Asymmetric Total Synthesis of (–)-4-Hydroxyzinowol, a Highly Oxygenated Dihydro- β -Agarofuran

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Abstract: (–)-4-Hydroxyzinowol (**1**) is a potent inhibitor of P-glycoprotein, which has been implicated in multi-drug resistance in the treatment of cancer. The highly oxygenated structure of **1**, comprising a *trans*-decalin AB-ring and a tetrahydrofuran C-ring, with six acyloxy groups and one hydroxy group has posed a formidable synthetic challenge. We achieved the total synthesis of this extremely complex structure in 36 steps from 5-acetoxynaphthalen-1-ol. Here our efforts to complete the total synthesis of **1** are described in detail.

1. Introduction

Many cancers fail to respond to chemotherapy due to acquired multi-drug resistance (MDR).¹ One major form of resistance to chemotherapy has been correlated with the presence of molecular pumps that actively transport anticancer drugs out of the cell. The most prevalent of the MDR transporters is P-glycoprotein (P-gp), a member of the adenosine triphosphate (ATP)-binding cassette superfamily.² Since MDR is a major barrier to successful chemotherapy, development of selective inhibitors for P-gp is of high clinical relevance.

Jiménez, Gamarro and co-workers isolated and determined the structure of a series of natural products with P-gp inhibitory activity from the South American medical plant *Zinowiewia costaricensis*. One of the most potent compounds, (–)-4-hydroxyzinowol (**1**, Figure 1), blocked P-gp-mediated transport of daunorubicin, a clinically used anticancer drug, at low micromolar concentration.^{3,4} Thus, **1** is considered to be a lead compound for further development of specific inhibitors for treatment of MDR malignancy.

Compound **1** belongs to the dihydro- β -agarofuran sesquiterpenes family, which comprise a *trans*-decalin ring (the AB-ring) and a tetrahydrofuran ring (the C-ring).⁵ To date, over 400 structurally different dihydro- β -agarofurans have been identified from plant sources, and have attracted a great deal of interest due to their various biological functions such as antiviral (triptofordin C-2),⁶ anti-tumor promoting (triptofordin F-2),⁷ cytotoxic (emarginatine B),⁸ and anti-HIV (triptonine B)⁹ activities. These diverse yet selective biological activities of agarofurans are affected not only by the number and stereochemistries of the oxygen-based functional groups, but also by the various acyl groups attached to the oxygens. Some bioactive agarofurans are even fabricated by structurally complex macrocyclic rings. Interestingly, high inhibitory activity towards P-gp was found to require at least two aromatic ester moieties (e.g., the two Bz groups of **1**) by a comprehensive structure–activity relationship study of 76 natural agarofurans by Jiménez and Gamarro.^{3b}

Motivated by the complex architectures and promising biological activities of these compounds, a number of synthetic laboratories have been engaged in the chemical construction of

Figure 1. Structures of highly oxygenated dihydro- β -agarofuran sesquiterpenes.

dihydro- β -agarofuran sesquiterpenes.¹⁰ However, despite overall progress, the total synthesis of only one highly oxygenated agarofuran had been reported before 2014, ($\pm$)-euonyminol, which is the core structure of various polyacylated agarofurans, was synthesized by the White group in 1995.¹¹ In 2014, we reported the first asymmetric total synthesis of (–)-4-hydroxyzinowol (**1**).¹² The entire structure of **1** was assembled in 36 steps from 5-acetoxynaphthalen-1-ol by stereoselectively constructing nine consecutive centers (C1, 2, 4, 5, 6, 7, 8, 9, and 10) and regioselectively attaching two Bz and four Ac groups. Here we describe in detail our efforts towards completing the total synthesis of this extremely complex natural prod-

uct (–)-4-hydroxyzinowol (**1**).¹³

2. Initial Synthetic Plan of 4-Hydroxyzinowol

Our initial synthetic plan of target molecule **1** is illustrated in Scheme 1. To prepare for site-selective benzylation and acetylation at the last stage of the synthesis, we designed the bis-TBS-protected intermediate **2a**, in which the C8- and 9-secondary hydroxy groups are differentiated from their C1, 2, 6, and 15 counterparts. Retrosynthetic opening of the C-ring of **2a** gives rise to **3**.

