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Graphical Abstract

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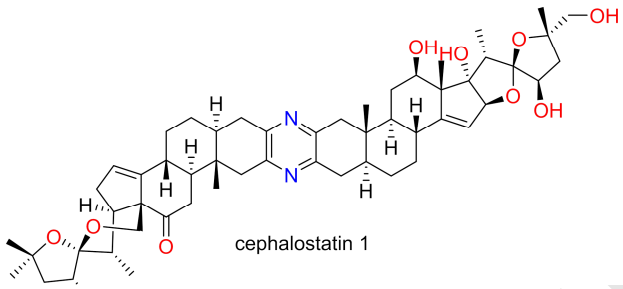

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A Synthesis of Cephalostatin 1

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ABSTRACT

A synthesis of cephalostatin 1 from hecogenin is described in detail. The gram-scale synthesis of south part features a Baeyer–Villiger oxidation of hecogenin to 16,20-diol, a selective oxidation of C16-OH with Dess–Martin periodinane, a Rh(I)-catalyzed C15–C16 double bond shift to C14–C15 position, and a $Hg(OAc)_2$-mediated spiroketal formation from cyclic enol ethers with alkenyl side chain at 2-position. Key transformations in the synthesis of north part, also on gram scale, include an abnormal Baeyer–Villiger oxidation of hecogenin to the corresponding dinorcholanic lactone, where a catalytic amount of iodine acts as a traceless and catalytic switch, an umpolung of steroidal 22-aldehyde to forge C22–C23 bond with good stereochemical control, a cascade spiroketal-forming process to establish DEF rings in one operation, and a selective oxidation of C3-OH. There are also other noteworthy transformations that, although not used in our final route, are valuable and could be applied to other syntheses, including: intra- or intermolecular S_N2' processes of C14-heteroatom-substituted C15–C16 alkenes, an unprecedented rearrangement of β-adduct of D-ring dienes and singlet oxygen, a chelation-controlled methylallylation of C23 aldehyde, and so on.

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1. Introduction

Searching for natural products possessing anti-tumor effects, the Pettit group from Arizona State University isolated 20 cephalostatins[1-9] from the marine worm *Cephalodicsus gilchristi* (represented by cephalostatin 1 (**1**), Figure 1), and the Fusetani group from Tokyo University isolated 26 ritterazines[10-13] from the tunicate *Ritterella tokioka* (represented by ritterazine B (**2**)). The cephalostatins and ritterazines formed a family of 46 trisdecacyclic bissteroidal pyrazines with striking cytotoxicity against human tumors at low nanomolar level, hence ranking them among the most powerful anticancer agents ever tested by the US National Cancer Institute.[14] Although an increasing amount of research is being focused on these issues, the cellular target and mechanism of them have not been fully elucidated.[15-20] Unlike the taxol, growing in large and easy-to-harvest forests, the limited availability of marine organisms are scattered on the bottom of the ocean and makes it impossible to obtain large amounts of cephalostatins or ritterazines by harvesting. Chemical synthesis is the only resort.

With up to thirteen rings annulated to the pyrazine with a C2-symmetry in the lipophilic bissteroidal core moiety and highly oxygenated outer spiroketal areas, cephalostatins/ritterazines represent some most fascinating and challenging structural elements, stimulating a broad spectrum of organic synthesis efforts in a number of laboratories.[21-33] These endeavors have put forward elegant and creative solutions to some long-standing synthetic problems, such as, three processes of preparing unsymmetrical pyrazines developed by Heathcock[34], Fuchs[35], and Winterfeldt[36], and an unprecedented oxidation of C18-Me from C14-C15 double bond developed by Shair.

Three groups (the Fuchs group from Purdue University[37-38], the Shair group from Harvard University[39], and our group[40]) accomplished the synthesis of cephalostatin 1. Some key transformations in these syntheses were listed in Figure 1b. All the syntheses started with hecogenin (**3**), a cheap steroidal sapogenin, or its derivatives, except the synthesis of the north part of **1** by Shair, which started with epiandrosterone (**4**). Both Fuchs and Shair used Marker degradation[41] to transform the spiroketal of hecogenin derivatives to steroidal 16,17-en-20-ones, which set the stage for introducing other functionalities. In our synthesis, we employed 3,12,16,20-tetraol **7** and lactone **8**, both prepared from hecogenin, to synthesize south part (**5**) and north part (**6**) of **1**, respectively. In our previous communication[40], only the final route was briefly reported, leaving most of the details undiscussed. This article describes in detail our synthesis of cephalostatin 1.

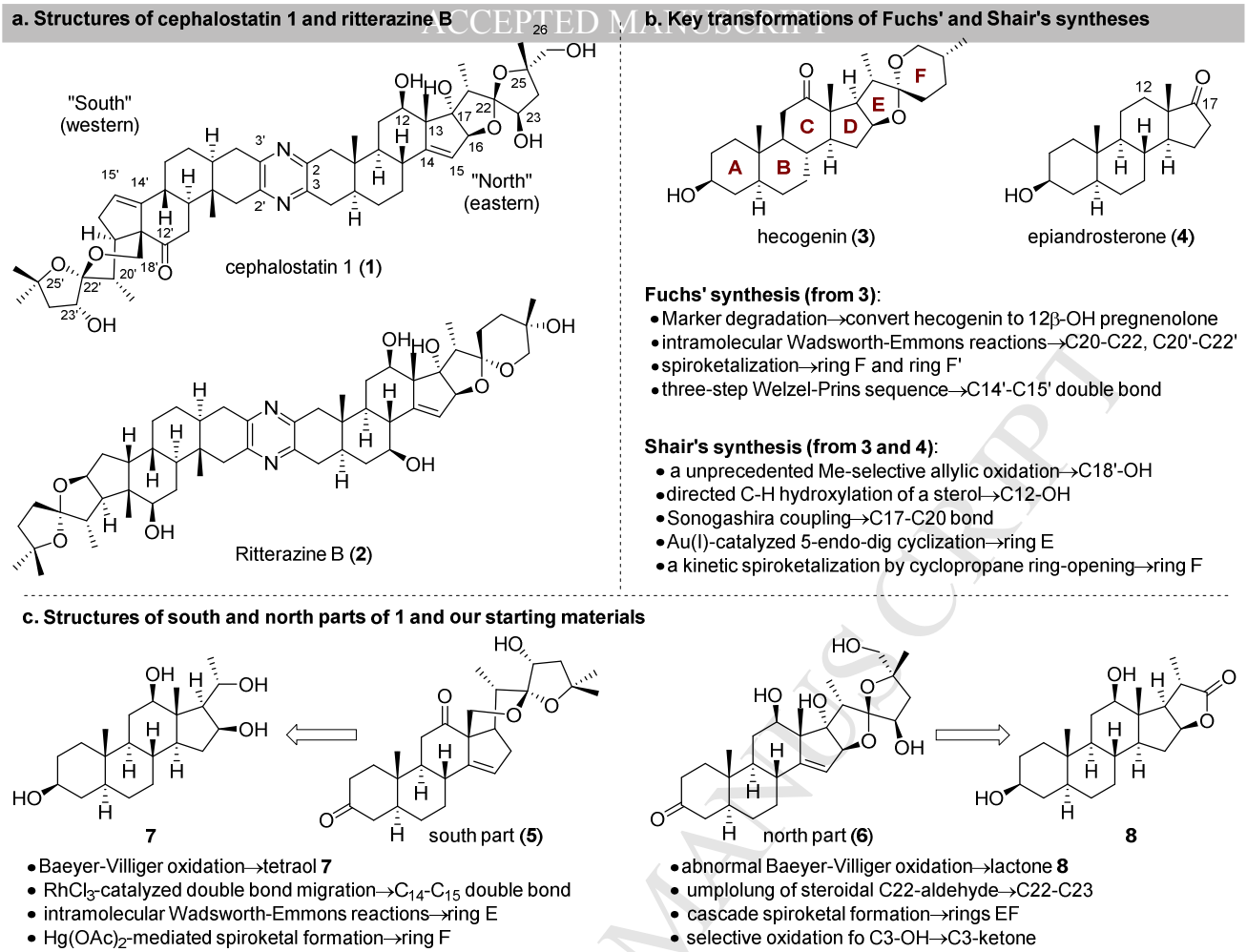


Figure 1. A Brief Overview of Three Syntheses of Cephalostatin 1

2. Results and Discussions

2.1. Synthesis of the South Part of Cephalostatin 1

Two basic problems in the synthesis of the south part (**5**) are the transformation of the EF rings from a 5/6 system, which is present in the starting material, to a functionalized 6/5 system and the introduction of C14-C15 double bond in the D ring. Starting with **7**, we needed to functionalize the C18 angular methyl group with the C20-OH, install the C14–C15 double bond with the C16-OH, and assemble the spiroketal with desired stereochemistry.

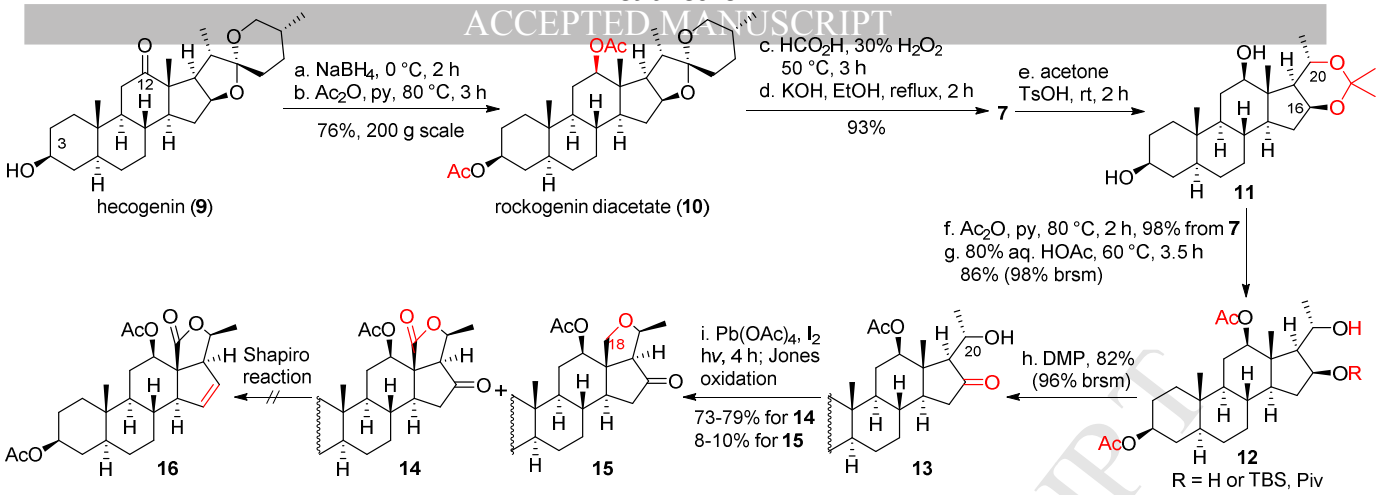
Our synthesis of south part (**5**) thus started with the preparation of the tetraol **7**. The transformation of the EF-ring spiroketal of steroidal sapogenins into 16,20-diol via Baeyer–Villiger oxidation was first reported by Marker in 1940[42] and developed as a useful degradation tool by Morita and co-workers in 1960s[43-47]. Our group have independently developed a similar procedure without knowing the Morita's report.[48] The reactivities of these OHs and their use in natural product synthesis have been explored in our laboratory.[49-53]

As in Scheme 1, the C12 ketone of hecogenin (**9**) was reduced by $NaBH_4$ in MeOH/THF to yield C12 alcohol as a mixture of epimers in a ratio of 7–8/1 (β/α). The undesired C12α epimer was removed through acetylation and recrystallization from ethanol to afford rockogenin diacetate (**10**) in 76% yield. Baeyer–Villiger oxidation of **10** with performic acid (generated *in situ* from commercially available 30% H_2O_2 and formic acid) followed by saponification furnished **7** in 93% yield after recrystallization.

