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SELECTIVE INTRODUCTION OF FOUR CONTIGUOUS STEREOCENTERS ON THE B-RING OF 4-HYDROXYZINOWOL

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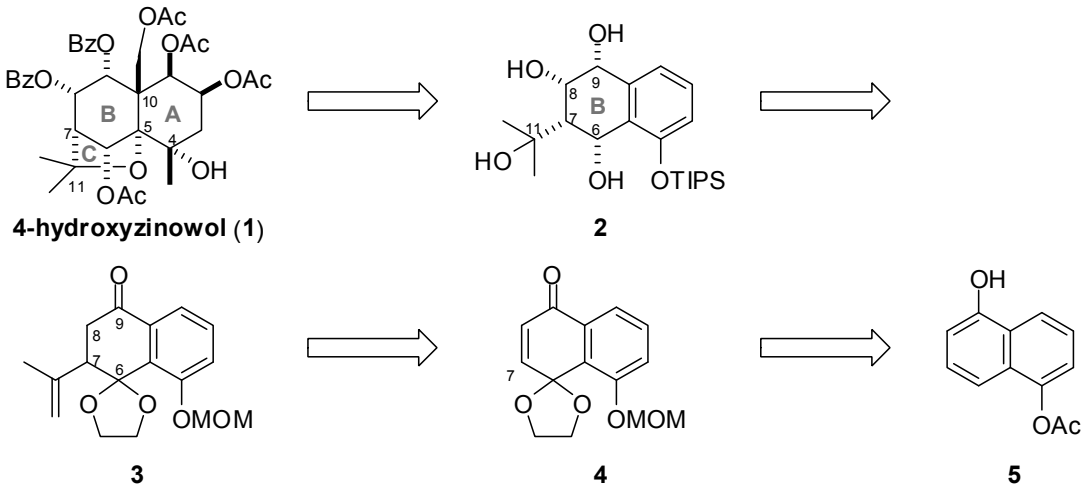
Abstract – 4-Hydoxyzinowol is a bioactive polyoxygenated dihydro-β-agarofuran sesquiterpenoid. Here we describe construction of four contiguous *cis*-oriented stereocenters on the B-ring of 4-hydroxyzinowol. Introduction of a C7-isopropenyl group by the 1,4-addition of isopropenyl magnesium bromide was effectively assisted by methyl aluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide). Taking advantage of the presence of the C7-substituent, three hydroxy groups were installed in a stereoselective fashion at the C6, 8 and 9 positions. In this study, we employed a new reagent combination of $Sc(OTf)_3$ and $Zn(OTf)_2$ for the hydrolysis of the cyclic acetal on the rigid oxabicyclo[3.2.1]octane structure.