The *trans*-decalin structure of **3** presents a formidable synthetic challenge because the six tri-substituted (C1, 2, 6, 7, 8, 9), two tetrasubstituted (C4, 5), and one quaternary (C10) stereocenters are concentrated on this ten-carbon framework. We envisioned constructing this heavily substituted AB-ring **3** from the naphthalene derivative **8**. In the synthetic direction, oxidative dearomatization of **8** and subsequent asymmetric introduction of the isopropenyl group would set the C7-stereocenter of **7**. To take maximum advantage of the C7-substituent as the steric bias in stereoselective transformations, we planned to form the caged tricyclic structure of **6** by intramolecular acetalization. Since the α -face would be sterically shielded by two methyl groups (C12, 13), the tricyclic ring system would allow reagents to approach from the β -face. After the second oxidative dearomatization of the phenol moiety of **6**, a series of stereoselective transformations were envisaged to convert **5** into *trans*-decalin scaffold **4**. Specifically, C2-hydroxylation, 1,4-addition of a carbon nucleophile to C10, and C4-methylation would establish the correct C2-trisubstituted, C10-quaternary, and C4-tetrasubstituted carbons, respectively. In turn, the C5-carbon would be hydroxylated from the opposite face of the C10-substituent to generate **4**. Hydrolysis of the acetals and the reductions at three ketones (C1, 6, 9) would lead to decalin **3**.

Scheme 1. Initial synthetic plan of 4-hydroxyzinowol (**1**).

3. Synthesis of the AB-ring Structure

Before asymmetric introduction of the isopropenyl group

at C7, 5-acetoxynaphthalen-1-ol **8**¹⁴ needed to be oxidatively dearomatized (Scheme 2). A reagent combination of $\text{PhI}(\text{OAc})_2$ and $\text{PhI}(\text{OCOCF}_3)_2$ converted **8** into the naphthoquinone monoketal **9** in a mixture of CH_3CN and ethylene glycol.¹⁵ The acetyl group of **9** was then removed by saponification to produce **10**. When **10** was treated with 2-propenyl trifluoroborate in the presence of catalytic $\text{Rh}(\text{cod})_2\text{BF}_4$ (10 mol%), (*S*)-BINAP (15 mol%), and stoichiometric Et_3N ,^{16,17} the asymmetric 1,4-addition proceeded smoothly, providing **7** in 91% yield and 90% ee.¹⁸

Scheme 2. Asymmetric 1,4-addition of the isopropenyl group.

Next, the three hydroxy groups at C6, 8, and 11 were constructed (Scheme 3). After protection of the C4-alcohol of **7** as the MOM ether of **11**, the C11-oxygen functional group was introduced as the epoxide using *m*-CPBA, leading to **12**. Stereoselective C8-oxidation was then explored. As expected, C8-hydroxylation of ketone **12** proceeded selectively from the β -face under typical conditions (e.g., TMS enol ether formation and subsequent *m*-CPBA oxidation) due to the presence of the bulky α -oriented C7-substituent. Given this stereochemical bias, an *in situ* inversion process was investigated to attain the requisite α -selectivity. Accordingly, **12** was treated with $\text{PhI}(\text{OAc})_2$ and *t*-BuOK in MeOH¹⁹ to afford the desired C8-alcohol **13** as the sole stereoisomer. In this Moriarty's procedure, the C8-position of **12** was first iodinated from the less-hindered β -face with $\text{PhI}(\text{OAc})_2$ to afford **A**, then the iodide group was intramolecularly displaced by the alkoxide in $\text{S}_{\text{N}}2$ fashion to form epoxide **C**. Subsequent methanolysis of the reactive epoxy acetal of **C** provided **13**.

