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Article

Bioinspired Two-Phase Synthesis of Gibbosterol A

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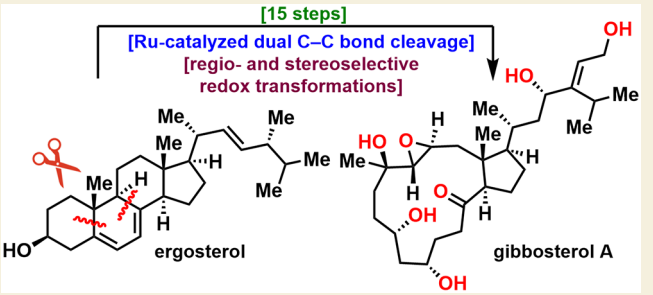
ABSTRACT: The disecosteroid natural product gibbosterol A—which has a 14/5-bicyclic framework, a high oxidation state, and a twisted *trans*-9,11-epoxy motif—is the first water-soluble 5,10:8,9-disecosteroid. Herein, we report a bioinspired two-phase synthesis of this natural product in only 15 steps from inexpensive ergosterol. In the first (isomerase) phase, the core bicyclic framework is rapidly installed by the skeletal reorganization of ergosterol endoperoxide via a ruthenium-catalyzed dual C−C bond fragmentation. In the second (oxidase) phase, chemoselective, regioselective, and stereoselective redox transformations precisely introduce the requisite oxygenated functional groups. This work demonstrates that the ingenious two-phase synthesis logic that has been applied to terpenes is also a powerful strategy for steroid synthesis.



KEYWORDS: *steroid, natural product, biomimetic synthesis, two-phase synthesis, endoperoxide fragmentation*

INTRODUCTION

Secosteroids represent an important class of rearranged steroids that feature cleavage of at least one ring of the classic tetracyclic framework.[1] A unique member of this family is the disecosteroid natural product gibbosterol A (**1**, Figure 1), the

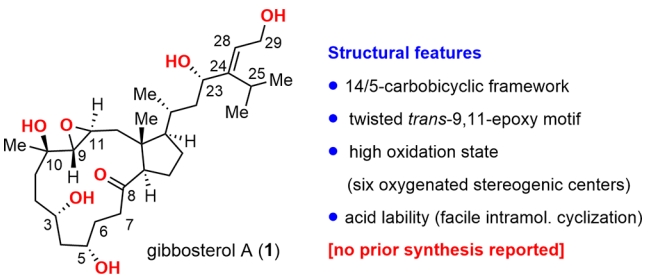


Figure 1. Gibbosterol A, the first water-soluble disecosteroid.

first water-soluble 5,10:8,9-disecosteroid, which was isolated by Wu and co-workers in 2021 from the culture liquid of the South China Sea dinoflagellate *Amphidinium gibbosum*.[2] This compound possesses a 14/5-bicyclic framework with a twisted *trans*-9,11-epoxy motif and exhibits potent agonistic effects against the human pregnane X receptor in a dose-dependent manner (in the concentration range from 100.0 nM to 10.0 μM). The high oxidation state of **1**, which has six oxygenated stereogenic centers, poses a formidable challenge to its chemical synthesis. In addition, it is unstable under acidic conditions, readily undergoing intramolecular cyclization to give a tetrahydrofuran derivative. No synthesis of gibbosterol A has yet been reported.

It has been proposed that **1** is biosynthesized from β-sitosterol (**2**) via a stepwise oxidation−fragmentation process (Scheme 1A).[2] Specifically, oxidation of the side chain and C5−C6 olefin of **2** and subsequent C5−C10 bond cleavage give 10-membered intermediate **3**. This intermediate undergoes epoxidation and subsequent cleavage of the C8−C9 bond to generate 14-membered intermediate **4**, which can be converted to **1** through olefin epoxidation and C5-ketone reduction. In contrast to this proposed biosynthetic pathway, our proposed biosynthesis of **1** was largely inspired by the two-phase biosynthesis of terpenes.[3] In the cyclase phase, the polycyclic framework is rapidly generated by enzymatically controlled cyclization and rearrangement of linear isopentenyl pyrophosphates of various chain lengths; in the oxidase phase, enzymatic oxidation of C−H or C−C bonds results in highly selective installation of diverse functional groups. Notably, this biosynthesis has inspired Baran and co-workers to develop an ingenious two-phase terpene synthesis logic[4] that has been successfully used for concise syntheses of a series of complex terpenoid natural products,[5] including Taxol.[6] Given the close interrelationship between the biosyntheses of steroids and terpenes,[7] we wondered whether the two-phase terpene biosynthesis could be extended to steroid biosynthesis. Could rearranged steroid **1** be biosynthetically derived from