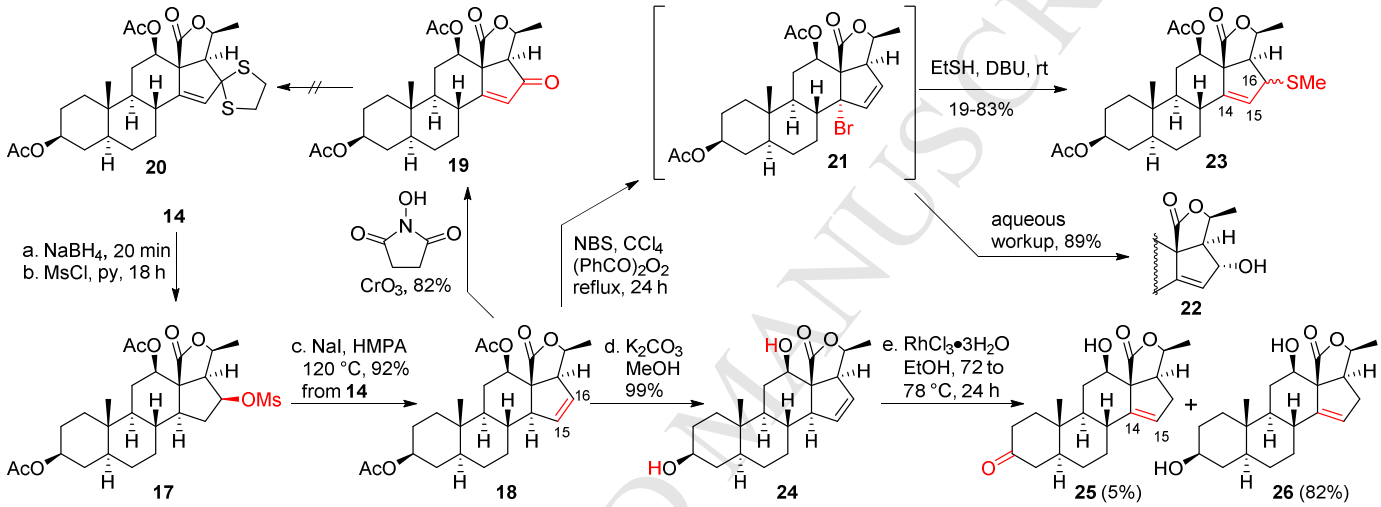
The intramolecular remote functionalization of C18 methyl group from C20-OH was routinely accomplished by trapping the δ-carbon radical generated by 1,5-hydrogen transfer to alkoxyl free radical with iodine.[54-56] The presence of unprotected hydroxyls might cause severe side reactions, selective protection of hydroxyl groups at C3, C12 and C16 was therefore needed.

By stirring **7** in dry acetone at room temperature in the presence of TsOH (20 mol%), its C16-OH and C20-OH were protected as acetonide, and then the C3-OH and the C12-OH of **11** were protected as acetates to give the fully protected tetraol in 95% yield after recrystallization from EtOAc/hexane. Removal of the acetonide with 80% aqueous HOAc at 60 °C gave **12** in high yield (86%, 98% brsm). Although the C16-OH of **12** could be selectively protected as pivalate or *t*-butyldimethylsilyl ether in good yields, the steric crowdedness at the upper face of the D ring made the remote functionalization impossible.

Selective oxidation of C16-OH was considered a good option because the resultant C16 ketone could minimize the steric interference and be used to install the C14–C15 double bond. Interestingly, Dess–Martin oxidation of **12** proved superior to other typical oxidations (NBS, PDC, Swern, etc.), and delivered the desired ketone **13** in excellent yield. It was noteworthy that running the oxidation at low concentration was crucial for the high selectivity of this oxidation, with the ratio of C16 ketone to C20 ketone being *ca*. 3/1 at 0.17 M and 86/3 at 0.08 M. Then,



Scheme 1. Toward south part: functionalization of the C18 angular methyl group



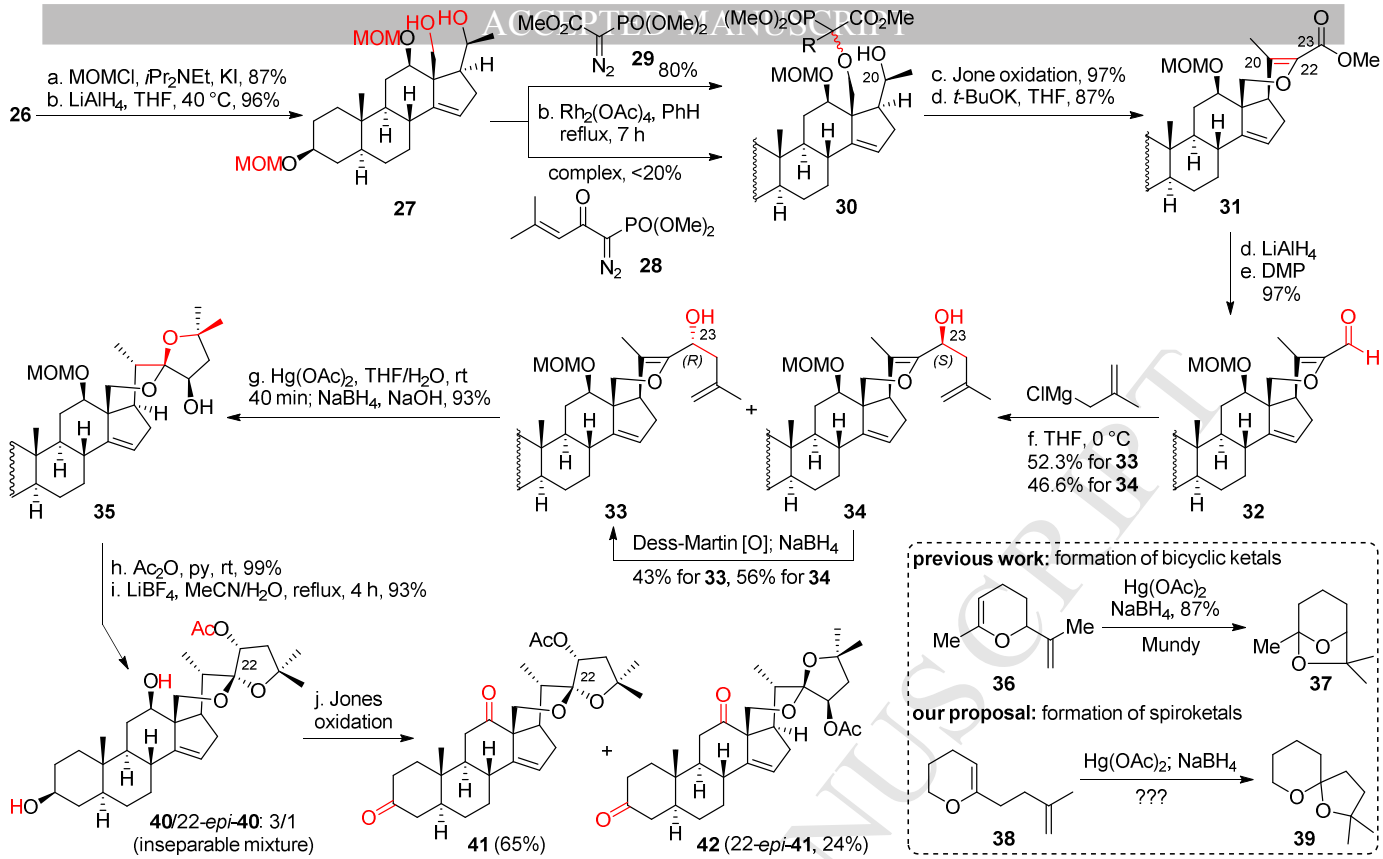
Scheme 2. Introduction of the C14–C15 double bond from C16-ketone.

according to Meystre's hypoiodite method[57] (lead tetraacetate/I_2, *hν*), proximal functionalization of the C18 methyl group in **13** proceeded smoothly, providing lactone **14** in 73–79% yield after Jones oxidation, along with ether **15** in 8–10% yield. Oxidation of ether **15** with $RuCl_3/NaIO_4$ failed to convert it into **14**.[58] Further investigation revealed that the C18 functionalization of C20*S*-alcohols, as in **13**, is of faster reaction rate and higher yield than that of their C20*R*-counterparts. The ease of preparation also made them good choices for this type of reaction.

Various methods have been reported to introduce the C14–C15 double bond from suitable precursors,[59-62] but none from the C16 ketone. Direct dehydrogenation of **14** with DDQ and $(PhSeO)_2O$ was infeasible, presumably due to the difficulty in forming enolate at the D ring. We then tried to introduce the C15–C16 double bond and to migrate it to C14–C15 position (Scheme 2). Shapiro reaction, a straightforward method to convert ketones into double bonds, was also infeasible because the tosylhydrazone of **14** was difficult to prepare. Finally, a stereoselective reduction of **14** with $NaBH_4$ in MeOH–THF afforded the C16β-OH, which underwent mesylation (optimal condition: 3.0 equiv MsCl, 6.0 equiv pyridine, DMAP, CH_2Cl_2, rt) and iodination-elimination (NaI, HMPA, 110–120 °C, 4 h) to introduce the C15–C16 bond, giving **18** in 92% yield over three steps.

Allylic oxidation of **18** with CrO_3 in the presence of a catalytic amount of *N*-hydroxysuccinimide (NHS) delivered the unsaturated enone **19** in good yield, but we failed to remove its C16-carbonyl group via forming a thioketal and Raney Ni-mediated reduction. We assumed that an allylic bromination/debromination sequence would be the solution. Treating **18** with *N*-bromosuccinimide (NBS) and benzoyl peroxide (BPO) in refluxing tetrachloromethane produced a less polar product **21** (TLC), which was unstable and converted into allylic alcohol **22** in 89% yield after aqueous workups, presumably via an allylic bromination/S_N2' reaction. Attempt to reduce the crude bromide **21** in situ with Zn/HOAc in MeOH formed only the C16α methyl ether; and treatment of the crude **21** with EtSH in the presence of DBU formed thioether **23** as a mixture of C16 epimers, the reduction of which with Raney Ni/H_2 system could not remove the thioether group at C16. Albeit not usable in this synthesis, this reaction was successfully adopted in our glaucogenin project.[52]

To migrate the double bond of **18** from the disubstituted C15–C16 position to the trisubstituted C14–C15 position, we investigated several typical conditions (TsOH, HCl,[59] I_2[63], $PdCl_2(PhCN)_2$[64] and $RhCl_3$[65-67]). All failed. However, although $RhCl_3$-catalyzed double bond migration (10 mol% $RhCl_3$ in EtOH, 72–78 °C, 24 h) did not work on **18**, it worked well on **24**, whose C3 and C12 hydroxyl groups were exposed, giving the desired Δ^{14}-lactone **26** in 82% yield on multigram scale, along with a small amount of 3-oxo byproduct **25** (*ca.* 5%). This result indicated that the rhodium(I) (generated by oxidizing the substrate) might be the real active catalyst and that ethanol could not be oxidized to generate the Rh(I). To test this hypothesis, we



Scheme 3. Completion of the synthesis of the protected south part **41**.

used isopropanol as solvent; the reaction of **18** indeed took place, but could only reach 90% conversion rate after heating at 100 °C for 24 h. Furthermore, adding a small amount (5–10 mol%) of dihydropregnenolone to the reaction mixture could dramatically accelerate the reaction of **18** and progesterone was isolated as byproduct.