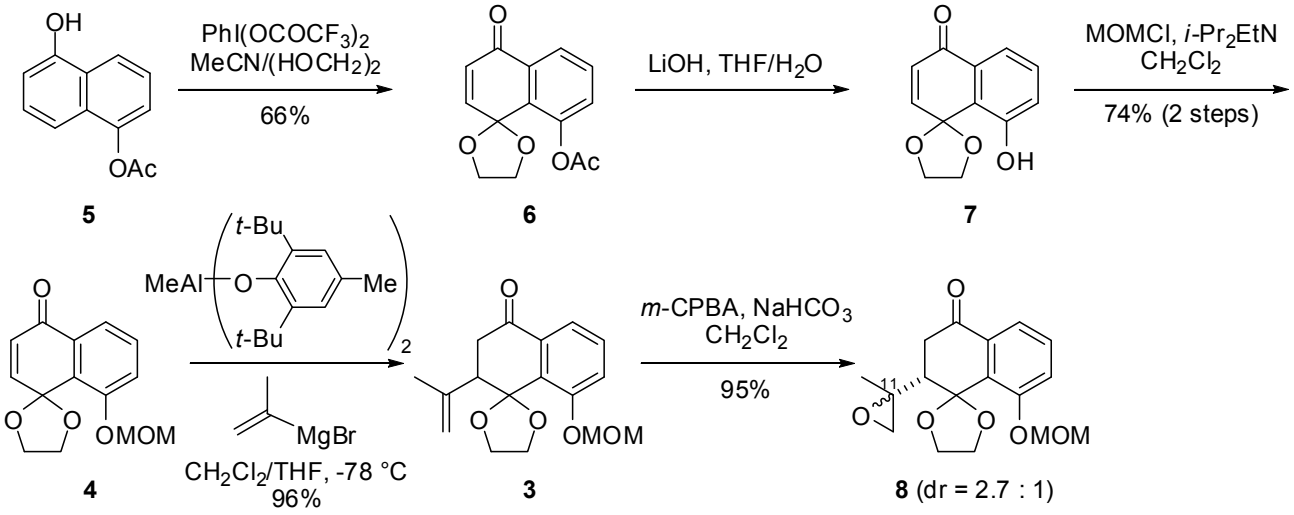
4-Hydoxyzinowol (**1**), isolated from *Zinowiewia costaricensis*, is a polyoxygenated dihydro-β-agarofuran sesquiterpenoid.[1,2] The compound shows a reversal effect against P-glycoprotein-overexpressing multi-drug resistant (MDR) cells, and thus it is expected to be used in the treatment of MDR cancer. The core structure of **1** is composed of *trans*-decaline (AB-ring) attached by a tetrahydrofuran moiety (C-ring), and six acyloxy and one hydroxy groups densely decorate the AB-ring. Because of its highly oxygenated tricyclic structure, **1** poses a formidable synthetic challenge.[3] As an initial phase of our synthetic study on **1**, we decided to develop an efficient route to the functionalized B-ring structure. Here we report the stereoselective synthesis of compound **2** bearing four contiguous *cis*-oriented stereocenters on the B-ring (Scheme 1). Compound **2** would serve as an advanced intermediate for construction of the entire structure of **1**.

This paper is dedicated to Prof. Ei-ichi Negishi on the occasion of his 77th birthday.

The retrosynthesis of **2** is illustrated in Scheme 1. Compound **2** was envisioned to be prepared from **3** through C8-hydroxylation and stepwise reduction of C6- and C9-ketones. Stereochemistries at the C6, 8 and 9 positions would be established by taking advantage of the presence of the C7-substituent. Specifically, the bulky C7 three-carbon unit was expected to exert a conformational or steric bias for controlling the face-selective reactions on the B-ring. Installation of the C7-substituent of **3** would in turn be achieved by 1,4-addition of the isopropenyl group to the naphthoquinone monoketal **4**. The 1,4-acceptor **4** was then to be prepared from the known naphthalene derivative **5**[4] via chemoselective oxidative dearomatization.



Scheme 1. Synthetic plan of **2** bearing four contiguous stereocenters on the B-ring of **1**

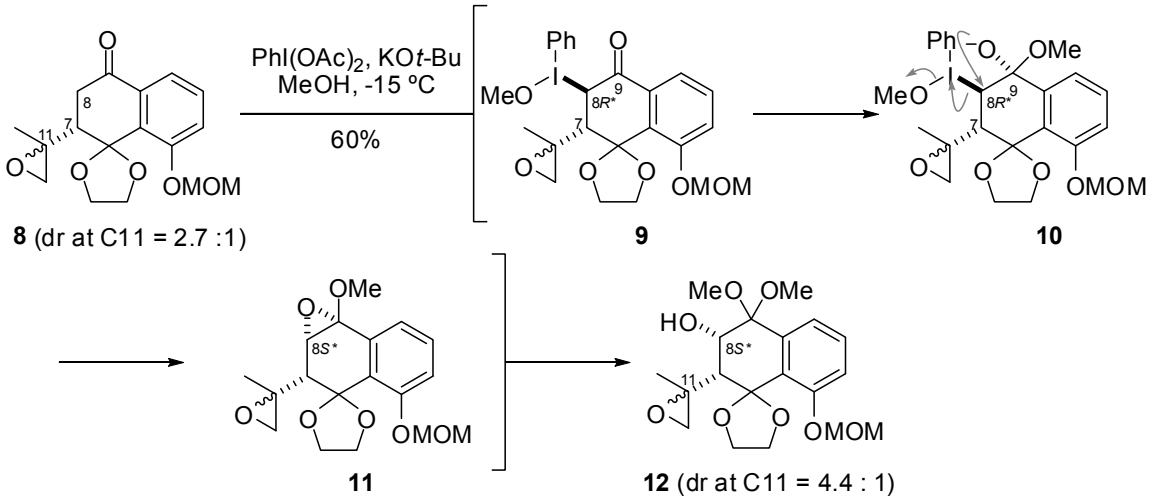


Scheme 2. Synthesis of **8** via MAD-assisted 1,4-addition of the isopropenyl group