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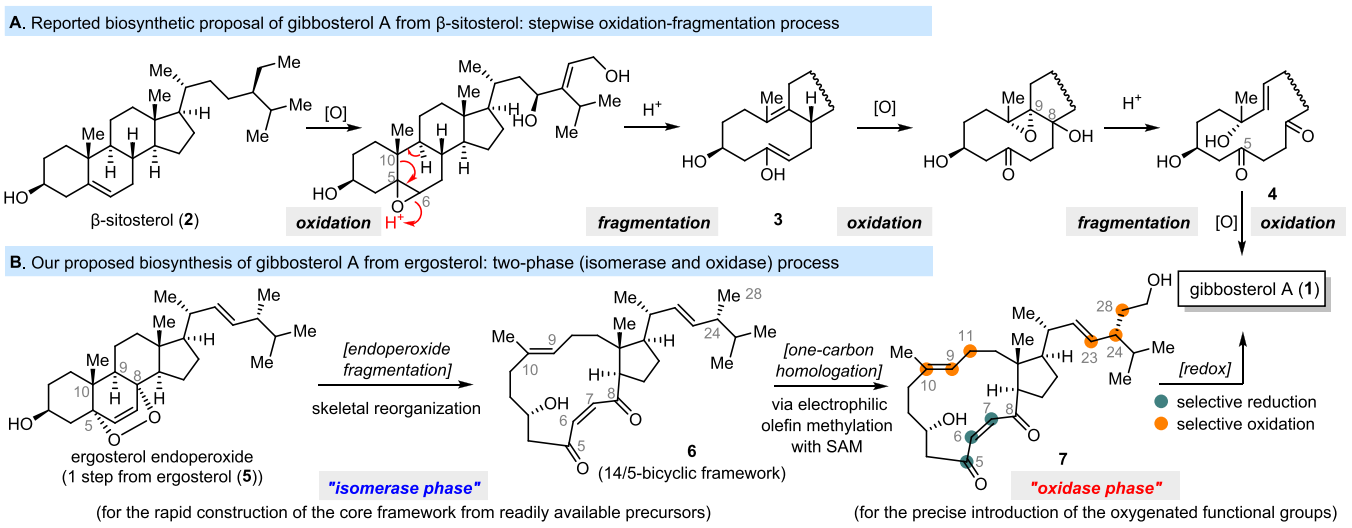
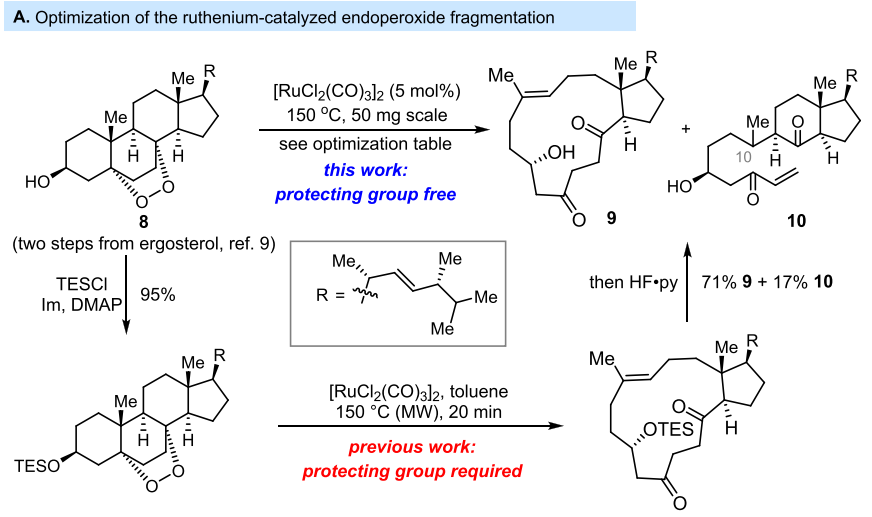
Scheme 1. Proposed Biosynthetic Pathways for Gibbosterol A

