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First total synthesis of natural andytriol and a biomimetic approach to varioxiranes

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ABSTRACT

The first diastereoselective synthesis of natural fungal metabolite (+)-andytriol **1**, the proposed biosynthetic precursor of varioxirane, was accomplished in nine linear steps from 2,3-*O*-isopropylidene-D-ribose. A biomimetic Katsuki–Sharpless epoxidation was then applied to construct the oxirane ring of the varioxiranes. The absolute configuration of the target molecule (+)-**1** was for the first time confirmed by the single X-ray analysis.

1. Introduction

(+)-Andytriol **1** (Fig. 1) was first isolated from a static culture of a pure strain of the fungus, *Aspergillus variecolor* (imperfect state of *Emericella variecolor*) as an unknown substance (X) along with other metabolites-6-methoxymellein, siderin, andibenin, and andilesin A–C.[1] Its structure was later identified by A. Dunn and R. Johnstone as 2-methoxy-6-(3,4-dihydroxyhepta-1,5-dienyl)benzyl alcohol.[2] However, the absolute configuration of natural compound **1** remained unresolved.

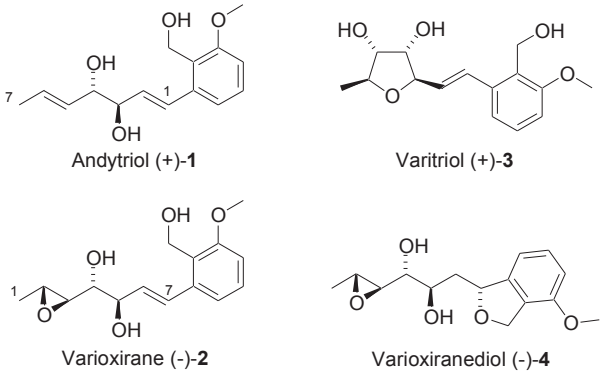

Fig. 1. Natural compounds **1**–**4**.

In 2002, Malmstrøm et al. reported the isolation of natural compounds, varioxirane (−)-**2** and varitriol (+)-**3** from a marine derived strain of a fungus *E. variecolor*.[3] Interestingly, initial results of the biological screening of varitriol (+)-**3** against the (NCI) 60-cell line in vitro panel showed remarkable cytotoxic activity toward renal, breast and CNS cancer cell lines. Authors also proposed a hypothetical biogenetic relationship between these products via enzymatic intramolecular S_N2 epoxide ring opening and pointed out that natural andytriol **1** could be involved in this biosynthetic pathway to **3** via epoxide **2**. Accordingly, it could be surmised that the absolute stereochemistry of natural benzyl alcohol **1** might be 3*R* and 4*S* considering the configuration of natural varitriol (+)-**3** and varioxirane (−)-**2**. Recently, another related secondary metabolite, varioxiranediol (−)-**4** was isolated from the same endophytic fungus. The structure and absolute configuration of this epoxide **4** was confirmed by the X-ray analysis supporting the structural relationship of the isolated natural compounds.[4] To this date, only little attention has been devoted to the chemistry of **1** and **2**. In 2013, G. Sudhakar and J. Raghavaiah reported the first synthesis of (−)-**2** (9 steps, 4% overall yield) starting from crotonaldehyde applying a Sharpless kinetic resolution. The authors supported the proposed biosynthetic pathway by converting the epoxide **2** to varitriol **3**.[5] Moreover, using the same strategy, they

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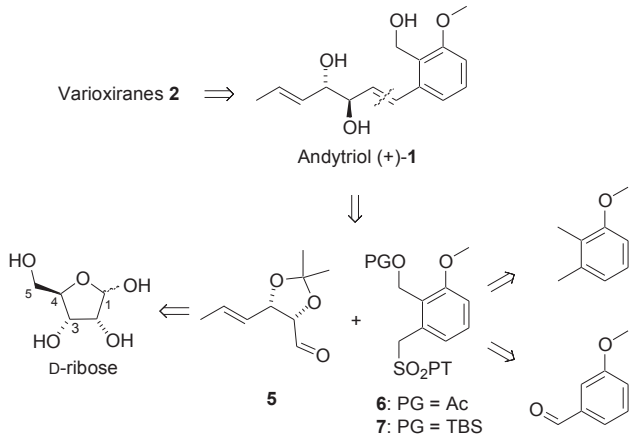
were able to accomplish the synthesis of the antipode of natural andytriol (+)-**1** in nine steps (3% overall yield, $[\alpha]_D^{30}$ −36 (*c* 0.05, $CHCl_3$), lit.[2] $[\alpha]_D^{24}$ +43 (*c* 0.22, $CHCl_3$)) and indirectly confirm the absolute configuration of natural (+)-**1**.

In the course of our long-term program directed towards the synthesis of bioactive natural compounds,[6] we have developed the synthesis of varitriol[7] and examined its antitumor activity. Although, the biological activity of the synthetic varitriol (+)-**3** has not been proven,[8] we turned our attention towards other potentially bioactive and structurally related compounds (+)-**1** and (−)-**2**. Herein, we report the first total synthesis of natural andytriol **1** and a biomimetic approach to varioxiranes.