The synthesis started with the oxidative dearomatization of **5** using $PhI(OCOCF_3)_2$ in a 1 : 4 mixture of CH_3CN and ethylene glycol, leading to the naphthoquinone monoketal **6** (Scheme 2).[5] After the protecting group of the phenolic hydroxy group of **6** was changed from Ac to MOM using the standard deprotection/protection procedure, 1,4-addition of the isopropenyl group was investigated. The copper-promoted addition of the isopropenyl group to **4** provided **3** in low yield, due to reductive formation of dihydroquinone from the quinone monoketal **4**. On the other hand, methyl aluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) smoothly enabled conjugate addition of isopropenyl magnesium bromide to **4**, providing **3** in 96% yield.[6] Then, the isopropenyl group of **3** was epoxidized by treating with *m*-CPBA to afford **8** as the C11 epimeric mixture (dr = 2.7 : 1).

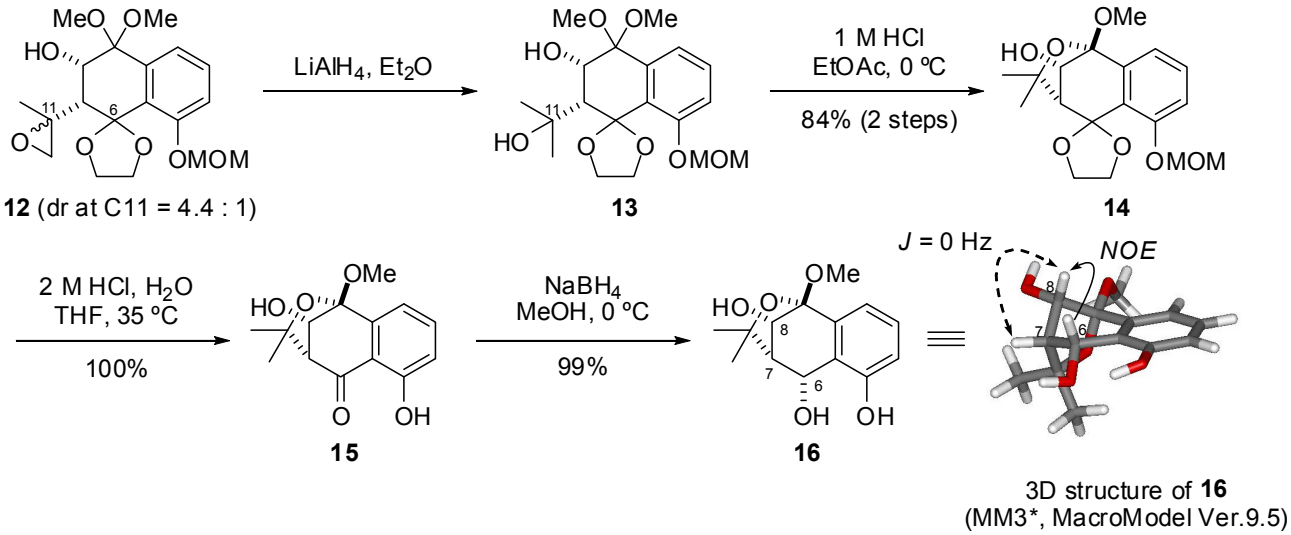
Next, introduction of the C8*S**-hydroxy group was explored (Scheme 3). The typical protocols for the α-hydroxylation of the ketone (e.g. TMS enol ether formation and subsequent *m*-CPBA epoxidation) proceeded exclusively from the opposite face to the bulky C7-substituent, generating the undesired C8*R**-hydroxy group. Thus, an in situ inversion process was investigated to attain C8*S**-hydroxylation from the sterically hindered side. After many unsuccessful experiments, it was found that subjection of **8** to $PhI(OAc)_2$ and KO*t*-Bu in MeOH[7] afforded the desired C8*S**-isomer **12** in 60% yield.[8]