With the C14–C15 double bond being installed, focus turned to facile construction of the E ring. When synthesizing cephalostatin 1, Fuchs and co-workers have developed an elegant and unified procedure to build the E ring, from 16,20-diol for north part and from 18,20-diol for south part, namely employing a sequence involving selective Rh-mediated insertion reaction of α-diazophosphate ester, Jones oxidation, and intramolecular Horner–Wadsworth–Emmons (HWE).[62] Finding no better approach, we borrowed this strategy.

Diol **26** was protected as MOM ethers and treated with $LiAlH_4$ to furnish 18,20-diol **27** in high yield (Scheme 3). Direct introduction of the side chain to diol **27** by selective oxidation of C20-OH and intra- or intermolecular HWE reaction was fruitless. Reaction of **27** with **28** afforded the desired product in low yield. We thus referred to Fuchs' procedure and prepared pentacyclic aldehyde **32** from diol **27**. Reaction of α-diazophosphate ester **29** with diol **27** smoothly provided the desired insertion product **30** as a mixture of diastereomers which was subjected to Jones oxidation to give C20 ketone in high yield. Treatment of the crude ketone with sodium hydride in THF for four hours (Fuchs' condition) did not afford the desired **31** in our hands. Instead, we found *t*-BuOK to be a better base for our substrate, furnishing **31** at 0 °C in 30 min and 87% yield. Meanwhile, Masamune–Roush condition (DBU, LiCl, CH_2Cl_2)[68] was equally effective for this HWE reaction. Reduction of **31** with $LiAlH_4$ followed by Dess–Martin oxidation gave **32** in 97% yield.

To introduce the C24–C27 unit and the C23*R*-OH, we examined various methylallylation procedures and none of them exhibited apparent selectivity. The optimal condition was the reaction with methylallylmagnesium chloride at 0 °C, affording separable **33** and **34** (23-*epi*-**33**) as a 1.1/1 mixture in nearly quantitative yield. The C23 stereochemistry of **33** was secured by X-ray crystallography of its 3-hydroxyl derivative to be the desired *R*. Reaction at lower temperature (−20 °C) gave a 2/3 mixture favoring the unwanted **34**. Unable to achieve by Mitsunobu inversion, converting **34** into **33** was realized by Dess–Martin oxidation and $NaBH_4$ reduction in 43% yield (with 56% **34** recovered). The poor stereoselectivities observed herein indicated no dominant inherent facial bias in substrates like **32**, which were in agreement with the results reported by Fuchs and Shair.

We then focused on the construction of the spiroketal moiety from **33**. Mundy and co-workers have reported a tandem oxymercuration-solvomercuration protocol to construct bicyclic ketals from enol ethers (Scheme 3).[69] We envisaged that a similar procedure performed on cyclic enol ethers with alkenyl side chain at 2-position would provide best chance to yield spiroketals in single operation. As we expected, treatment of **33** with 2.2 equiv of mercuric acetate in a solution of degassed THF followed by reduction with $NaBH_4$ in aqueous NaOH solution afforded **35** in 93% yield. The stereochemistries at C20 and C22 of **35** were confirmed by X-ray crystallography of its 3-silyl ether derivative, which were similar to those reported by Fuchs (via acid-mediated cyclization) and Shair (via a bromoetherification/reductive debromination sequence). The observed stereochemical outcome at C20 might result from oxymercuration from the less hindered convex face of the dihydropyran E-ring. It was noteworthy that reaction of **34** under the same condition was much slower and with poor selectivity, giving a mixture of many isomers, suggesting that the C23*R*-OH might play an important role on the

formation of C22-configuration, presumably via the interaction between the C21 methyl group and the C23*R*-OH.

Another observation on this reaction worth further investigation was that only 50% of **33** was transformed into **35** when 1.1 equiv of $Hg(OAc)_2$ was used. We assumed that the reaction might not simply proceed via an oxymercuration of enol ether-solvomercuration of the C25–C26 double bond-spiroketal formation sequence, but via some more complex mode.

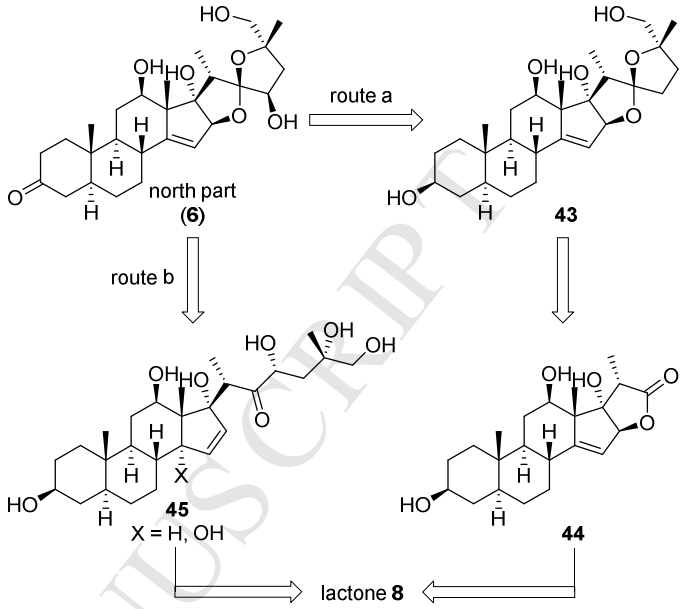
The C22 spiroketal of south part **41** is in a thermodynamically favorable configuration, therefore, the *S*-configured C22 of **35** could epimerize to the more stable *R*-configuration under suitable acidic conditions. After protecting its C23-OH as acetate, **35** was submitted to a series of acid-catalyzed equilibration conditions. Some reagents (BF_3•Et_2O, Tr^+BF^-, BBC, Dowex-50W, etc.) gave complex mixtures of partially deprotected (of the acid-labile MOM ethers) and epimerized products, and some (PPTS or CSA in *t*-BuOH) resulted in partial deprotection of C23 acetate. Finally, treating **35** with $LiBF_4$ in refluxing aqueous acetonitrile for 4 h removed the MOM ethers and epimerized the C22 stereocenter in one pot, leading to an inseparable 3/1 equilibrium mixture of **40** (C22*R*) and its C22-epimer (22-*epi*-**40**, C22*S*) in 93% yield. Longer reaction time or higher temperature could not improve the ratio, indicating a relatively stable equilibrium. Jones oxidation of the mixture provided south part **41** (less polar product) and its C22-epimer **42** in 65% and 24% yield, respectively. Our procedure for establishing the spiroketal of **41** from **33** required only four steps.

2.2. Synthesis of the North Part of Cephalostatin 1

The north part **6** exists in 18 cephalostatins and, indicated by the structure-activity relationship (SAR) research, is strongly associated with the most potent antitumor activity of these natural products. An efficient synthesis is thus important. As mentioned above, our synthetic studies started with the steroidal lactone **8**, whose functionalities at C16 and C22 were considered as good handles to build the DEF-ring functionalities of **6**. During our course of studies, two routes have been explored (Scheme 4). In route a, we first introduced the C14–C15 double bond and C17α-OH, reaching another lactone **44**, from which we established stepwise the needed C23-OH and F ring. In route b, we tried to prepare a well-tailored substrate **45** and to construct the EF rings simultaneously from it.

A robust method of preparing lactone **8** from hecogenin **9** was thus crucial for us. Dinorcholanic lactones, to which **8** belongs, are versatile intermediates that preserve all the stereocenters on the ring E of steroidal sapogenins, and thus received much attention from synthetic chemists. Several methods were reported[70-81] and our solution is an abnormal Baeyer–Villiger oxidation of steroidal sapogenins[82]. In the presence of a catalytic amount of iodine and H_2SO_4, oxidation of rockogenin diacetate **10** with freshly prepared peracetic acid afforded the desired **8** after a sequential saponification on 200 g scale and in 84% yield (Scheme 5).

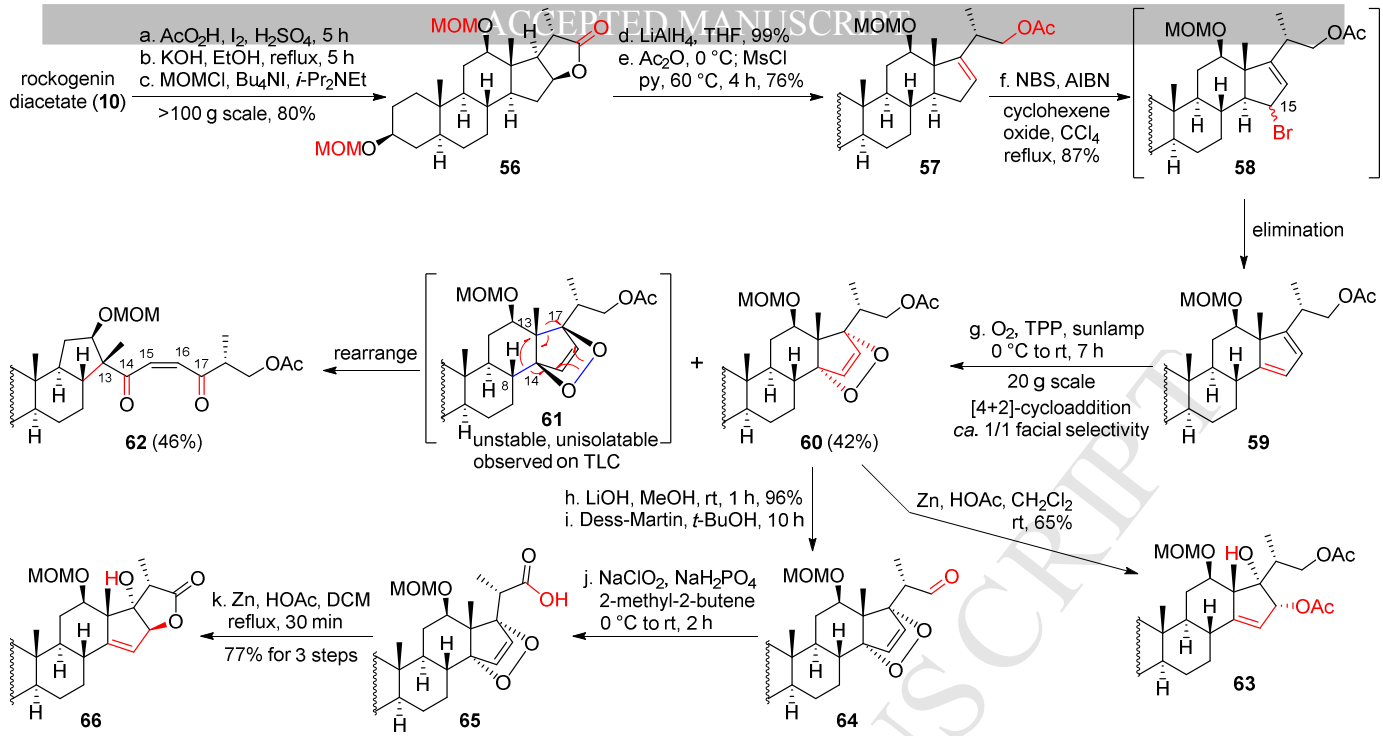
A plausible mechanism of this oxidation is illustrated in Scheme 6. We reasoned that the iodination at C23 during the reaction elevated the migratory aptitude at C23, hence altered the inherent regioselectivity of the oxidation. In acidic medium, the F ring of steroidal sapogenin (**10** as example) was opened to form an oxonium ion **46**, to which the addition of peracid generated a Criegee intermediate **47**. Then migration of the tertiary C20 from carbon to oxygen gave 16,20-diol **7** (as esters) and acid **48**. In the presence of iodine, however, **46** was first iodinated at the C23 and the resultant **50** was then attacked by peracid, forming another Criegee intermediate **51**. Migration of the iodinated C23 in **51** led to the formation of **52**, which, upon hydrolysis, released lactone **8**, iodide ion, and aldehyde **53**. The iodide ion and **53** were oxidized by peracid to regenerate iodine and to provide acid **54**, respectively. Therefore, at least 3 equiv of the peracid was needed.