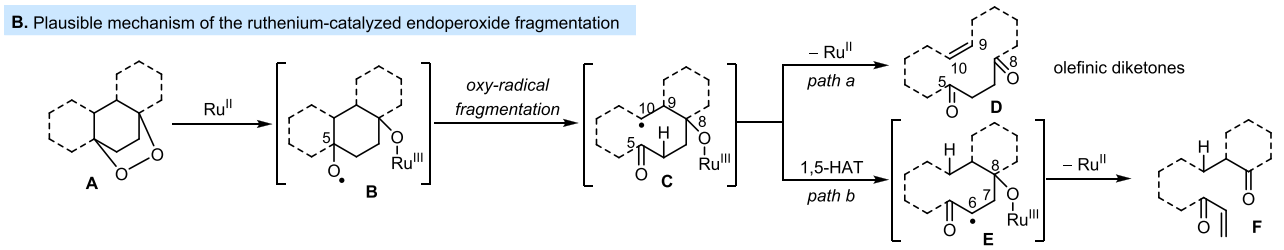


Scheme 2. Optimization of the Ruthenium-Catalyzed Endoperoxide Fragmentation and Its Plausible Mechanism



entry	conditions	isolated yields (%)		
		8	9	10
1	toluene, 120 °C, 4 h	0	30	-[a]
2	toluene, 20 min	0	44	27
3	$PhCF_3$, 20 min	0	47	21
4	PhCl, 20 min	0	45	22
5	HOAc[b], toluene, 20 min	0	19	6
6	DBU[b], toluene, 20 min	0	27	0
7	DIPEA[b], toluene, 20 min	0	48	0
8	TMEDA[b], toluene, 20 min	71	5	trace
9	NMP[b], toluene, 20 min	0	54	38
10	Py[b], toluene, 20 min	19	40	6
11	Py[b], toluene, 30 min	0	60	12
12	2,6-lutidine[b], toluene, 30 min	0	44	23
13	DTBMP[b], toluene, 30 min	0	55	28
14[c]	Py[b], toluene, 30 min	0	60	29

[a]Not determined. [b]2.0 equiv. [c]Sealed tube, gram scale.



ergosterol (**5**) via an analogous two-phase process (Scheme 1B)? We surmised that in such a process, the cyclase phase of terpene biosynthesis (in which cyclization and rearrangement play an essential role in construction of the polycyclic core framework) would be replaced by an isomerase phase, in which a controllable skeletal reorganization[8] of the 6/6/6/5-tetracyclic ring system of steroids would rapidly generate the structurally complex skeleton of the rearranged steroid. Specifically, skeletal reorganization of ergosterol endoperoxide (obtained in one step from **5**) by means of an endoperoxide fragmentation[9] would quickly produce the 14/5-bicyclic framework of **6**. In the ensuing oxidase phase, one-carbon homologation of **6**, possibly via an electrophilic olefin methylation process with SAM,[10] could generate **7**. Further selective redox manipulation then delivers **1**. Indeed, we herein report the application of the two-phase terpene synthesis logic to steroid synthesis, leading to the first synthesis of gibbosterol A, which was accomplished in only 15 steps from ergosterol.