The inversion process is rationalized as the following (Scheme 3). The present hydroxylation of **8** is initiated by enolization of the C9-ketone by KO*t*-Bu, and the following anti-selective C8*R**-iodination generates **9**. Potassium methoxide attacks the C9-ketone of **9** and subsequent S_N2 displacement of the iodine atom with the resultant C9-alkoxide inverts the C8-stereocenter of **10** to generate **11**. Methanolysis of the unstable epoxide **11** gives the requisite **12**.



Scheme 3. Stereoselective C8*S**-hydroxylation

Having constructed the C8*S**-hydroxy group, the C6-hydroxy group was installed through stereoselective reduction (Scheme 4). Before doing so, the epoxide of **12** was reduced by $LiAlH_4$ to form the C11-tertiary alcohol **13**. The C6-ketone **15**, the reduction substrate, was then constructed through a two-step process. Treatment of **13** under the anhydrous protic conditions promoted intramolecular acetal formation between the C11-hydroxy group and the C9-dimethyl acetal to afford **14**, and simultaneous removal of the cyclic acetal and the MOM groups of **14** under the aqueous protic conditions produced **15**.[9] Reduction of the C6-ketone of the oxabicyclo[3.2.1]octane structure **15** with $NaBH_4$ proceeded from the convex face, leading to the C6-alcohol **16** as a single product. The NOE correlation between H6 and H8, and the coupling constant between H7 and H8 (J = 0 Hz) determined the relative stereochemistry at the C6, 7 and 8 positions of **16**.

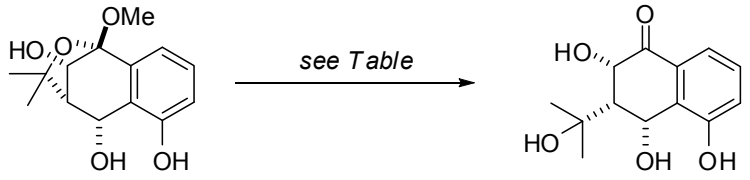


Scheme 4. Construction of oxabicyclo[3.2.1]octane and stereoselective reduction of the C6-ketone

To synthesize the requisite C9-alcohol of **2** from **16**, hydrolysis of the acetal was required to liberate the C9-ketone (Table 1). Although the strong Brønsted acid, H_2SO_4, was effective for the hydrolysis of **16**, the tetrahydroxylated ketone **17** decomposed under the reaction conditions (entry 1). After an extensive screening of Lewis acids, it was found that $Sc(OTf)_3$ converted the rigid acetal **16** to ketone **17** in higher yield (entry 2). Although the lower catalyst loading of $Sc(OTf)_3$ decreased the yield of **17** (entry 3), the reagent combination of a catalytic $Sc(OTf)_3$ and a stoichiometric $Zn(OTf)_2$ allowed the high-yielding formation of **17** (97% yield, entry 4). To clarify the role of $Zn(OTf)_2$, **16** was treated only with $Zn(OTf)_2$ (entry 5). However, these conditions resulted in no transformation, and the clean recovery indicated that $Zn(OTf)_2$ functioned as the assisting reagent for the $Sc(OTf)_3$-catalyzed reaction.[10] LiOTf was less effective to increase the yield, suggesting that the multivalent nature of $Zn(OTf)_2$ was important for acetal cleavage (entry 6).

From these experiments, the mechanism of the hydrolysis is proposed in Scheme 5. Strongly Lewis-acidic $Sc(OTf)_3$ initially cleaves the acetal of **16** to afford the Sc^{3+}-complex **18**, which is stabilized by the three chelating hydroxy groups. $Sc(OTf)_3$ in the complex **18** is exchanged by multivalent and more concentrated $Zn(OTf)_2$, regenerating the $Sc(OTf)_3$ catalysis.[11,12] Finally, the aqueous workup converts the Zn^{2+}-complex **19** to **17**. In this proposed mechanism, the acid-labile **17** is not exposed in the reaction mixture, and thus its facile decomposition is prevented.

