bond and lactonization. Alternatively, the pentenolide **10** could be obtained via the enantioselective Jacobsen hetero Diels—Alder reaction between **15** and **16**. Finally, epoxide **11** could be accessed via epoxide-opening of (*R*)-epichlorohydrin **13** with the Grignard reagent **14** followed by base-catalyzed epoxide formation.



Scheme 1. Retrosynthetic analysis for **1** and **2**.

2. Results and discussion

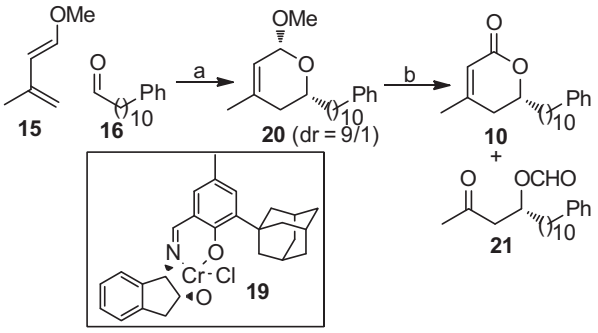
The synthesis of the key intermediate **18** started by a copper-ring opening of (*R*)-epichlorohydrin **13** with known (9-phenylnonyl) magnesium bromide **14**[12] followed by treatment of the resulting chlorohydrin with NaOH to give the (*R*)-epoxide **11** in 79% yield (Scheme 2). Regioselective ring-opening of **11** with the lithium salt of ethyl propiolate **12**, in the presence of $BF_3{\cdot}Et_2O$,[13] afforded the secondary alcohol **17** in nearly quantitative yield. Stereoselective addition of lithium dimethylcuprate[14] and subsequent lactonization



Scheme 2. Reagents and conditions: (a) $Ph(CH_2)_9MgBr$ (**14**) (1.3 equiv), CuCN (0.1 equiv), THF, −78 °C, 2 h; (b) NaOH (5 equiv), THF, rt, 4 h, 79% for two steps; (c) ethyl propiolate (3 equiv), THF, −90 °C, *n*-BuLi (3 equiv), 20 min, $BF_3{\cdot}Et_2O$ (3 equiv) then **11**, −78 °C→rt, 98%; (d) Me_2CuLi (3 equiv) then **17**, THF, −78 °C, 0.5 h; (e) *p*TsOH (0.1 equiv), MeOH, rt, 4 h, 84% for two steps; (f) H_2O_2 (30%, 3.5 equiv), NaOH (6 N, 0.6 equiv), MeOH, 0 °C→rt, 3 h, 82%.

of the resulting *Z*-enoate with *p*-toluenesulfonic acid in methanol at room temperature gave the lactone **10** in 84% overall yield. Epoxidation of **10** with alkaline hydrogen peroxide furnished the epoxy lactone **18** as a single diastereomer in 82% yield. This *trans*-selective epoxidation of pentenolides is well-precedented.[15]

We also studied a more straightforward access to unsaturated lactone **10** using as a key step asymmetric catalytic hetero Diels—Alder (HDA) reaction developed by Jacobsen (Scheme 3).[16]



Scheme 3. Reagents and conditions: (a) MS 4 Å, **19** (5 mol %), rt, 24 h, 62% based on recovered aldehyde **16**; (b) PDC, AcOH, CH_2Cl_2, rt, 3 h, 66% (ratio **10**/**21**=88/12).

Exposure of a neat mixture of diene **15**[17] and freshly prepared aldehyde **16**[18] to catalyst (1*S*,2*R*)-**19**[16c] gave HDA adduct **20** in 62% yield and good diastereoselectivity (dr=9/1). Oxidative cleavage of the acetal of **20** with PDC in the presence of acetic acid furnished the desired lactone **10** in moderate yield accompanied by the formate **21**. Optical purity of **10** was determined by comparison of its specific rotation with that obtained from enantiopure epichlorohydrin **13** and found to be 86% ee. This route for the construction of the unsaturated lactone **10** was dismissed because of its moderate enantiomeric excess and its overall yield in comparison with that obtained from epichlorohydrin (36% vs 52%).

We next turned our attention to the methylenation of the C_2 and C_6 positions of epoxy lactone **18** (Scheme 4). To attain this goal we developed an efficient one-pot two-step reaction involving the saponification of lactone function of **18** followed by RuO_4 oxidation[19] of the resulting hydroxy sodium carboxylate. Treatment of the crude keto acid with diazomethane afforded the keto ester **22** in nearly quantitative yield. The regio- and chemoselective methylenation of the carbonyl function of **22** was troublesome. In the presence of Wittig, Lombardo (Zn, CH_2Br_2, $TiCl_4$),[20] Tebbe (Cp_2TiCl-CH_2AlMe_2),[21] Petasis (Cp_2TiMe_2)[22] reagents, keto ester **22** gave either decomposition products or a mixture of mono- and dimethylenation compounds. The use of Nysted reagent and $TiCl_4$[23] improved the chemoselectivity of the methylenation reaction nevertheless compound **23** was obtained in a modest yield (35%).

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