RESULTS AND DISCUSSION

Skeletal Reorganization Approach to the Core 14/5-Bicyclic Framework

Our synthesis commenced with the isomerase phase, that is, the reorganization of ergosterol's 6/6/6/5-tetracyclic skeleton to the 14/5-bicyclic framework of **9** (Scheme 2). The synthetic precursor, endoperoxide **8**,[9] was easily prepared from ergosterol (**5**) via photo-oxidation with singlet oxygen[11]

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followed by regioselective reduction of the C6−C7 olefin.[12] Previously, we developed a method for ruthenium(II)-catalyzed endoperoxide fragmentation that can be used to cleave the C5−C10 and C8−C9 bonds of classical steroids and thereby convert 6/6/5-tricyclic compounds into 14-membered macrocyclic diketones.[9] However, this reaction necessitated prior protection of the C3 hydroxyl group of **8** as the triethylsilyl (TES) ether and subsequent removal of the TES group by treatment with HF·pyridine after fragmentation (Scheme 2A). To avoid the tedious protection−fragmentation−deprotection procedure, we aimed to develop a protecting-group-free protocol using unprotected alcohol **8** as the substrate. Treatment of **8** with 5 mol % $[RuCl_2(CO)_3]_2$ at 120 °C in toluene for 4 h delivered **9** in only 30% isolated yield, even when the reaction was carried out on a 50 mg scale (entry 1). Increasing the temperature to 150 °C slightly improved the yield to 44%, together with a 27% yield of side product **10** (entry 2). Changing the solvent to $PhCF_3$ or PhCl gave similar results (entries 3 and 4). Next, we screened a series of additives and found that 2 equiv of pyridine was beneficial in terms of mass balance and product distribution (ratio of **9** to **10**) (entries 5−10). Gratifyingly, performing the reaction with Py for 30 min led to complete consumption of **8**, furnishing **9** and **10** in 60 and 12% yield, respectively (entry 11). Further screening of other bases revealed Py as the optimal base (entries 12 and 13). Notably, **9** could also be obtained in 60% yield from a gram-scale reaction (entry 14).

For the plausible mechanism of the ruthenium-catalyzed endoperoxide fragmentation (Scheme 2B), we propose that endoperoxide **A** first reacts with the Ru(II) catalyst to give alkoxy radical intermediate **B**, which undergoes *β*-fragmentation to furnish C10-alkyl radical **C**. Homolysis of the O−Ru(III) bond leads to cleavage of the C8−C9 bond, affording the desired olefinic diketone **D** with the release of the Ru(II) catalyst. Alternatively, **C** may undergo 1,5-hydrogen atom transfer to produce C6-alkyl radical **E**. Further fragmentation of **E** then delivers undesired vinyl ketone **F**. Of note, our modified protocol for the protecting-group-free endoperoxide fragmentation enabled us to generate the core 14/5-bicyclic framework in only three steps from ergosterol, thereby concluding the isomerase phase and setting the stage for the oxidase phase.

Redox Manipulation of the 14-Membered Macrocyclic Ring

Precise installation of the diverse oxygenated functional groups—that is, the C5 and C10 hydroxyl groups, the *trans*-9,11-epoxy motif, and the oxidized side chain—was found to be challenging. Our investigation began with regioselective and diastereoselective reduction of the C5 ketone of **9**. To determine the configuration of the newly established stereocenter at C5, we found that one of the diastereomers **11** could be readily converted to cyclic carbonate **12**, whose structure was confirmed by X-ray crystallographic analysis (Scheme 3). This result established the stereochemistry at C5 of **11** to be the opposite as that of **1**. Direct reduction of **9** with $NaBH_4$ or $LiAlH(O^tBu)_3$ under substrate control delivered the desired product **13** but with poor diastereoselectivity (ca. 1.3:1, Table 1, entries 1 and 2). Pleasingly, the regioselectivity was excellent: the C8 ketone remained intact during the reduction, possibly owing to steric hindrance. Treatment of **9** with (*R*)- or (*S*)-Me-Corey−Bakshi−Shibata catalyst and $BH_3{\cdot}Me_2S$ led to the formation of undesired **11** as the major product (entries 3 and 4).[13] Subjecting **9** to Kagan's reagent (SmI_2) in the presence of ^{i}PrOH or MeOH also resulted in low diastereoselectivity (entries 5 and 6).[14] After much trial and error, we were excited to find that Noyori reduction conditions ($[RuCl_2(PhH)]_2$, **L**, KOH) delivered a 59% yield of **13** and only a trace of **11** (entry 7).[15] Lowering the amount of KOH from 0.2 to 0.1 equiv and the reaction temperature from 50 °C to room temperature increased the yield to 94% (entries 8 and 9). When the reaction was performed on a gram scale, **13** and **11** were obtained in 90 and 3% yield, respectively (entry 10).