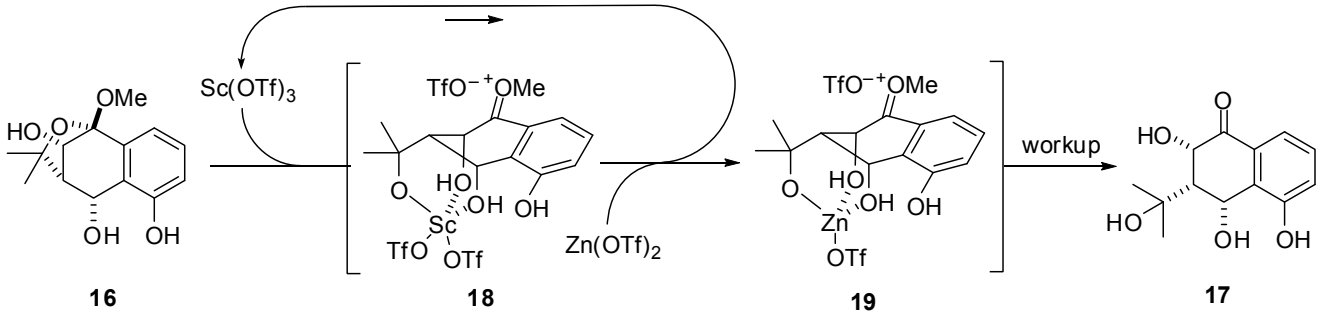
Table 1. Hydrolysis of the acetal of **16**



16 **17**

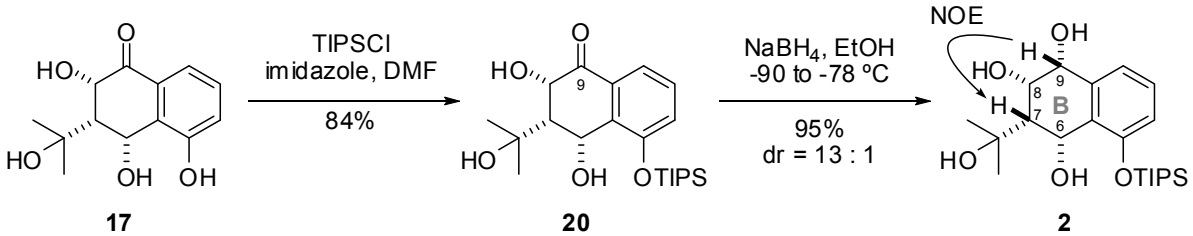
entry	acid (mol%)	additive (mol%)	yield
1[a]	H_2SO_4 (excess)	—	14%
2[b]	$Sc(OTf)_3$ (110)	—	78%
3[b]	$Sc(OTf)_3$ (10)	—	52%[c]
4[b]	$Sc(OTf)_3$ (5)	$Zn(OTf)_2$ (120)	97%
5[b]	$Zn(OTf)_2$ (120)	—	0%[d]
6[b]	$Sc(OTf)_3$ (5)	LiOTf (120)	76%

[a]Reaction was performed in a mixture of $THF/H_2O/H_2SO_4$ (v/v/v = 15/5/1, 50 mM) at 45°C. [b]Reaction was performed in a mixture of CH_2Cl_2/CH_3CN (v/v = 3/1, 0.1 M) at room temperature. [c]**16** was recovered in 28%. [d]**16** was recovered in 98%.



16 **18** **19** **17**

Scheme 5. Proposed mechanism for hydrolysis of the acetal of **16**



17 **20** **2**

Scheme 6. Synthesis of **2**

The targeted compound **2** was synthesized from **17** in two steps (Scheme 6). The phenolic hydroxy group of tetraol **17** was chemoselectively protected as the TIPS ether. The reduction of the C9-ketone of **20** with $NaBH_4$ proceeded selectively from the less hindered face of the B-ring to produce **2**[13] (dr = 13:1). The NOE correlation between H7 and H9 confirmed that all the three hydroxy groups at the C6, 8 and 9 positions, and the substituent at the C7 position in **2** were *cis*-oriented.