Having established the C8-stereochemistry, the C11-tertiary alcohol was generated from the C11-epoxide of **13** by the action of LiAlH_4 , generating **14**. Anhydrous HCl in THF then induced intramolecular acetal formation at C9 to afford **15**, recrystallization of which produced enantiopure **15**. After acid hydrolysis of the C6-acetal and the MOM group, the C6-ketone of tricycle **16** was stereoselectively reduced with NaBH_4 from the convex face to give the C6-alcohol of **6**. The NOE correlation between H6 and H8, and the coupling constant between H7 and H8 ($J = 0$ Hz), confirmed the α -orientations of the C6-, 7-, and 8-substituents of **6**.

4. Attempts to Construct the *trans*-Decalin Scaffold

Our attention then turned to construction of the *trans*-decalin scaffold by establishing the three stereocenters (C2-tri- and C5, 10-tetrasubstituted carbons) of the A-ring

Scheme 3. Introduction of the C6-, 8-, and 11-hydroxy groups.

(Scheme 4). To do so, the phenol of **6** was subjected to a second oxidative dearomatization with $\text{PhI}(\text{OAc})_2$ in MeOH, affording quinone monoketal **17**. The Dess–Martin oxidation²⁰ of the C6-hydroxy group produced **5**. Next, OsO_4 reacted chemo- and stereoselectively with the C2-olefin from the β -face in the presence of the hindered C5-olefin, providing **18** as a single isomer. The three-hydroxy groups of **18** were simultaneously protected to afford tris-TES ether **19**.

The next task was the construction of two tetrasubstituted

Scheme 4. A-ring functionalization.

carbons (C5, 10) by applying the Michael addition of the C1 unit at the C10 position and the subsequent hydroxylation at the C5 position. As a model study, we planned to install a methyl group at C10 instead of the hydroxymethyl group requisite for the total synthesis of **1**. In the presence of TMSCl ,²¹ the cuprate reagent derived from MeLi and CuCN reacted with **19** in a stereoselective manner, giving rise to the desired enol **20**. The MOM-ether formation of the enolic hydroxy group of **20**, removal of three TES groups of **21** and attachment of the benzoyl group at the C3-hydroxy group gave rise to **23**. SmI_2 then effected reductive cleavage of the C3–O bond, leading to **24**, the substrate of the C5-hydroxylation.²² Unfortunately, many oxidation reagents (e.g., *m*-CPBA, DMDO, OsO_4) failed to convert **24** to the desired compound **25**. The forcing conditions induced the Baeyer–Villiger oxidation of ketone **24** to generate the undesired 7-membered lactone. This low reactivity of the α -face of the C6-olefin of **24** was attributable to the unusual steric hindrance induced by the fused tetrahydrofuran ring.

The above consideration led us to modify the oxidation site from the C6-olefin to the C4-olefin, because the α -face of the C4-olefin was expected to be more spatially open in compari-

Scheme 5. Attempted oxidation of C4-olefin.

son to that of the C6-olefin (Scheme 5). Before conducting the C5-oxidation, the alternative substrate **27** was prepared from **24**. Attack of methyl lithium on the C4-ketone of **24**, followed by acid treatment, resulted in formation of α,β -unsaturated ketone **27** via elimination of the C4-hydroxy group and concomitant removal of the MOM group. Although dihydroxylation of **27** using OsO₄ occurred, only the undesired stereoisomer **28** was obtained. The *cis*-decalin structure of **28** was confirmed by the H2-H13 NOE correlation. Because stereoselective C5-hydroxylation from the α -face was not attained, this approach was abandoned.