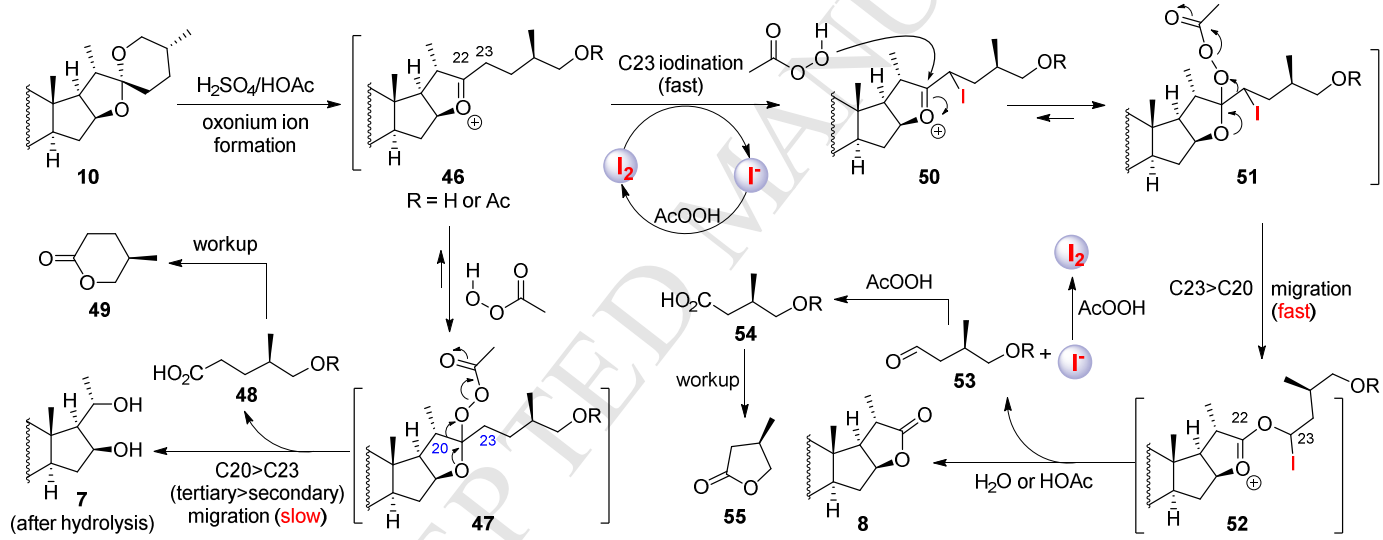
Scheme 4. Synthesis Plans for North Part **6** from Lactone **8** (protecting groups are omitted)

Since the oxidation of **10** could go both directions to give **7** and **8**, how could catalytic amount of iodine switch the reaction direction so thoroughly that no **7** was detected? The accepted two-step mechanism of Baeyer–Villiger oxidation tells that formation of Criegee intermediate is reversible and migration is rate determining.[83-84] We thus assumed that the migration of C23 in **51** was much faster than the migration of C20 in **47**. As the generations of Criegee intermediates **47** and **51** were reversible, the reaction was therefore driven to the formation of **8**.

With lactone **8** in hand, we first tried to introduce the required functional groups on its D ring. Its C3-OH and C12-OH were protected as MOM ethers under standard condition (MOMCl, Bu_4NI, *i*-Pr_2NEt, DCM, reflux) to afford **56**, which could be easily recrystallized from ethanol/hexane. Various conditions were investigated to open the lactone ring directly, however, all of them met with failure. Therefore, **56** was reduced with $LiAlH_4$. The primary C22-OH of the resultant diol was selectively protected as acetate, and the C16-OH was converted into mesylate in pyridine, which, at elevated temperature, spontaneously underwent elimination in the same pot to furnish steroid-16-en-22-acetate **57** in 76% yield. Attempting to introduce a bromine atom at the allylic C15, we treated **57** with *N*-bromosuccinimide (NBS) and azobisisobutyronitrile (AIBN) in refluxing tetrachloromethane for 10 hours, and found that the reaction introduced not the allylic bromide but a conjugated double bond at C14–C15 via a one-pot allylic bromination-elimination process. Because the reaction released hydrogen bromide that would pull the acid-sensitive MOM ethers down, cyclohexene oxide was added as an acid scavenger. This improvement allowed us to obtain diene-22-acetate **59** in 87% yield on the 20 g scale.



Scheme 5. Synthesis of north part.



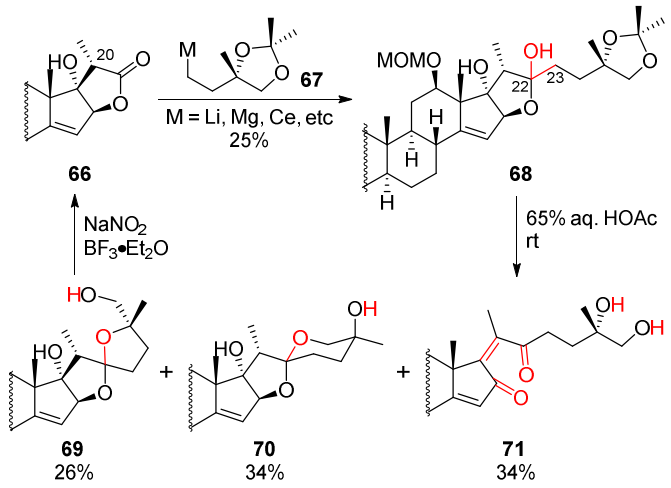
Scheme 6. Plausible mechanism of abnormal Baeyer–Villiger oxidation of steroidal sapogenins

Selective oxidation of the C16–C17 double bond in diene **59**, either via direct epoxidation or with C22-OH as directing group, suffered from low yield and poor selectivity. Treatment of **59** with singlet oxygen (O_2, TPP, sunlamp) also exhibited poor facial selectivity, giving the desired α-adduct **60** in 42% yield. The β-adduct **61**, however, disappeared during the reaction, and a rearrangement product **62** was isolated in 46% yield instead. We assumed that the O–O bond of **61**, with high structural tension, underwent homogeneous cleavage to generate two oxygen radicals, which triggered the another homogeneous breakage of C14–C8 and C17–C13 bonds to form ketones at C14 and C17, and the union of resultant radicals at C8 and C13 formed this exquisite tricyclic framework. We also tested the facial selectivity of the [4+2] cyclization on dienes with different protecting group at C22-OH and found that most of them (acetate, benzoate, benzyl ether, TBS ether, etc.) exhibited poor selectivity. As the reaction could be performed at multigram scale, we accepted this result.

Reduction of the α-adduct **60** with Zn/HOAc system in CH_2Cl_2 gave Δ^{14},16α-OAc product **63** in moderate yield. We reasoned that an intermolecular S_N2' reaction occurred at C16 between the resultant 14,16-diol and acetate acid, and we wanted to make it intramolecular. Therefore, **60** was hydrolyzed with LiOH in MeOH/THF, then submitted to Dess–Martin oxidation and Pinnick oxidation to afford the corresponding acid **65**. Treatment of **65** with Zn/HOAc in reflux CH_2Cl_2 triggered an intramolecular S_N2' reaction, furnishing lactone **66** in 74% yield from **60**.[85]

We then investigated the installation of C23–C27 side chain on **66** via a nucleophilic addition with **67** (Scheme 7). As **66** enolizes easily under basic conditions, it resists nucleophilic addition of metallic reagents. After much optimization on metallic reagents, the desired **68** was isolated in low yield, along with substantial amount of 20-*epi*-**66** (61%). Treatment of **68** with 65% aqueous solution of HOAc at room temperature provided 5/5-spiroketal product **69** (26%), 5/6-spiroketal product

70 (north part of cephalostatin 7 and ritterazine K, 34%), and diketone **71** (34%).



Scheme 7. Attempts of introducing ring F from lactone **61**

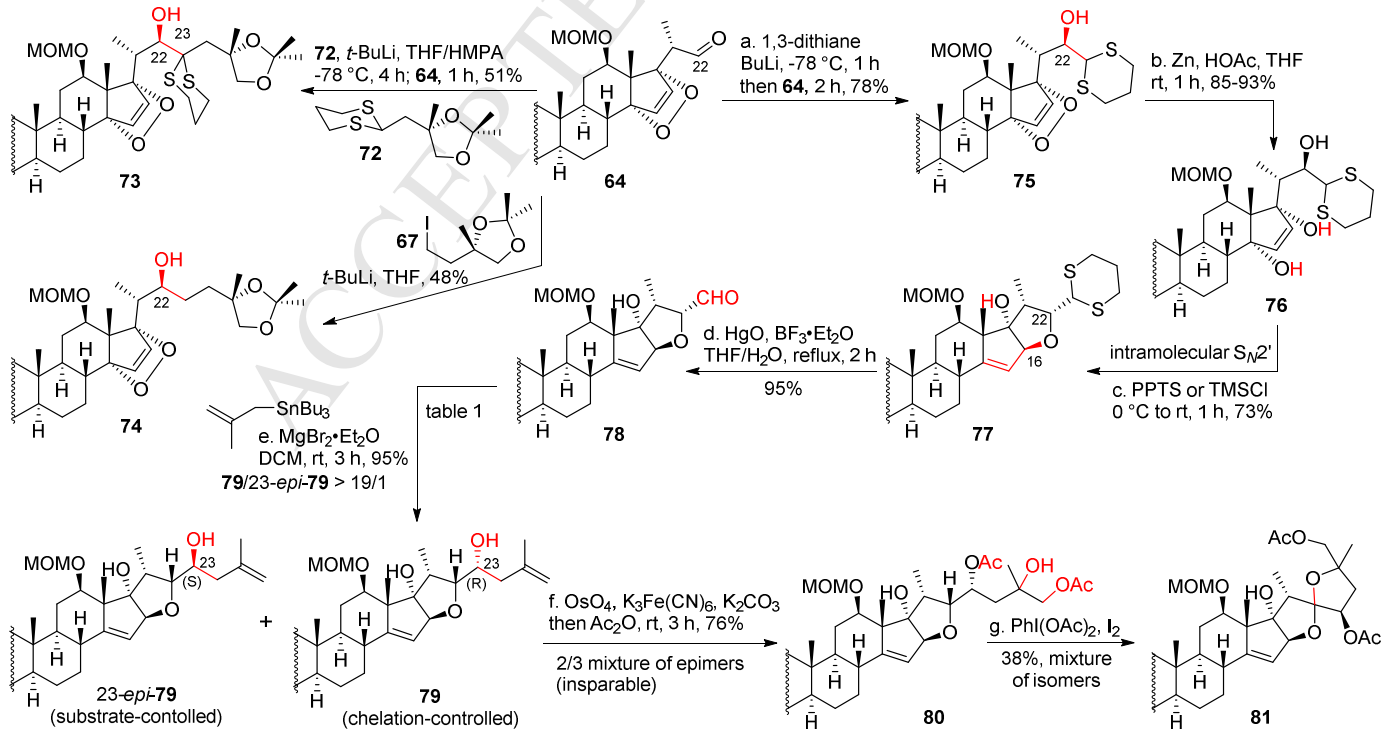
Further treatment of **69** with $NaNO_2/BF_3$•Et_2O, a routine process to introduce a ketone at C23 of steroidal sapogenins,[86] resulted in the excision of the F ring, returning to lactone **66**. Although both **69** and **70** were useful in the cephalostatin synthesis, the addition reaction was low-yielding and the product distribution of the following cyclization was uncontrollable, hence, prompting us to explore a more efficient route. With these concern, we went back to aldehyde **64** for further investigation.