In summary, introduction of four contiguous stereocenters at the C6, 7, 8 and 9 positions on the B-ring of 4-hydroxyzinowol was achieved from the naphthalene derivative in 13 steps. The C7-isopropenyl group was installed on the naphthoquinone derivative via MAD-assisted 1,4-addition. The hydroxy groups at the C6, 8 and 9 positions were introduced by taking advantage of the presence of the C7-substituent. Specifically, C8-hydroxylation proceeded from the face hindered by the C7-substituent by employing $PhI(OAc)_2$ and KO-*t*Bu in MeOH. Reduction from the convex face of the oxabicyclo[3.2.1]octane compound, which was constructed through intramolecular acetal formation, set the requisite C6-stereocenter. The C9-hydroxy group was then generated by stereoselective reduction of the C9-ketone from the less hindered side of the B-ring, affording **2** with the *cis*-oriented C6, 7, 8 and 9-substituents. In addition, the new reagent combination of $Sc(OTf)_3$ and $Zn(OTf)_2$ was established for the hydrolysis of the acetal on the rigid oxabicyclo[3.2.1]octane structure. Further study toward the total synthesis of 4-hydroxyzinowol from **2** is currently underway in our laboratory.

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8. Although the C11-stereochemistry of each stereoisomer of **8** was not determined, the separate experiments using major isomer **8A** and minor isomer **8B** revealed their different reactivities. The C8-hydroxylation of **8A** provided **12A** in 68% yield, while **8B** was transformed to **12B** in 49% yield under the same conditions. Therefore, the ratio of the C11-epimeric isomers was changed from 2.7 : 1 to 4.4 : 1 after the reaction of **8** in Scheme 3.
9. Single-step conversion of **13** to **15** with aqueous 2 M HCl in THF decreased the yield of **15** (39% yield).
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13. Physical data for **2**: colorless oil; IR (neat) ν_{max} 3390, 2944, 2867, 1585, 1467, 1280, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (9H, d, *J* = 7.8 Hz, C*H*$_3$ of TIPS x 3), 1.14 (9H, d, *J* = 7.8 Hz, C*H*$_3$ of TIPS x 3), 1.36 (3H, m, C*H* of TIPS), 1.46 (s, 3H, C*H*$_3$), 1.58 (s, 3H, C*H*$_3$), 1.61 (1H, d, *J* = 4.1 Hz, C*H*C(OH)(CH$_3$)$_2$), 2.99 (1H, d, *J* = 11.2 Hz, C=CCH(O*H*)CHOH), 3.34 (1H, d, *J* = 4.1 Hz, C=CCH(O*H*)CHC(OH)(CH$_3$)$_2$), 3.82 (1H, s, C(O*H*)(CH$_3$)$_2$), 3.97 (1H, d, *J* = 3.7 Hz, C=CCH(OH)CHO*H*), 4.50 (1H, dd, *J* = 11.2, 3.7 Hz, C=CC*H*(OH)CHOH), 4.70 (1H, dd, *J* = 3.7, 3.7 Hz, C=CCH(OH)C*H*OH), 5.53 (1H, dd, *J* = 4.1, 4.1 Hz, C=CC*H*(OH)CHC(OH)(CH$_3$)$_2$), 6.79 (1H, d, *J* = 8.0 Hz, C*H*=COTIPS), 7.25 (1H, dd, *J* = 8.0, 8.0 Hz, CH=C*H*-CH), 7.35 (1H, d, *J* = 8.0 Hz, C-C*H*=CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.9, 18.00, 18.03, 28.3, 28.7, 46.9, 65.1, 68.7, 71.4, 74.2, 116.8, 120.3, 126.9, 129.4, 138.1, 153.4; HRMS (ESI), calcd for $C_{22}H_{38}O_5SiNa$ 433.2386 ($M+Na^+$), found 433.2393.