Having established the C5 chiral hydroxyl group (4 steps from ergosterol, Scheme 4), we moved forward to install the C10 tertiary allylic alcohol, which we anticipated could be

Scheme 3. Determination of the Configuration of the Newly Established Stereocenter at C5

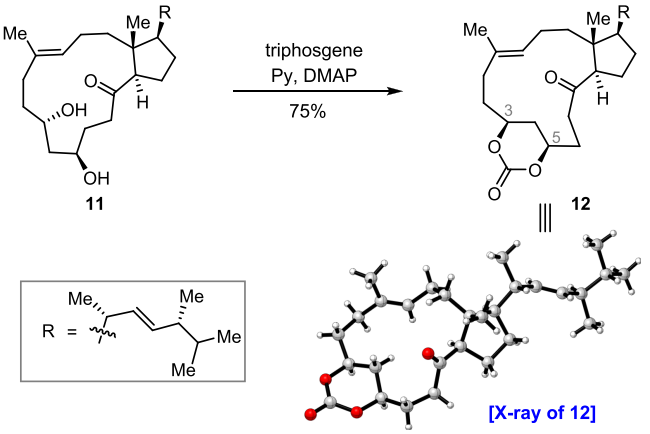
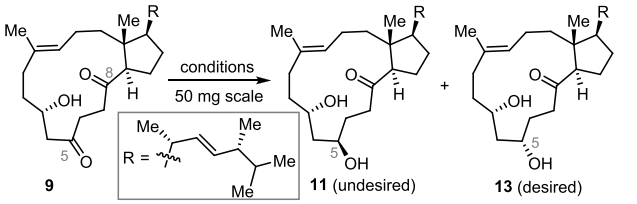
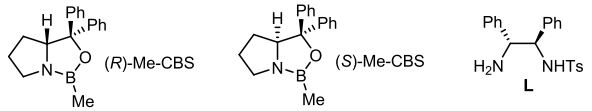


Table 1. Regioselective and Diastereoselective Reduction of C5 Ketone: Selected Optimization[g]



entry	conditions[a]	isolated yields (%) 11	13
1[b]	$NaBH_4$ (0.5), MeOH/THF, 0 °C, 0.5 h	42	56
2[c]	$LiAlH(Ot\text{-}Bu)_3$ (1.1), THF, 0 °C, 0.5 h	34	48
3[d]	(*R*)-Me-CBS (0.2), $BH_3{\cdot}Me_2S$ (1.5), THF	49	41
4[d]	(*S*)-Me-CBS (0.2), $BH_3{\cdot}Me_2S$ (1.5), THF	50	31
5	SmI_2 (2.5), *i*-PrOH (10.0), THF, rt, 1 h	21	41
6	SmI_2 (2.5), MeOH (10.0), THF, rt, 1 h	28	45
7[e]	$[RuCl_2(PhH)]_2$ (0.02), L (0.04), KOH (0.2), 50 °C	trace	59
8[e]	$[RuCl_2(PhH)]_2$ (0.02), L (0.04), KOH (0.1), 50 °C	trace	70
9[e]	$[RuCl_2(PhH)]_2$ (0.02), L (0.04), KOH (0.1), rt	trace	94
10[e,f]	$[RuCl_2(PhH)]_2$ (0.02), L (0.04), KOH (0.1), rt	3	90

[a]The amounts of the reagents (in equivalents) are shown in parentheses. [b]100 mg scale. [c]85 mg scale. [d]−78 °C, 30 min, then 0 °C, 10 min. [e]*i*-PrOH, 30 min. [f]1.1 g scale. [g]Abbreviations: CBS, Corey−Bakshi−Shibata catalyst; DMAP, 4-dimethylaminopyridine.