5. Revised Synthetic Plan

The above negative data suggested that the tricyclic frameworks of **24** and **27** were not suitable for introduction of the C5-oxygen functional group, because the tetrahydrofuran ring obstructed the α -hydroxylation. Therefore, the cyclic acetal was required to be hydrolyzed prior to the C5-oxidation in the revised synthetic plan. Furthermore, it was apparent that the powerful C5-oxidation reaction was necessary to install the sterically hindered C5-O bond. From these considerations, we planned an oxidative dearomatization from bicyclic derivative **32** for intramolecular introduction of the desired C5-oxygen functional group (Scheme 6). In the synthetic direction, hydrolysis of the cyclic acetal of **6** and subsequent C9-reduction would provide **32**. Next, oxidative dearomatization of the phenol was expected to occur by C5-oxidation through nucleophilic epoxidation of the α -oriented C6-hydroxy group. The diene part of **31** in turn would undergo a Diels-Alder reaction with a dienophile from the α -face to construct the C10-quaternary carbon of **30c**.²³ The oxidative dearomatization/Diels-Alder reaction sequence would establish the correct two-tetra-substituted carbons (C5, 10) on the *trans*-decalin scaffold in a stereoselective manner. Ring-opening of the epoxide at C6, ring-closure of the C-ring at C11, and introduction of the tetrasubstituted carbon at C4 would convert **30c** into tetracycle **29**. Finally, oxidative cleavage of the C3'-olefin, C2-desulfonylation, and C1,2-dihydroxylation from **29** would lead to the requisite **2a**. To realize this scheme, the most critical issues were the proper selection and orchestration of highly chemo- and stereoselective reactions within the rather compact matrices of the intermediates.

Scheme 6. Revised synthetic plan.

6. Construction of the *trans*-Decalin Scaffold

First, we focused on the hydrolysis of the cyclic acetal (Table 1). This turned out to be no easy task, mainly because the cyclic acetal of **6** was unusually stable under various acidic conditions. A strong Brønsted acid (H₂SO₄) in THF/H₂O hydrolyzed **6** to provide tetrahydroxylated ketone **33** in low yield due to concomitant decomposition of **33** (entry 1). Extensive screening of Lewis acids revealed that stoichiometric Sc(OTf)₃ converted acetal **6** to ketone **33** in high yield (entry 2). Whereas a lower loading of Sc(OTf)₃ decreased the yield of **33** (entry 3), the combination of a catalytic amount of Sc(OTf)₃ and a stoichiometric amount of Zn(OTf)₂ enabled the formation of **33** in higher, but variable, yields (64–97%, entry 4). The addition of 100 mol% of H₂O improved the reproducibility, leading to **33** in 97% yield (entry 5). Zn(OTf)₂ alone did not induce the conversion of **6** to **33** (entry 6), and LiOTf/Sc(OTf)₃ was less effective than Zn(OTf)₂/Sc(OTf)₃ in increasing the yield (entry 7). These data together suggested that multivalent Zn(OTf)₂ functioned as the assisting reagent for acetal cleavage.

A mechanism for this hydrolysis is proposed in Scheme 7. Strongly Lewis-acidic Sc(OTf)₃ initially cleaves the acetal of **6** to afford Sc³⁺-complex **D**, which is stabilized by the three chelating hydroxy groups. Sc(OTf)₃ in **D** is exchanged with the multivalent and more concentrated Zn(OTf)₂, regenerating the Sc(OTf)₃ catalyst.^{24,25} Finally, the *in situ* hydrolysis of Zn²⁺-complex **E** led to formation of **33**. In this proposed mechanism, the acid-labile **33** is mainly exposed to the weakly acidic Zn(OTf)₂, preventing its facile decomposition.

Reduction of the thus-formed C9-ketone realized the construction of the four stereocenters of the B-ring (Scheme 8). After chemoselective protection of the C4-pheno-

Table 1. Hydrolysis of the cyclic acetal of **6**.

entry	acid (mol%)	additive (mol%)	yield
1 ^a	H ₂ SO ₄ (excess)	none	14%
2	Sc(OTf) ₃ (110)	none	78%
3	Sc(OTf) ₃ (10)	none	52% ^b
4	Sc(OTf) ₃ (5)	Zn(OTf) ₂ (120)	64–97%
5	Sc(OTf) ₃ (5)	Zn(OTf) ₂ (120) H ₂ O (100)	97%
6	Zn(OTf) ₂ (120)	none	0% ^c
7	Sc(OTf) ₃ (5)	LiOTf (120)	76%

^aReaction was performed in a mixture of THF/H₂O/H₂SO₄ (v/v/v = 15/5/1, 50 mM) at 45°C. ^b28% of **6** was recovered. ^c98% of **6** was recovered.