Aldehyde **64** underwent nucleophilic addition with lithium reagents derived from dithiane **72** and iodide **67** to provide **73** and **74** in moderate yields (Scheme 8). Because reduction of their O–O bonds gave complex mixtures and deprotection of *S*,*S*-ketal of **73** was problematic, we decided to adopt a stepwise strategy that introduces functional groups separately. This alteration would simplify the functional-group manipulations and give us more candidate reactions and better control on the stereochemical outcome.

Addition of aldehyde **64** with the lithio anion of 1,3-dithiane provided the desired Felkin–Anh adduct **75** in 78% yield over two steps (from alcohol, as **64** is unstable, it was used without purification), on multigram scale. Treatment of **75** with Zn/HOAc in CH_2Cl_2 did not lead to **76** or **77**, but gave a complex mixture. We reasoned that the acidity of the reaction medium might be the main cause, which could be buffered with solvents having certain Lewis basicity. As expected, carrying out the Zn/HOAc reduction of **75** in ether or THF at room temperature cleanly provided the 14α,17α-diol **76** in high yield. It was noteworthy that **76** was stable enough in this reduction system that it could stand refluxing for several hours. Treating **76** with pyridinium *p*-toluenesulfonate (PPTS) or TMSCl in CH_2Cl_2 triggered the intramolecular S_N2' reaction to give the desired cyclization product **77**. The C22-stereochemistry was verified as *R* through a 2D NOESY analysis.

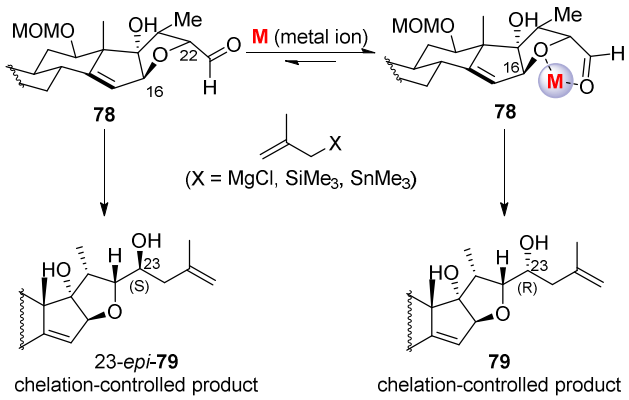
Hydrolysis of **77** to aldehyde **78** posed some difficulties. Commonly reported conditions such as $HgCl_2/CaCO_3$, NBS, $NCS/AgNO_3$, $PhI(TFA)_2$, and $MeI/CaCO_3$ were unsuccessful and failed to produce any aldehyde signal (NMR analysis) from **77**. When using $PhI(TFA)_2$ and MeI conditions, **77** disappeared on TLC but no aldehyde detected, presumably due to the formation of corresponding oxidized and methylated derivatives which resisted hydrolysis. Finally, the deprotection was accomplished in 95% yield by treating **77** with HgO/BF_3•Et_2O in reflux THF.[87] The stereochemistry at C22 retained during the deprotection step and no isomerization was observed during several-month storage.

With aldehyde **78** in hand, focus was turned to stereoselective introduction of the C23-OH and the 25,26-vicinal diol unit. We envisioned that a chelation-controlled methylallylation would give **78**, a α-chiral aldehyde, the chiral C23-OH, which in turn



Scheme 8. First-generation synthesis of the north part.

would serve as a handle to control the stereochemistry of the 25,26-vicinal diol (Scheme 9). Treatment of **78** with 2-methylallylic Grignard reagent in THF at −78 °C afforded an inseparable 1.0/3.3 mixture of isomers favoring the undesired 23*S*-stereoisomer 23-*epi*-**79** in 90% yield (Table 1, entry 1). Elevating the reaction temperature or premixing the aldehyde with $MgBr_2$ slightly improved the 23*R*-selectivity (entries 2–4), but the inherited 23*S* product still dominated. A changeover of the selectivity was made by performing the reaction in DCM, affording a 7.3/1 mixture of isomers favoring the desired 23*R*-isomer **79**.



Scheme 9. Methylallylation Models for Aldehyde **78**

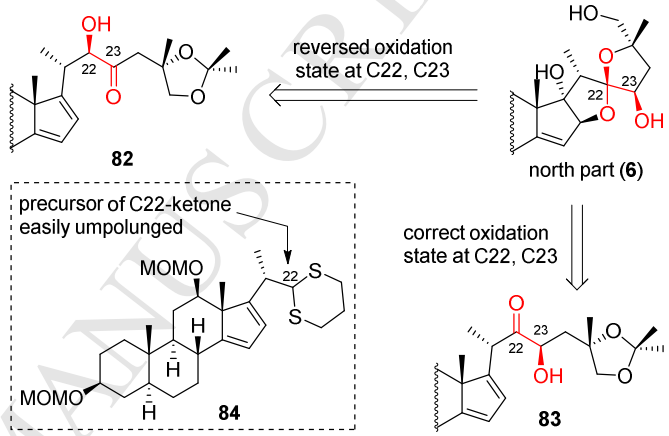
Table 1. Methylallylation of aldehyde **78**

Entry	Conditions	Results (*R*:*S* by NMR)
1	methylallyl-MgCl, THF, −78 °C, 14 h	90% (1.0:3.3)
2	methylallyl-MgCl, THF, 0 °C, 10 h	100% (1.0:1.8)
3	methylallyl-MgCl, THF, reflux, 2 h	93% (1.0:1.3)
4	methylallyl-MgCl, $MgBr_2$•Et_2O, THF, −78 °C, 2 h to RT	100% (1.0:2.3)
5	methylallyl-MgCl, DCM, −78 °C, 6 h	90% (1.0:1.0)
6	methylallyl-MgCl, $MgBr_2$•Et_2O, DCM, −78 °C, 6 h	83% (7.3:1.0)
7	methylallyl-TMS, $MgBr_2$•Et_2O, DCM, −78 °C to RT	No Reaction
8	methylallyl-TMS, $SnCl_4$, DCM, −78 °C	40% (5–6:1)
9	methylallyl-TMS, $TiCl_4$, DCM, −78 °C	< 20% (10:1)
10	methylallyl-$SnMe_3$, $MgBr_2$•Et_2O, DCM, RT, 3 h	95% (>19:1)

Sakurai allylation and Keck allylation were also evaluated, as shown in entries 7–10. Due to the low reactivity of trimethyl(2-methylallyl)silane, relatively strong Lewis acids ($SnCl_4$ and $TiCl_4$)[88] should be used to activate the aldehyde group, which brought about deprotection of acid-labile MOM ethers and epimerization of C22. On the other hand, under the activation of $MgBr_2$•Et_2O in CH_2Cl_2, treating **78** with trimethyl(2-methylallyl) stannane provided **79** in high yield and stereoselectivity.

We then evaluated several asymmetric dihydroxylation systems to install the last two hydroxyl groups on **79** and disappointingly found that none of them gave usable stereochemical selectivity and the isomers were inseparable (best result: 2/3, the stereochemistry was not identified). After acetylation of C23-OH and C26-OH, the inseparable mixture of epimers **80** could undergo Suárez iodine(III) oxidation[25, 89] to form a mixture of 5/5-spiroketals in moderate yield, but the configurations of these products were unable to assign. Hydroxyl group-directed epoxidation and intramolecular halogenation of the homoallylic alcohol unit (**79**), and Mukaiyama aldol of **78** with hydroxyacetone derivative and asymmetric methylation of the resulting β-chiral ketone also failed to achieve the desired stereochemical control.

Our stepwise strategy had all kinds of selectivity issues, and this detour provided an opportunity to scrutinize our original design concept. As depicted in Scheme 10, to establish the EF-spiroketal unit of **6** from intermediate **82**, exchanging the oxidation states at C22 and C23 was required, which not only brought about many unexpected difficulties but also was not attractive in strategic level. To elevate the redox-economy[90], we put on schedule the preparation of compounds **83**, which has the correct oxidation states at C22 and C23, through the coupling of dithiane **84** and a properly protected β-chiral aldehyde.

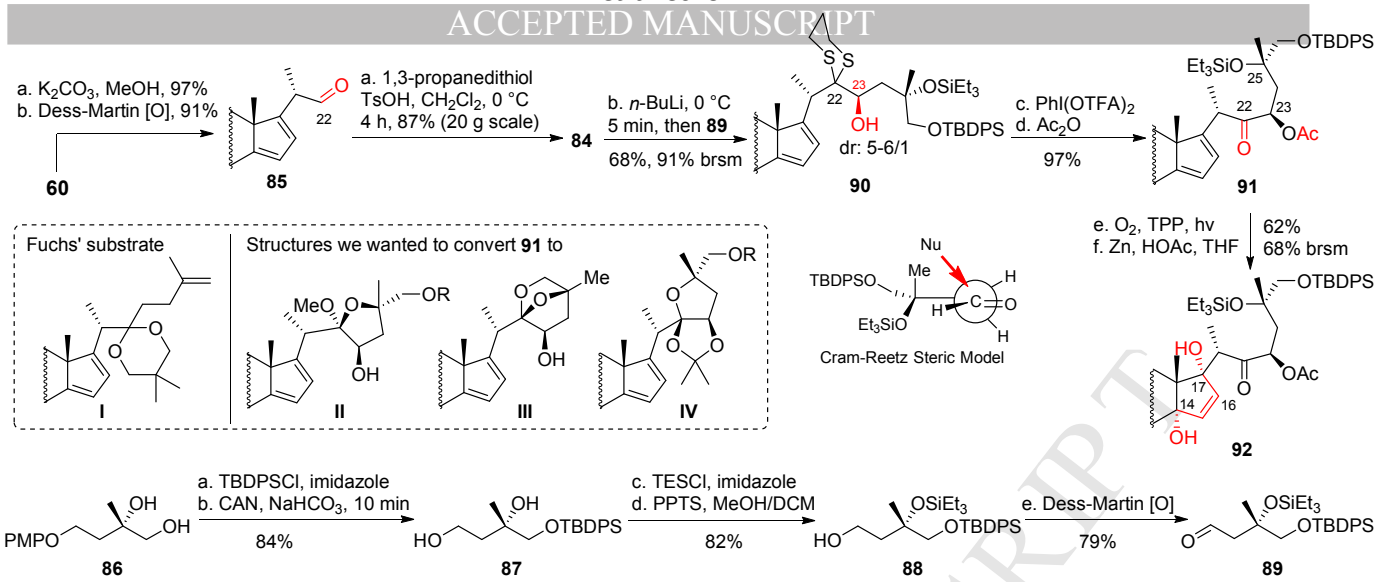


Scheme 10. Concerns about Oxidation States at C22, C23

Our preparation of the β-chiral aldehyde **89** started with the known diol **86** (Scheme 11).[91] The primary OH was protected as a TBDPS ether and the PMP group was removed by CAN oxidation. Then, the exposed OHs were protected as TES ethers, and the primary one was removed upon treating with PPTS in MeOH/DCM (1/40). Dess–Martin oxidation of the resulting **88** provided **89** in 54% yield from **86**. Similar aldehydes with the vicinal diol being protected as isopropylidene, cyclopentylidene, or cyclohexylidene ketals were also prepared.