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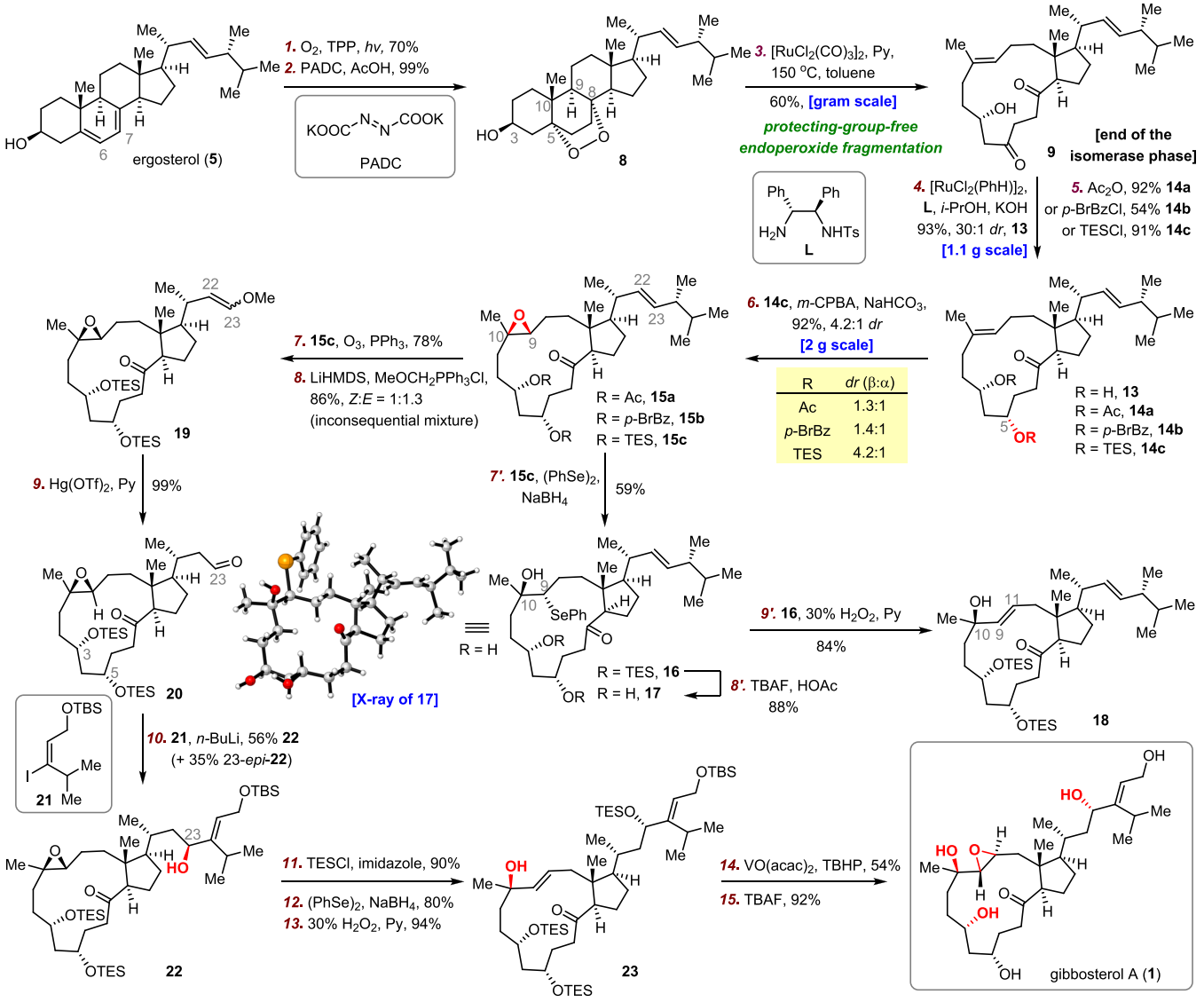
Scheme 4. Bioinspired Two-Phase Synthesis of Gibbosterol A