Scheme 7. Proposed mechanism for the hydrolysis of the acetal of **6**.

lic hydroxy group of tetraol **33** as the TIPS ether, the C9-ketone of **34** was reduced with NaBH₄ from the less hindered β -face, stereoselectively affording **32** (dr = 18:1). The NOE correlation between H7 and H9 confirmed the correct C9-stereochemistry of **32**. Due to the equatorial preference of the bulky C7-substituent, the B-ring of **32** adopted the half chair form to orient the C6-hydroxy group in the axial position.

Scheme 8. Construction of the C5-tetrasubstituted carbon by the oxidative dearomatization.

The stage was now set to introduce the angular C5-stereogenic center through an oxidative dearomatization. Before doing so, regioselective acetone formation of the C8,9-diol in the presence of the C6,11-diol and subsequent TIPS removal transformed tetraol **32** to triol **36**. By using **36** as a substrate, the oxidative dearomatization of the phenol was explored. Although the oxidation of **36** with PhI(OCOCF₃)₂ provided a low yield of desired compound **31**, NaIO₄ cleanly converted **36** into **31** in aqueous methanol through the nucleophilic attack of the proximal C6-hydroxy group of **35** on C5.²⁶ As seen in the conformation of **32**, the preferred boat conformation of the B-ring of **F** accelerates the nucleophilic attack of the axial C6-hydroxy group. Importantly, diene **31** was isolated in excellent yield without suffering from the self-dimerization by the Diels-Alder reaction, presumably due to the kinetic protection of the diene moiety by the surrounding

bulky substituents.

The constructed diene structure of **31** was next utilized for the Diels-Alder reaction to install the C10-quaternary center in the sterically congested format (Table 2).²⁷ Reaction of various dienophiles with **31**²⁸ showed that methyl acrylate (entry 1), methyl propiolate (entry 2), and ethynyl *p*-tolyl sulfone (entry 3) provided excellent yields and stereoselectivities. When diene **31** was heated to 80 °C with neat methyl acrylate or methyl propiolate, the Diels-Alder adduct **30a** or **30b** was obtained in high yield as a single isomer. Alternatively, the reaction between **31** and 5 equivalents of ethynyl *p*-tolyl sulfone²⁹ occurred at 80 °C in toluene, providing the tricyclic structure **30c** with simultaneous introduction of the C10-stereocenter. Since the *p*-tolyl sulfone moiety could easily be detached from the molecule, we selected **30c** as the intermediate for the total synthesis (*vide infra*).

Table 2. Introduction of the C10-quaternary carbon by the Diels-Alder reaction.

entry	dienophile	product and yield
1		 30a : 79%
2		 30b : 81%
3 ^a		 30c : 70%

^aReaction was performed using 5 equiv of ethynyl *p*-tolyl sulfone in toluene (0.1 M) at 80 °C.

Since the observed NOE between H7 and H15 proved the structure of **30c**, the dienophile approached from the α -face. The remarkable stereo- and regioselective outcome of the Diels-Alder reactions is rationalized by the intrinsic three-dimensional structure of **31** (Scheme 9). The J_{H6H7} and J_{H6H8} values indicate that the B-ring of both diene **31** and adduct **30c** adopt similar twist-boat conformations, presumably due to the presence of the sterically cumbersome moiety at C7. The β -face of **31** bears a concave nature in this conformation. Thus, the approach of the dienophile from the α -face of **31**, with the bulky *p*-tolyl sulfonyl group outside the fused ring, becomes favored compared to the β -face approach, resulting in highly stereo- and regioselective formation of **30c** through the transition state **G**. In addition to the steric effects, the regio-

Scheme 9. Rationale for the selective outcome of the Diels–Alder reaction. (A) Observed H6/H7 and H6/H8 coupling constants, and the plausible transition state of the Diels–Alder reaction. (B) HOMO and LUMO energies and coefficient values estimated by DFT calculations (B3LYP/6–31G^{*}).

selective outcome would also be explained by the frontier orbital interaction of the diene and the dienophile. The orbital energies of **30** and ethynyl-*p*-tolyl sulfone, which were calculated by the DFT method (B3LYP/6–31G^{*} level of theory),³⁰ suggested that the cycloaddition proceeds in a normal-electron-demand manner. The energy gap between the dienophile LUMO (–1.49 eV) and diene HOMO (–6.47 eV) is smaller than that of the diene LUMO (–2.22 eV) and dienophile HOMO (–7.53 eV). The computed atomic orbital coefficients of the diene HOMO and the dienophile LUMO by the same method indicated favorable C1–10 and C2–3 bond formations. Accordingly, both the steric and electronic factors contribute synergistically to the highly selective formation of **30c**.