To prepare dithiane **84**, compound **60** was subjected to hydrolysis and Dess–Martin oxidation. Treatment of the resultant 22-aldehyde **85** with 1,3-propanedithiol in the presence of 0.1 equiv of TsOH in CH_2Cl_2 at 0 °C for 4 h, without affecting the acid-labile MOM ethers, afford **84** in 87% on the multigram scale.

As the bulkiness of the steroidal skeleton might make the metalation of **84** difficult, to probe the efficiency of forming the desired lithiated derivative, we performed a D_2O quenching experiment, leading to the conclusion that the lithiated species was short-lived and required quick trapping with the nucleophilic partners. After treating **84** with *n*-BuLi at 0 °C for 5–10 min, **89** was added to the reaction mixture, delivering an inseparable 5–6/1 mixture of epimers. The major epimer was assigned as 23*R*-configured by a late-stage intermediate; the stereochemical outcome could be rationalized by Cram–Reetz steric model.[92-95] When other aldehydes (isopropylidene, cyclopentylidene, or cyclohexylidene ketals) were used, the reaction gave a *ca*. 1/1 mixture of the inseparable diastereomeric alcohols.

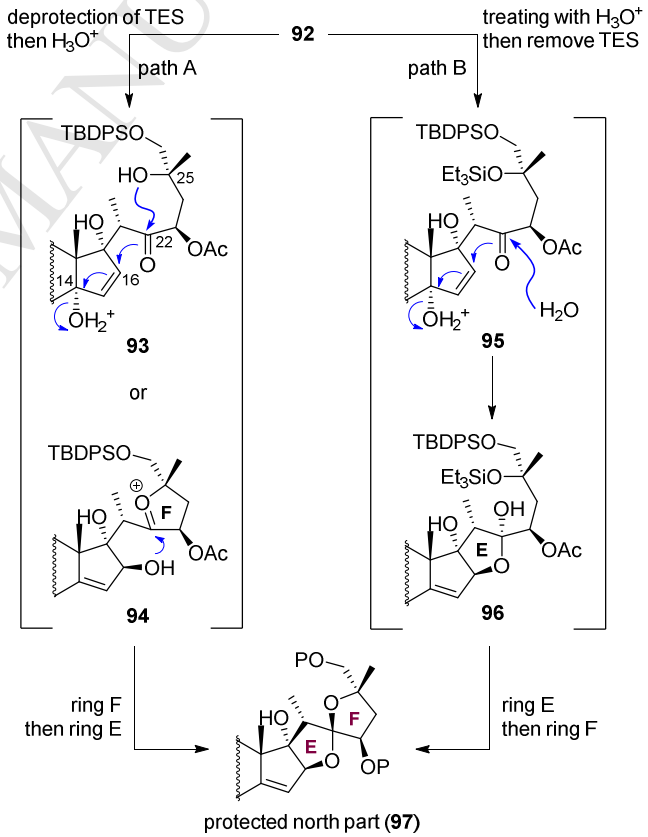


Scheme 11. Synthesis of the north part.

In a synthesis of cephalostatin 7, Fuchs and co-workers submitted several substrates, represented by diene **I** in Scheme 11, to [4+2] cycloaddition with singlet oxygen, and found that C22 ketal rings could shield the upper face of the D-ring dienes to achieve the exclusive α-facial selectivity control in cycloaddition reactions.[27] It was desirable to employ the C22 thioketal ring in **90** to do the same job. Moreover, considering that thioketal could also be unmasked with oxygen and irradiation (the cycloaddition condition), and that both reductive cleavage of the O–O bond and the EF-ring spiroketalization could take place in acidic medium, we hypothesized that these steps could be compressed in one pot to convert **90** into **6** directly. But, the reality was not as attractive as the hypothesis. Treatment of diene **90** with singlet oxygen delivered a very complex mixture. Reasoning that the complexness might be caused by incomplete oxidation of sulfur atoms, we performed an extra dethioketalization step but isolated no identifiable product. We had to perform these reactions step by step.

Oxidative dethioketalization of **90** ($PhI(OCOCF_3)_2$, $CaCO_3$, MeCN/water) followed by acetylation of the C23-OH afforded **91** in 97% yield. The cycloaddition of **91** with singlet oxygen (TPP in CH_2Cl_2, sunlamp, −78 °C) delivered a readily separable 2.5–4.5/1 mixture of isomers (by ^1H NMR analysis of the crude product) favoring the desired α-adduct. In THF, reduction of the crude product with Zn/HOAc gave **92** (dr 10/1) in 62% yield on the multigram scale. In order to improve the facial selectivity of the cycloaddition, we also tried to transform the side chain of **91** to cyclic systems **II**–**IV**, an interesting attempt which proved difficult and inefficient and was abandoned quickly.

With multigram of **92** in hand, we turned to construct the 5/5 spiroketal. As **92** already contains all the functionalities that needed to build the desired spiroketal, we conceived two paths to reach the protected north part **97**, as depicted in Scheme 12. Path A was an F-ring-then-E-ring tactic, where the TES ether was selectively deprotected and, under acidic medium, the exposed C25-OH would attack the C22 ketone either to trigger a cascade ketalization/intramolecular S_N2' process to reach **97** (via **93**), or to form a F-ring hemiketal which reacted with C16-OH, generated by intermolecular S_N2' reaction on D ring with water, to form the E ring (via **94**). In contrast, path B featured an E-ring-then-F-ring tactic, in which **92** initially underwent intramolecular S_N2' reaction (or intermolecular S_N2' reaction with water then form hemiketal) to generate an E-ring hemiketal **96**, and its TES ether was deprotected and the F ring was closed to yield **97.**



Scheme 12. Possible Paths of Spiroketal Formation

Selective deprotection of the TES ether of **92** without affecting the adjacent TBDPS ether proved quite challenging (Table 2). Treatment of **92** with tetrabutylammonium fluoride (TBAF) in THF showed no selectivity, and running the reaction at low temperature showed no improvement (entry 1). When buffering TBAF with acetic acid or employing other deprotection conditions ($Et_3N{\cdot}3HF$, HF·pyridine, SiO_2, etc.), we recovered **92** completely (entries 2–5).

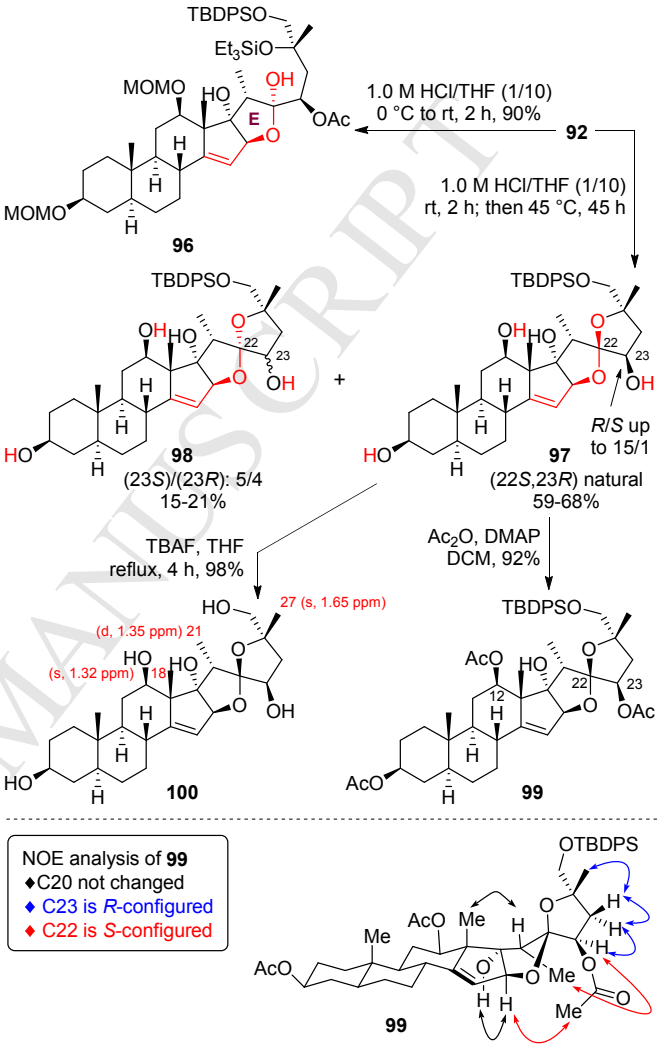
Table 2. Conditions for Spiroketal Formation

entry	Conditions	Results [a]
1	TBAF (1.0–2.0 or 5.0 equiv), THF, −78 to 0 °C	nonselective desilylation
2	TBAF, HOAc, THF, rt, 24 h	No Reaction
3	$Et_3N·3HF$ (22 equiv), THF, rt, 6 d	No Reaction
4	$Et_3N·3HF$ (22 equiv), THF, 55 °C, 15 h	No Reaction
5	Silica gel, DCM, rt, 24 h	No Reaction
6	20 equiv HOAc, DCM or DCM/*i*-PrOH, rt, 24 h	No Reaction
7	PPTS, DCM/MeOH (20:1), rt	MeOH anticipated S_N2', TES retained
8	2 equiv PPTS, THF/H_2O, rt to 40 °C	complex (S_N2', TES retained)
9	HOAc:THF:H_2O (8:1:1), rt	complex (**96**)
10	HOAc:THF:H_2O (3:3:1), rt	clean (50% **96** isolated)
11	CH_3CN, HF (1.2 to 12 equiv), 0 °C to rt	complex (**96**)
12	CH_3CN, HF (12 equiv), 60 °C, 1.5 h	**97** (23-OAc, mixture)
13	PPTS (10 to 20 equiv), *t*-BuOH, rt to 80 °C, 10 h	complex, all PGs cleaved
14	1 M aqueous HCl/THF (1/10), 0 °C to rt, 2 h	**96** (90%)
15	1 M aqueous HCl/THF (1/10), 0 °C 2 h; 45 °C, 27 h	**97** (5/1 dr)
16	1 M aqueous HCl/THF (1/10), 45 °C, 40–50 h	**97** (15/1 dr)
17	**96**, 1 M aqueous HCl/THF (1/10), 45 °C, 40–50 h	**97** (15/1 dr)

[a]Based on thin layer chromatography (TLC) and ^1H NMR analysis of the crude product.

Several acidic conditions triggered the intramolecular or intermolecular S_N2' reaction with solvent (methanol and water) on D ring, with the acid-labile protecting groups (MOM ethers, TES ether, and acetate) being deprotected in different degree, therefore producing complex mixtures in most cases (entries 7–13). Further optimization revealed that treatment of **92** in THF with 1 M HCl solution at 0 °C for two hours cleanly afforded **96** in 90% isolated yield (entry 14, and Scheme 13). Elevating the temperature to 45 °C produced a complex mixture (more than eight spots on TLC plate) in two hours; longer reaction time greatly simplified the reaction, showing two spots on TLC plate after 24 hours. The major spot (more polar) was assigned as an inseparable mixture of C22*S* isomers (**97**/23-*epi*-**97**: 5/1), and the minor one an inseparable mixture of the former's C22*R* counterparts (entry 15). Reacting for another 20–24 hours at 45 °C, the ratios of the products were improved (**97**/23-*epi*-**97**: up to 15/1, **98** as a *ca*. 1/1 mixture) and stayed stable (entries 16, 17).[96] Higher temperature and longer time would result in dramatic drop in yield; hence, the optimal condition was therefore set as: 1 M aqueous HCl/THF (1/10), 45 °C, 40–45 h. The reaction was performed on the multigram scale to give **97** in 59–68% yield.