achieved by means of epoxidation of the C9−C10 olefin followed by epoxide opening.[16] Protection of **13** with acetic anhydride delivered acetate **14a**. However, epoxidation of **14a** with *m*-chloroperoxybenzoic acid furnished the desired epoxide **15a** with poor diastereoselectivity (1.3:1). A similar result was obtained for the epoxidation of *p*-bromobenzoate **14b**. Pleasingly, when the protecting group was changed to TES, the epoxidation of **14c** led to **15c** in 92% yield with 4.2:1 diastereoselectivity. We hypothesized that the steric hindrance of two TES groups might influence the conformation of the 14-membered macrocycle, which could in turn lead to the improved diastereoselectivity of the olefin epoxidation. To confirm the configuration of the epoxide, we transformed **15c** to phenylselenide **16**, which was treated with tetra-*n*-butylammonium fluoride (TBAF) and HOAc to give alcohol **17**. The X-ray structure of **17** unambiguously confirmed that the configuration of the C10 tertiary alcohol was the same as that of **1**. Notably, oxidation of selenide **16** with 30% H_2O_2 and pyridine smoothly generated allylic alcohol **18**, which has a *trans*-C9−C11 olefin[16] that could potentially be employed for late-stage introduction of the *trans*-9,11-epoxy motif.

Completing the Synthesis of Gibbosterol A

With **16** in hand, our next task lay in the introduction of the allylic diol side chain, which we hoped to achieve by means of olefin ozonolysis and fragment coupling (Scheme 5). Ozonolytic cleavage of the C22−C23 olefin of **16**, followed by in situ reduction of the resulting aldehyde with $NaBH_4$, furnished alcohol **24**, which was smoothly converted to bromide **25**. Unfortunately, coupling of **25** and aldehyde **26** under a variety of conditions (^{t}BuLi, SmI_2, etc.) failed to deliver the desired allylic alcohol **27**, possibly owing to steric hindrance at the adjacent C20 position. To circumvent this issue, we planned to perform one-carbon homologation to convert C22 aldehyde **28** or **29** to C23 aldehyde **30** or **31**,[17] which could be utilized to install the allylic diol side chain through a nucleophilic addition reaction with an alkenyl lithium reagent. Ozonolysis of **16** without or with in situ oxidation of the selenide generated a moderate yield of aldehyde **28** or **29**, both of which were found to be unstable during long-term storage. Furthermore, attempted preparation of one-carbon homologated aldehyde **30** or **31** by means of a Wittig reaction and hydrolysis of the resulting methyl enol ether also met with failure,[17] perhaps due to the instability of

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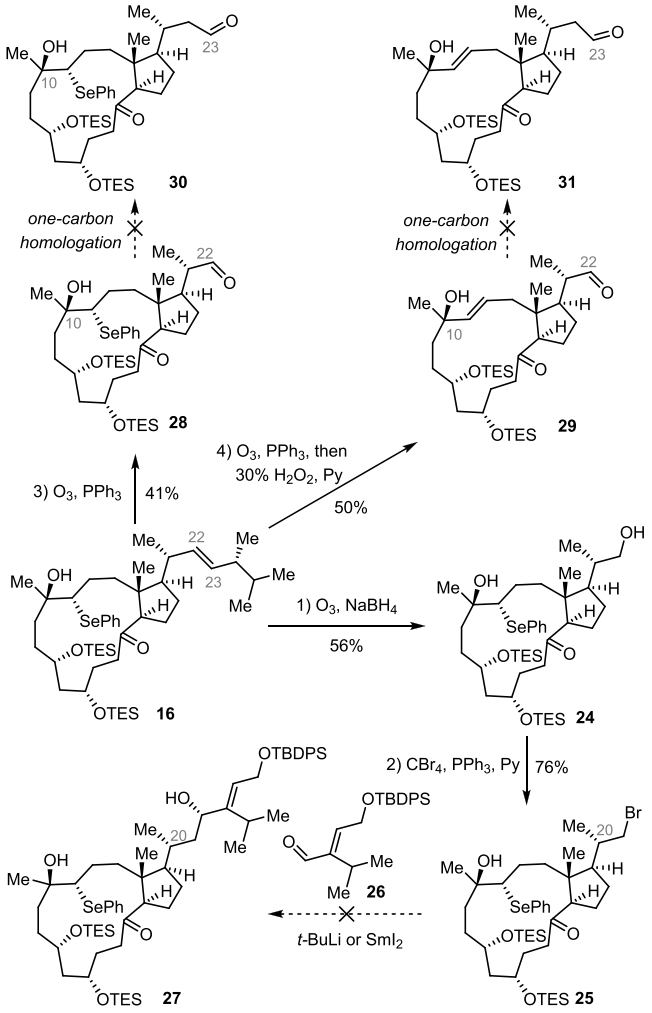
Scheme 5. Initial Forays into Introduction of the Allylic Diol Side Chain



the C10 tertiary alcohol and the TES groups under acidic hydrolysis conditions. Therefore, we decided to install the side chain before introducing the C10 tertiary alcohol.