7. C-ring Formation

Since the entire AB-ring skeleton **30c** was efficiently assembled at this stage, the next focus was construction of the

C-ring. The tetrahydrofuran C-ring was to be formed by epoxide opening and etherification. A model study was first performed to optimize the procedure using **30b** as the substrate (Scheme 10). After deprotection of the 1,2-diol of **30b** with $\text{Ce}(\text{OTf})_3$,³¹ regioselective nucleophilic opening of the epoxide of **37b** proceeded by the action of CsOAc or CsOBz in DMF to afford acetylated **38ba** or benzoylated **38bb**.³² The subsequent C-ring cyclization necessitated acid-promoted etherification from the two tertiary alcohols at C5 and C11. Interestingly, while treatment of **38ba** with *p*-tolSO₃H in benzene at 50 °C generated olefin **39ba** with concomitant loss of the Ac group, the desired acid-promoted etherification occurred from **38bb** to give **39bb**. The distinct outcomes from **38ba** and **38bb** were attributable to their conformational preferences induced by the Ac and Bz groups, respectively. The large H6–H7 coupling constant ($J = 11.4 \text{ Hz}$) of **38ba** indicates the twist-boat B-ring, in which the C11-hydroxy group points away from the C5-hydroxy group. Cyclization is thus disfavored and the alternative C11-olefination gives unwanted **39ba**. On the other hand, judging from the H6–H7 coupling constant ($J = 5.5 \text{ Hz}$), the B-ring of the benzoylated **38bb** adopts the chair form with axially oriented C6- and 7-substituents, probably because the equatorial orientations of these 1,2-vicinal groups suffer from larger gauche interactions.³³ Consequently, the C5 and 11-hydroxy groups are preorganized for the requisite etherification, resulting in successful formation of the C-ring.

Scheme 10. Model study of the C-ring formation.

Having clarified the critical role of the Bz group for C-ring formation, **30c** was subjected to the optimized procedure (Scheme 11). The acetone group of **30c** was first removed by TFA-mediated hydrolysis, affording the substrate for the epoxide opening. In accordance with the above model study, **37c** was treated with CsOBz in DMF to open the epoxide. However, the reaction conditions also epimerized the C5-stereocenter, leading to a mixture of *trans*-decalin **38ca** and *cis*-decalin **38cb**. The H1–H6 NOE correlation clarified the isomerized *cis*-decalin structure of **38cb**.

Scheme 11. C5-isomerization of the *trans*-decalin to *cis*-decalin ring.

The C5-epimerization is considered to occur through the following mechanism (Scheme 12). After the epoxide opening, the resultant C5-alkoxide triggers cleavage of the C-C bond (**H**→**I**), which is facilitated by the presence of the anion-stabilizing C2-sulfonyl group. The anion **I** undergoes C-C bond formation with the C5-ketone to lead to *trans*- and *cis*-decalins **38ca/cb**. Since the C5-epimerization was not observed in the model study, the strong electron-withdrawing nature of the C2-tosyl group is responsible for the reaction.

Scheme 12. Plausible mechanism of the C5-epimerization.

Rapid protonation of C5-alkoxide **H** would suppress the retro-aldol type reaction and, thereby the C5-epimerization. Under modified conditions, BzOH was used as a proton source in combination with nucleophile CsOBz in DMF (Scheme 13). This procedure effectively delivered **38ca** without the C5-epimerization. Subsequent acid treatment of **38ca** constructed

Scheme 13. Successful construction of the C-ring.

the C-ring, affording **39c** in 59% yield over 2 steps.