The stereochemistries of **97** was identified through 2D-NOESY analysis of its triacetate **99** to be C22*S*- and C23*R*-configured. The crosspeak between C18-methyl group and C20-H indicated that the configuration at C20 did not change. The crosspeaks between C27-methyl group and C24β-H and between C22-H and C24α-H, along with the fact that the configuration of C25 was known, confirmed that the C23 was *R*-configured, which also supported the structural assignment of **90**. The crosspeaks between C21-methyl group and C23-H and between C16-H and C23-OAc led to the conclusion that the configuration at C22 was *S*. These assignments were further confirmed by comparing the ^1H NMR resonance signals of methyl groups in **100** with those of the known sample and cephalostatin 1.



Scheme 13. Synthesis of North Part

Having four acid-labile protecting groups (C26 TES ether, C23 acetate, and C3/C12 MOM ethers) removed and the EF-ring spiroketal established in the correct configuration, our protocol represented the most efficient way to this challenging structural unit.

Both the configurations of C23 and C25 contribute to the excellent stereochemical outcome of the spiroketal-forming step, we anticipated, as illustrated in Scheme 14. The stereochemistry of C23 would determine from which face of the E-ring oxocarbenium ion the C25-OH would attack C22 to close the F ring, which is the kinetic aspect of the reaction. The 23*S*-configured substrate prefers the lower-face attack, where the repulsive force between the C21 methyl group and the C23 acetate group is minimized, to form the 22*R*-configured spiroketal (via up **TS I** to **98R**), whereas its 23*R* counterpart prefers the upper-face attack to form the 22*S*-configured spiroketal (via down **TS II** to **97**). Since **96** was mainly 23*R*-configured, the spiroketal would be mainly assembled as the needed 22*S*. On the other hand, the products would adopt

conformations that better minimize the interactions among substituents at C20, C22, and C25. To lower the interaction between the C21 methyl group and the C26-OTBDPS group, the C22*S*-configured isomers would adopt the bent conformation, which possesses two anomeric effects, and the C22*R*-isomers adopt the extended conformation, which possesses one anomeric effect. As the 22-epimers were inseparable, **97** and **98**, and **97R** and **98R** were collected separately. According to our results, compound **97** is both the kinetic and the thermodynamic product. However, attempts to convert other isomers to **97** could not give **97** in synthetically usable yields.

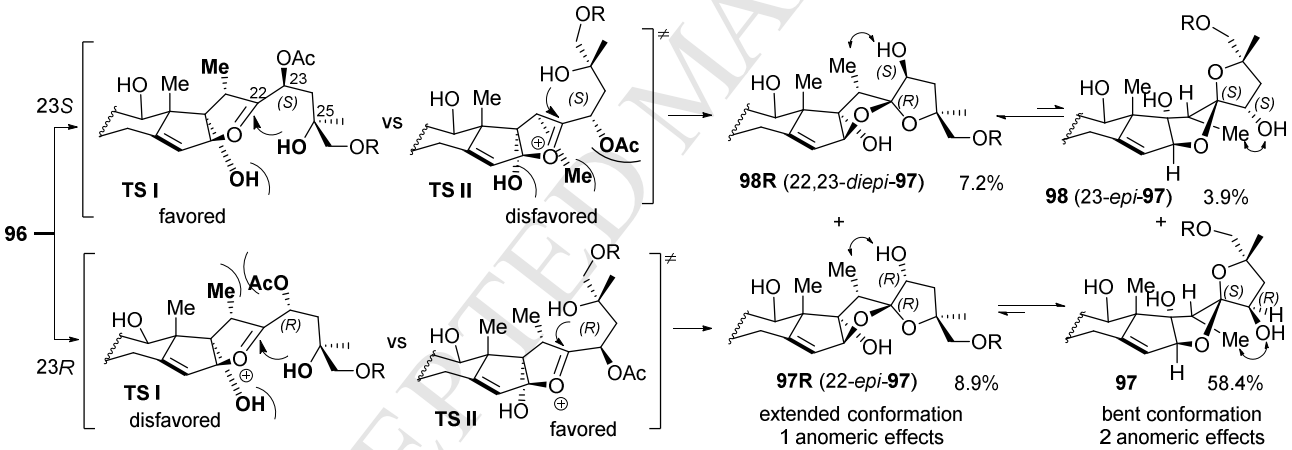
Selective hydrolysis of the C3 acetate in triacetate **99** failed because the C23 acetate was also hydrolyzed easily. We investigated selective oxidation of the C3-OH in **97** and found that treatment of **97** with freshly prepared Ag_2CO_3/Celite in refluxing toluene provided the north part **6** in 92% yield after acetylation of other two secondary hydroxyl groups (Scheme 15). In 13 steps with an overall yield of 18%, we accomplished the synthesis of **6** from **8** and prepared more than 2.5 g of **6** for further exploration.

2.3. Completion of the Synthesis of Cephalostatin 1

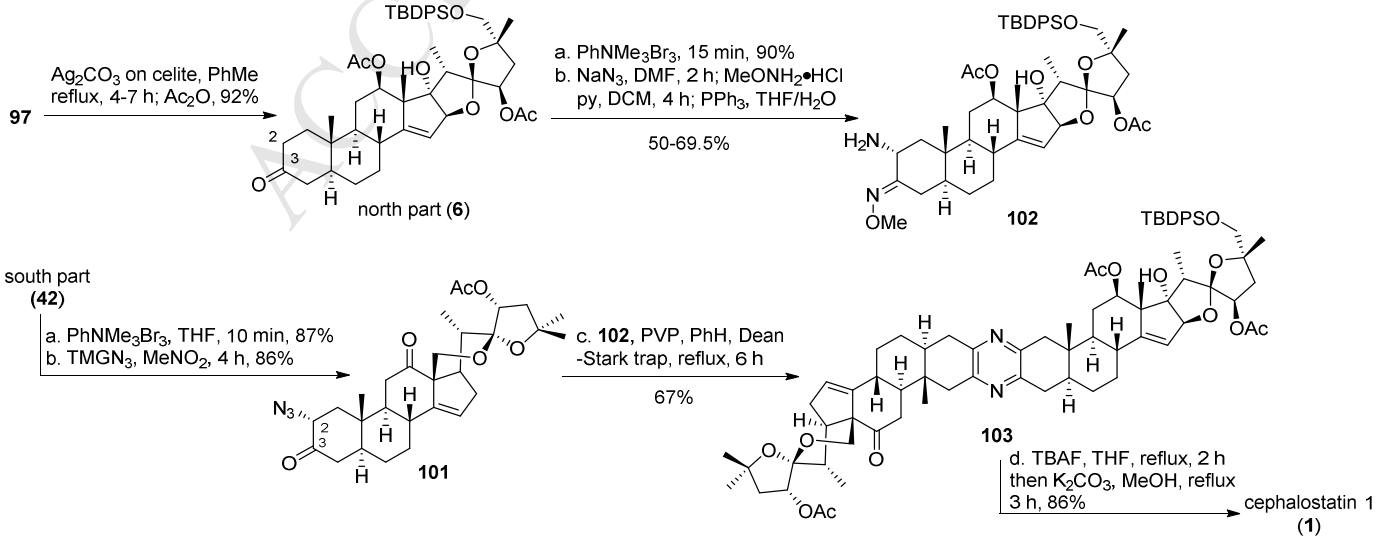
With subunits **42** and **6** in hand, we reached the final stage of the synthesis. Having been extensively investigated and used by Fuchs et al., the pyrazine synthesis was easy to perform, as illustrated in Scheme 15.[35] Adjacent to the easily enolized C3 ketone, the C2 of south part **42** was easily brominated by treating with phenyltrimethylammonium tribromide (PTAB) in THF, and substitution of the resultant α-bromo ketone with tetramethylguanidinium azide (TMGA) in $MeNO_2$[97] provided the α-azido ketone **101** in good yield. In a similar way, we prepared the α-amino methoxime **102** in good yield through a sequence involving bromination at the C2 of **6** with PTAB, substitution with sodium azide in DMF, formation of the C3 methoxime with *O*-methylhydroxylamine, and Staudinger reduction of the azide group. Treatment of the pyrazine coupling partners, **101** and **102**, with polyvinylpyridine (PVP) and Bu_2SnCl_2 in refluxing benzene delivered the protected cephalostatin 1 (**103**) in 67% yield. Removal of the TBDPS group with TBAF and hydrolysis of three acetates with K_2CO_3/MeOH gave (+)-cephalostatin 1 (**1**) in 86% yield. The spectroscopic properties of our synthetic **1** are consistent with those reported in the literature.

3. Conclusion

To summary, we have developed efficient, gram-scale routes to south part **42** and north part **6**, respectively, and thus accomplished a synthesis of cephalostatin 1. Our synthesis presented two controllable and regiodivergent Baeyer-Villiger oxidations of steroidal sapogenins, which could efficiently convert hecogenin either to tetraol **7** or to lactone **8**, both on more than 100 g scale, hence laying a solid foundation for subsequent exploration. In the latter oxidation, iodine tracelessly switches the reaction direction: entering the reaction via *in situ* iodination, being released as iodide ion, and being recycled through oxidation of peracid. Our method provides not only an excellent



Scheme 14. Rational Pathways for Spiroketal Formation (R = TBDPS)



Scheme 15. Completion of the synthesis of cephalostatin 1.

example of using chemical method to alter the inherent migratory preference of Baeyer-Villiger oxidation without adding extra steps, but also a practical and scalable method for preparing dinorcholanic lactones. The lactones prepared through our method have been used in the syntheses of several natural products by us and others.[98-101]

Key steps in the south part synthesis include Rh(I)-catalyzed migration of the C15–C16 double bond to C14–C15 and $Hg(OAc)_2$-mediated spiroketal formation of cyclic enol ethers with alkenyl side chain at 2-position. Key steps in the north part synthesis include umpolung of steroidal moiety to form the C22–C23 bond, [4+2]-cycloaddition of D-ring dienes with singlet oxygen combined with intramolecular/intermolecular S_N2' process to establish the functional groups on D ring, and one-pot construction of the DEF rings. Successful application of cascade reactions (construction of both spiroketals) and one-pot reactions (removal of MOM ethers of **35** together with spiroketal epimerization, allylic bromination and elimination of **57**, etc.) made our synthesis flask-economic and efficient.

In the course of our synthesis, two transformations, although not used in the final route, are notable. First, the C14–C15 double bond, when there is a leaving group at C14, tends to undergo S_N2' reaction, either inter- or intramolecularly (from **21** to **22** and **23**, from **60** to **63**, **65** to **66**, **76** to **77**, and **92** to **96**). Second, the rearrangement of the β-adduct of D-ring diene with singlet oxygen would form an unprecedented tricyclic structure (from **59** to **62**).

4. Experimental section

General Methods: All reactions sensitive to air or moisture were performed in flame-dried round bottom flasks with rubber septum under a positive pressure of argon or nitrogen atmosphere, unless otherwise noted. Air and moisture-sensitive liquids and solutions were transferred via syringe and stainless steel cannula. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone, methylene chloride (DCM), toluene, and 2,6-lutidine from calcium hydride, *N*,*N*-dimethylformamide (DMF) and dimethylsulfoxide from calcium hydride under reduced pressure, acetone from K_2CO_3 onto activated 3Å molecular sieves, others according to the standard procedures described in *Purification of Laboratory Chemicals*. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates using UV light as visualizing agent and an ethanolic solution of phosphomolybic acid, and heat as developing agents. NMR spectra were recorded on 300 MHz or 400 MHz instrument and calibrated using residual undeuterated solvent as an internal reference [^{1}H NMR: $CHCl_3$ (7.26), DMSO-d_6 (2.50); ^{13}C NMR: $CDCl_3$ (77.16)]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad.