2. Results and discussion

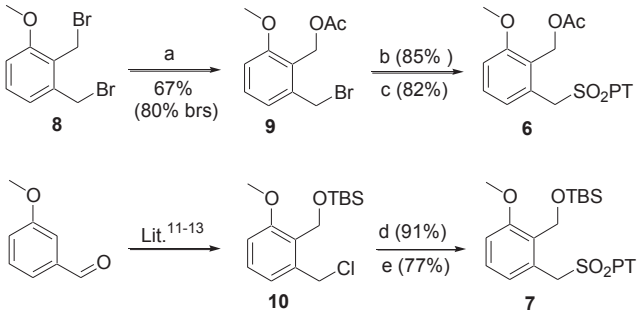
The retrosynthetic analysis of natural (3*R*,4*S*)-diene **1** pointed to the coupling of hexenose **5** and suitable sulfone (**6** or **7**) via Kocieński-Julia olefination[9] (Scheme 1). The protected sulfone could be readily obtained from 2,3-dimethylanisole or 3-anisaldehyde. The aldehydic partner for the olefination, carbohydrate subunit **5** having the same configuration at C-2 as natural enantiomer **1**, could be accessible from D-ribose by diastereoselective introduction of the prop-1-enyl group at C-1 followed by the carbon chain shortening at the other end (C-3). Finally, the key operation in the synthesis of varioxiranes would be a biomimetic chemo- and diastereoselective epoxidation of the corresponding C5–C6 double bond of **1**.



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

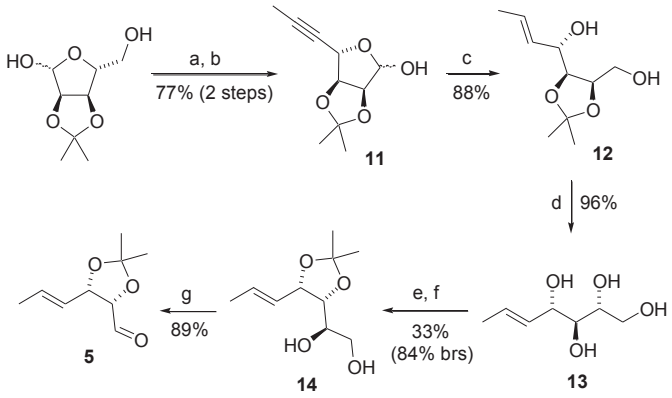
The synthesis of the aromatic sulfones **6** and **7**, having an *O*-acetyl or *O*-TBS protecting group, respectively, is shown in Scheme 2. Starting dibromo-compound **8** was prepared from 2,3-dimethylanisole applying a known radical bromination method.[10] Subsequently, selective replacement of the bromide in **8** with sodium acetate gave compound **9** in 80% yield. Next, the second bromide of **9** was substituted with potassium phenyltetrazolylthiolate followed by oxidation using hydrogen peroxide-ammonium molybdate provided the corresponding methylene partner for the olefination, *O*-acetyl protected sulfone **6** in 70% yield over two steps.

The aromatic sulfone **7** bearing the *O*-TBS protecting group was synthesized using a similar strategy. The chloro-compound **10** is available in four steps from *m*-anisaldehyde using known literature methods.[11–13] Substitution of the chloride group in **10** and oxidation of the corresponding sulfide gave *O*-TBS protected sulfone **7** in 70% yield over two steps.



Scheme 2. Synthesis of sulfones **6** and **7**. Reagents and conditions: (a) AcONa, AcOH, 110 °C, 2 h; (b) KSPT, DMF, rt, 15 h; (c) Mo(VI)/H_2O_2, MeOH, 0 °C to rt, 10 h; (d) KSPT, DMF, rt, 15 h; (e) Mo(VI)/H_2O_2, MeOH, 0 °C to rt, 15 h.

The aldehydic fragment for the olefination, hexenose derivative **5** was prepared from D-ribose or its commercially available acetonide derivative in seven steps (48% overall yield) (Scheme 3). Grignard addition of propyn-1-ylmagnesium bromide at C-1 of 2,3-*O*-isopropylidene-D-ribose provided the corresponding alkyne with excellent anti-diastereoselectivity.[14] Oxidative cleavage of the vicinal diol using $NaIO_4$ delivered single diastereomer **11** in 77% yield as anomeric lactols. The configuration at C-4 of compound **11** was confirmed on the basis of ^1H NMR spectroscopy. LAH reduction[15] of both, the triple bond and carbonyl group in **11**, afforded partially protected tetrol **12**. Finally, tetraol **14** bearing a 3,4-*O*-isopropylidene protection group was prepared using a selective protection–deprotection sequence.[16] Thus, the protection of all hydroxyl groups with 2,2-dimethoxypropane in the presence of Dowex H^+ followed by hydrolysis of the terminal acetonide gave vicinal diol **14**, which was isolated in 33% yield together with **13** (51%); the latter can be recycled. All attempts to increase the yield of this sequence failed.



Scheme 3. Synthesis of the aldehyde **5**. Reagents and conditions: (a) propyn-1-ylmagnesium bromide, THF, rt, 1 h; (b) $NaIO_4$, *t*BuOH/H_2O, rt, 1.5 h; (c) LAH, THF, reflux, 2 h; (d) 60% AcOH, 60 °C, 2 h; (e) DMP, CH_2Cl_2, DOWEX marathon (H^+), rt, 2 h; (f) 80% AcOH, 40 °C, 2 h; (g) $NaIO_4$, *t*BuOH/H_2O, rt, 1.5 h.

Having the diol **14** in hand, the synthesis continued with a mild $NaIO_4$ oxidation to produce crude hexenose **5** in 89% yield. The aldehyde **5** was then subjected to Kocieński-Julia olefination with sulfones **6** and/or **7** without further purification. The final steps in the synthesis of natural (3*R*,4*S*)-2-methoxy-6-(3,4-dihydroxyhepta-1,5-dienyl) benzyl alcohol **1** are shown in Scheme 4. Thus, the Kocieński-Julia coupling was performed with KHMDS in dimethoxyethane applying the so-called Barbier protocol.[9c] The reaction using *O*-acetylated sulfone **6** provided olefin **15** as a single *E*-isomer in 75% yield. Subsequent removal of all