8. Synthesis of the Dihydro- β -agarofuran Framework

With the requisite tricyclic framework in hand, the remaining transformations en route to the dihydro- β -agarofuran structure of **1** included removal of the extra carbon (C3'), and generation of the five hydroxy groups (C1, 2, 4, 6, 15) and methyl group (C14). Because of the densely functionalized structures of the intermediates, the multiple functional group manipulations must be judiciously arranged.

The C8,9-hydroxy groups of **39c** were capped as the TBS ethers, and the C6-hydroxy group was liberated from **40** under basic conditions, giving rise to **41** (Scheme 14). The C14-methyl group was then stereoselectively installed. When MeMgBr was allowed to react with the Bz-protected **40** in Et₂O, no product was observed. The proximal functional groups appeared to kinetically block the C4-ketone of **40**. In contrast, the C4-ketone of the deprotected **41** accepted the nucleophile under the same conditions, resulting in formation of the adduct **29** as a single stereoisomer. The distinct reactivity and excellent stereoselectivity in the conversion of **41** to **29** could arise from the intramolecular transfer of the methyl group from the magnesium ate complex **J**.³⁴ The requisite orientation of the C14-methyl group of **29** was determined by an NOE experiment.

Scheme 14. Introduction of the C4-tetrasubstituted carbon.

A carefully tuned sequence from **29** achieved C3'-decarboxylation and C2-desulfonylation. Ozonolysis of diene **29** resulted in reaction with the more electron-rich C3'-olefin in the presence of the sulfone-substituted C2-olefin. Subsequent reductive workup provided **42** with the C15-hemiacetal and C3'-aldehyde. NaClO₂-promoted oxidation of the C3'-aldehyde of **42** generated carboxylic acid **43a**,³⁵ and the reaction conditions also induced acetalization of **42** to form stable bis-acetal **43b**.

The obtained two compounds **43a** and **43b** converged to **44** in one and three steps, respectively (Scheme 15). The C2-sulfonyl group of **43a**, which served as the reactivity-controlling element for both the Diels-Alder reaction (**31**→**30c**) and ozonolysis (**29**→**42**), was reductively removed with Na/Hg in buffered aqueous CH₂Cl₂ to produce carboxylic acid **44** (Scheme 15A).³⁶ On the other hand, the hemiacetal of **43b** was oxidized to lactone **48**, the C2-sulfonyl group of which was removed with Na/Hg (Scheme 15B). Saponification of the lactone of **49** delivered carboxylic acid **44**.

The C3'-carbon of **44** was then eliminated as CO₂ through the intermediacy of Barton ester **45** (Scheme 15A). After condensation of carboxylic acid **44** with 1-hydroxypyridine-2(1*H*)-thione,³⁷ treatment of **45** with AIBN and Ph₃SnH generated allyl radical **K** that abstracted hydrogen at the more accessible C3-position over the C1-position to produce **46** without olefin transposition. The C15-hemiacetal of **46** was reductively opened using LiBH₄ in refluxing THF to produce

Scheme 15. Synthesis of triol **47** from **43ab**.

47.

The next task was the synthesis of compound **2a** from **47**, which possessed the seven suitably differentiated hydroxy groups of 4-hydroxyzinowol (**1**) (Scheme 16). The C6-secondary alcohol of **47** was chemoselectively oxidized in the presence of the C15-primary alcohol by utilizing Trost's conditions [(NH₄)₆Mo₇O₂₄ and H₂O₂],³⁸ leading to **50** via C6-hemiacetal formation.³⁹ The C1-olefin was dihydroxylated with OsO₄ to introduce the C1- and 2-hydroxy groups of **51** in a completely stereoselective fashion. The C9-TBS-ether is likely to impede the approach of OsO₄ from the α-face, resulting in β-face addition of the OsO₄. The NOE correlation of the product **51** confirmed the correct stereochemistry of the newly introduced diol, and supported the close proximity of the α-face of the A-ring and the C9-TBS ether group.

Scheme 16. Functionalization of the decalin scaffold.