As shown in Scheme 4, ozonolytic cleavage of **15c** delivered the corresponding C22 aldehyde (not shown, 78% yield), which smoothly underwent Wittig olefination to furnish methyl enol ether **19** as a *Z*/*E* mixture (inconsequential). However, hydrolysis of **19** to generate C23 aldehyde **20** turned out to be nontrivial: commonly used mild acidic conditions (pyridinium *p*-toluenesulfonate, $CuCl_2/H_2O$, etc.) inevitably led to the fast removal of the TES groups at C3 and C5 before the desired hydrolysis of the methyl enol ether could proceed. After extensive optimization (for details, see Table S2, Supporting Information), we found that treatment of **19** with $Hg(OTf)_2$ under neutral conditions delivered desired aldehyde **20** in 52% yield.[18] To suppress partial removal of the TES groups, we added 5 equiv of pyridine, which increased the yield of **20** to almost quantitative.

To complete the synthesis of **1**, we carried out a diastereoselective 1,2-addition reaction of **20** with a lithium reagent generated by a Li−I exchange reaction of known vinyl iodide **21**,[19] which gave desired alcohol **22** in 56% yield, together with a 35% yield of undesired compound 23-*epi*-**22**.[20] Protection of **22** as the TES ether, followed by the two-step installation of the C10 allylic alcohol using the previously established method, furnished **23** in good yield. Treatment of **23** with $VO(acac)_2$ (acac = acetylacetonate) and *t*-butyl hydroperoxide,[21] followed by global deprotection with TBAF, completed the synthesis of gibbosterol A. The spectroscopic data of the synthetic compound were in good agreement with those reported in the literature.[2]

CONCLUSIONS

We have accomplished the first synthesis of gibbosterol A. The route requires only 15 steps from ergosterol and features ruthenium(II)-catalyzed protecting-group-free endoperoxide fragmentation and a series of highly selective redox transformations. This work demonstrates that the two-phase synthesis logic that has been widely employed for terpene synthesis is also a powerful strategy for the concise synthesis of highly complex steroid natural products. In particular, skeletal reorganization plays a critical role in the isomerase phase in which the diverse core framework of rearranged steroids can be rapidly accessed from inexpensive, commercially available steroidal compounds. This bioinspired two-phase approach is expected to facilitate the efficient synthesis of other highly oxygenated steroids.

METHODS

Procedure for the Ruthenium-Catalyzed Endoperoxide Fragmentation

To a dried 100 mL sealed tube equipped with a magnetic stir bar were charged endoperoxide substrate **8** (1.0 g, 2.3 mmol, 1.0 equiv) and $[RuCl_2(CO)_3]_2$ (59 mg, 0.12 mmol, 0.05 equiv). The tube was evacuated and backfilled with argon for three times. Dry toluene (61 mL) and pyridine (0.38 mL, 4.6 mmol, 2.0 equiv) were added via syringe under argon, and the resulting mixture was stirred at rt for 10 min. Then, the tube was sealed and heated at 150 °C for 30 min. After cooling to rt, removal of the solvent under reduced pressure afforded the crude residue, which was purified by flash chromatography (SiO_2, 4:1 → 3:1 petroleum ether:EtOAc) to afford compound **9** (0.60 g, 60%) as colorless oil.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.3c00698.

General information, full synthetic sequence, selected optimization of the endoperoxide fragmentation and hydrolysis of vinyl ether **19**, experimental procedures and characterization data for compounds **9**−**29**, NMR comparison of synthetic and natural gibbosterol A, X-ray crystallographic data for compounds **12** and **17**, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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