Next, the stereoselective construction of the C6-hydroxy group was explored. However, several reduction conditions only resulted in recovery of **51** (Scheme 17). The low reactivity of the C6-ketone of **51** was attributed to its protected nature as the hemiacetal: ¹H NMR analysis in CDCl₃ revealed that the hemiacetal form was the only observable structure. The screening of reduction conditions including reductants, solvents, and temperature eventually led us to find that LiBH₄ was effective in the C6-reduction.⁴⁰ Although reduction of **51**

Scheme 17. Stereoselective reduction of the C6-ketone. The ratio of **2a** and **2b** was determined by ¹H NMR analysis.

with LiBH_4 in THF provided a 1:1 mixture of **2a** and **2b**, we found 1,2-dichloroethane was the most effective solvent to increase the desired stereoselectivity, furnishing desired **2a** as the major product (dr = 5:1).

9. Total Synthesis of 4-Hydroxyzinowol

For the total synthesis of **1**, the last challenge was regioselective acetylation of the four hydroxy groups (C1, 2, 6, 15) and benzylation of the two hydroxy groups (C8, 9). Extensive reactivity mapping clarified that the C1-hydroxy group was the most resistant to acetylation among the five hydroxy groups of **2a**. Specifically, only one primary hydroxy group at C15 and two secondary hydroxy groups at C2 and C6 of **2a** were acetylated using Ac_2O and DMAP in a mixed solvent of CH_2Cl_2 and Et_3N , affording **52** (Scheme 18). Subjection of **2a** to more forcing conditions [e.g., Ac_2O , $\text{Sc}(\text{OTf})_3$, CH_3CN]⁴¹ only resulted in acetylation of the tertiary C4-hydroxy group in addition to the C2-, 6-, and 15-hydroxy groups. Since the low reactivity of the C1-hydroxy group would be affected by the surrounding bulky C15-OAc and C9-OTBS groups, the TBS groups of **52** were removed with TBAF prior to the C1-acetylation, producing tetraol **53**.

When **53** was treated with Bz_2O and Et_3N in CH_2Cl_2 , the least hindered C9-hydroxy group of the three secondary hydroxy groups was first benzyloated (Scheme 19). The addition of DMAP in the same pot accelerated the second benzylation to produce diol **55**. Lastly, acetylation of the remaining C1-hydroxy group of **55** under the same conditions as the first

acetylation proceeded without touching the C4-hydroxy group, delivering (–)-4-hydroxyzinowol (**1**). All the analytical data of synthetic **1** (^1H - and ^{13}C NMR, IR and $[\alpha]_D$) were identical with those of **1** from the natural source.

10. Conclusion

The asymmetric total synthesis of 4-hydroxyzinowol (**1**), a highly oxygenated dihydro- β -agarofuran, was accomplished in 36 steps from 5-acetoxynaphthalen-1-ol **8**. After rhodium-catalyzed asymmetric 1,4-addition of the isopropenyl group at C7, stereoselective introduction of the eight stereocenters on the decalin framework was realized by controlling the three-dimensional structures of the intermediates and selecting the appropriate conditions for each reaction. These include the following: i) C8-hydroxylation from the hindered face; ii) reduction of the C6- and C9-ketones; iii) C5-epoxidation by oxidative dearomatization and subsequent formation of the C5-ether; iv) construction of the C10-quaternary center through the Diels-Alder reaction; v) hydroxy-directed addition of the methyl group at C4; vi) C1,2-dihydroxylation; and vii) introduction of the C6-stereochemistry through an oxidation/reduction sequence. The highly optimized acetylation and benzylation of **2a** furnished the targeted structure **1**. In addition to the series of selective transformations, application of the combination of $\text{Sc}(\text{OTf})_3$ and $\text{Zn}(\text{OTf})_2$ for the hydrolysis of the stable acetal and use of ethynyl *p*-tolyl sulfone as the reactive acetylene equivalent for the Diels-Alder reaction should have wider applications beyond this synthesis. The synthetic route to **1** developed here will accelerate the structure-activity relationship studies for identification of effective inhibitors of P-glycoprotein for reversing multi-drug resistance in cancer chemotherapy.

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