*4.1.1. Enone **19***

To a solution of alkene **18** (200 mg, 0.47 mmol) in acetone/H_2O (1.8 mL/0.20 mL) were added *N*-hydroxysuccinimide (59 mg, 0.51 mmol) and a solution of CrO_3 (186 mg, 1.86 mmol) in acetone/H_2O (5.6 mL/0.60 mL). The mixture was stirred at 40-45 °C for 20 h, filtered, and washed with acetone. The filtrate was concentrated; the residue was dissolved with DCM and filtered through celite. The filtrate was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification through flash column chromatography on silica gel (PE/EA: 2/1) gave enone **29** (170 mg, 82%) as a white solid. Mp 175-176 °C; $[\alpha]_D^{20}$ +6.3 (*c* 1.05, $CHCl_3$); IR (KBr): 1767, 1747, 1729, 1713, 1614, 1234 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (m, 1H), 4.77 (dd, *J* = 11.7, 6.8 Hz, 1H), 4.74 (m, 1H), 4.72 (m, 1H, 1H), 3.02 (d, *J* = 9.0 Hz, 1H), 2.88 (m, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.45 (d, *J* = 5.9 Hz, 3H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 181.1, 172.8, 171.3, 170.8, 129.3, 77.5, 76.5, 73.7, 61.5, 55.3, 50.5, 44.6, 37.5, 37.1, 37.0, 34.4, 29.9, 28.1, 28.0, 26.7, 22.1, 21.8, 18.3, 12.7; Anal calcd for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.55; H, 7.24.

*4.1.2. Allylic alcohol **22***

A solution of **18** (43 mg, 0.10 mmol), cyclohexene oxide (88 mg, 0.9 mmol), dibenzoyl peroxide (BPO, 1.2 mg, 0.005 mmol) and NBS (18 mg, 0.10 mmol) in dry CCl_4 (2.0 mL) was stirred at reflux under an argon atmosphere for three hours. TLC showed the generation of a less polar product. The mixture was subjected to flash column chromatography on silica gel (PE/EA: 1/1) to provide the more polar product **22** (40 mg, 89%). $[\alpha]_D^{20}$ -33 (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45 (m, 1H), 5.02 (brs, 1H), 4.91 (dd, *J* = 11.4, 4.9 Hz, 1H), 4.69 (m, 1H), 4.68 (m, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.50 (d, *J* = 5.9 Hz, 3H), 0.91 (s, 3H); LRMS-ESI (*m/z*): 325 ([M-H-2AcOH]$^+$).

*4.1.3. Allylic sulfide **23***

A solution of **18** (128 mg, 0.30 mmol), cyclohexene oxide (88 mg, 0.9 mmol), dibenzoyl peroxide (BPO, 4.0 mg, 0.016 mmol) and NBS (53 mg, 0.30 mmol) in dry CCl_4 (4.0 mL) was stirred at reflux under an argon atmosphere for 24 h. Another portion of NBS (37 mg, 0.20 mmol) was added and the reaction was kept at reflux for 12 h. The mixture was cooled to 40 °C; EtSH (2.6 mL) and DBU (0.03 mL) were added. The reaction was stirred for 18 h, then cooled to ambient temperature and filtered and washed with CCl_4. The filtrate was concentrated and purified through flash column chromatography on silica gel (PE/EA: 7/1) to afford 16α-**23** (55 mg, 37%) as a white solid and 16β-**23** (68 mg, 46%) as a white solid. Compound 16α-**23**: mp 108-109 °C; $[\alpha]_D^{20}$ -45 (*c* 0.60, $CHCl_3$); IR (KBr): 1746, 1726, 1540, 1246 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (m, 1H), 4.87 (dd, *J* = 11.4, 4.9 Hz, 1H), 4.68 (m, 1H,), 4.67 (m, 1H), 3.96 (m, 1H), 2.86 (t like, *J* = 6.4 Hz, 1H), 2.55 (q, *J* = 7.4 Hz, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.28 (t, J = 7.4 Hz, 3H), 0.92 (s, 3H); LRMS-EI *m/e*: 429 (4.2, M$^+$-SEt), 297 (100). Compound 16β-**23**: mp 99-100 °C; $[\alpha]_D^{20}$ -81 (*c* 0.90, $CHCl_3$); IR (KBr): 1745, 1732, 1540, 1234 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (m, 1H), 4.75 (dd, *J* = 10.4, 4.7 Hz, 1H), 4.73 (m, 1H), 4.68 (m, 1H), 3.96 (br d, *J* = 8.0 Hz, 1H), 3.11 (m, 1H), 2.53 (q, *J* = 7.5 Hz, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.72 (d, *J* = 6.9 Hz, 3H), 1.24 (t, *J* = 7.5 Hz, 3H), 0.92 (s, 3H); LRMS-EI *m/e*: 430 (0.87, M$^+$-AcOH), 429 (2.52, M$^+$-SEt), 297 (100).

*4.1.4. Dinorcholanic lactones and (R)-4-methyldihydrofuran-2(3H)-one (**55**)through iodine-catalyzed abnormal Bayer-Villiger oxidation of steroidal sapogenin: general procedure*

To a 2000 mL flask was added HOAc (300 mL), H_2SO_4 (4.6 mL, cat.), iodine (2.60 g, 0.10 equiv.) and the mixture was stirred at room temperature for 30 min before substrates (steroidal sapogenin, 100 mmol) was added. A peracetic acid solution (freshly prepared, *ca.* 1 M, 600 mL) was added. The temperature of the mixture rose to ca. 60 °C in one hour and another 3-4 hours was needed for fully consumption of the starting material at this temperature (in some cases, an oil bath was needed). The reaction was cooled with a water/ice bath and quenched carefully by addition of a saturated aqueous Na_2SO_3 solution, and then concentrated in vacuo. The residue was filtered and washed with

toluene and the filtrate was concentrated under reduced pressure (*co-evaporation with toluene would minimize the residual HOAc, the presence of which would slow the hydrolysis and increase the use of KOH*). The crude was dissolved in EtOH (400 mL) and KOH was added slowly (pH > 14). The reaction was stirred vigorously at reflux for five hours and cooled to ambient temperature. A diluted aqueous HCl solution (pH < 3) was added to give a copious yellow-white precipitate. The solid was collected by filtration, washed by water, and then dried in vacuo overnight. The crude lactone could be used in the next step without further purification (typical yield: 80-95%). The analytic sample was obtained by recrystallization with EtOH as white microcrystal. The aqueous layer was extracted with DCM to provide lactone **55**. **55**: bp: 92–94 °C/16 mmHg; $[\alpha]_D^{24}$ + 27 (*c* 0.64, $CHCl_3$); IR (film): 2971, 1780, 1460, 1242, 1174, 1018, 838, 601, 499 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.37 (dd, *J* = 8.9, 7.1 Hz, 1H), 3.83 (dd, *J* = 8.9, 6.3 Hz, 1H), 2.69 – 2.50 (m, 2H), 2.10 (q, *J* = 10.5 Hz, 1H), 1.11 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 74.8, 36.1, 30.4, 17.9; Anal. Calcd for $C_5H_8O_2$: C, 60.00; H, 8.00. Found: C, 60.05; H, 7.85.

*4.1.5. Cycloaddition with singlet oxygen to adduct **60** and **62***

A solution of **59** (3.113 g, 6.5 mmol) and 5,10,15,20-tetraphenylporphine (TPP, 20 mg, 0.32 mmol, 0.5 mol%) in dry CH_2Cl_2 (130 mL) was purged with oxygen at 0 °C for 5 min. The reaction was stirred with irradiation by a sunlamp (200 W) at 0 °C for 7.5 h until TLC showed that the **59** was completely consumed. The reaction mixture was concentrated under reduced pressure, purified though flash column chromatography on silica gel (PE/EA: 12/1–10/1–7/1) to provide α-adduct **60** (1.134 g, 42%) as a white crystal, and **62** (1.242 g, 46%, more polar) as a brownish oil. **60**: mp 96–97 °C; $[\alpha]_D^{20}$ +30 (*c* 0.90, $CHCl_3$); IR (film): 3059, 2941, 2866, 1743, 1231, 1039, 917 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, 1H, *J* = 2.1 Hz), 5.85 (dd, t like, 1H, *J* = 2.1 Hz), 4.70, 4.65 (AB, 2H, J_{AB} = 6.6 Hz), 4.68 (s, 2H), 4.20 (m, 1H), 3.89 (m, 1H), 3.45 (m, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 3.07 (dd, 1H, *J* = 13.2, 6.6 Hz), 2.87 (dd, 1H, *J* = 11.7, 4.2 Hz), 2.04 (s, 3H), 1.15 (d, 3H, *J* = 6.9 Hz), 1.06 (s, 3H), 0.92 (s, 3H); Anal. Calcd for $C_{28}H_{44}O_8$: C, 66.12; H, 8.72. Found: C, 66.15; H, 8.72. **62**: $[\alpha]_D^{20}$ –44.4 (*c* 0.82, $CHCl_3$); IR (film): 2937, 2860, 1745, 1699, 1606, 1451, 1374, 1234, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (d, 1H, *J* = 6.1 Hz), 6.44 (d, 1H, *J* = 6.1 Hz), 4.68 (s, 2H), 4.62, 4.55 (AB, 1H, J_{AB} = 6.6 Hz), 4.20 (dd, 1H, *J* = 11.0, 4.4 Hz), 4.06 (dd, 1H, *J* = 10.7, 6.0 Hz), 3.45-3.55 (m, 2H), 3.36 (s, 3H), 3.32 (s, 3H), 2.32-2.43 (m, 1H), 2.06 (s, 3H), 1.11 (d, 3H, *J* = 6.7 Hz), 1.06 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 200.6, 170.8, 135.1, 134.5, 96.2, 94.7, 80.0, 76.4, 65.0, 58.8, 55.5, 55.2, 51.1, 51.0, 45.0, 44.4, 37.7, 35.4, 34.5, 32.2, 29.3, 28.4, 27.9, 20.9, 18.0, 13.3, 11.4; Anal. Calcd for $C_{28}H_{44}O_8$: C, 66.12; H, 8.72. Found: C, 66.04; H, 8.78.

*4.1.6. Compound **63***

To a solution of **60** (80 mg, 0.16 mmol) in CH_2Cl_2 (15 mL) was added zinc powder (103 mg, 1.6 mmol, 10 equiv) and acetic acid (20 μL, 2.5 equiv). The reaction was stirred at room temperature for five hours, filtered through short pad of silica and washed with CH_2Cl_2. The filtrate was neutralized with saturated aqueous $NaHCO_3$ solution, washed with brine and dried over Na_2SO_4. Concentration under reduced pressure and flash column chromatography on silica gel (PE/EA: 2/1) afforded **63** (56 mg, 65%) as a pale yellow oil. $[\alpha]_D^{20}$ –41.9 (*c* 0.56, $CHCl_3$); IR (film): 3500, 2933, 2860, 1742, 1467, 1375, 1242, 1041, 917 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.53 (d, 1H, *J* = 1.2 Hz), 5.24 (s, 1H), 4.81, 4.58 (AB, 2H, *J* = 6.3 Hz), 4.68 (s, 2H), 4.08 (m, 3H), 3.45 (m, 1H), 3.37 (s, 6H), 2.87 (s, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 1.07 (d, 3H, *J* = 8.1 Hz), 1.01 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 170.0, 156.0, 117.1, 96.9, 94.3, 84.1, 81.7, 75.8, 68.0, 57.9, 55.2, 54.9, 49.7, 43.8, 37.9, 36.5, 35.4, 34.8, 34.1, 29.5, 29.2, 28.4, 28.3, 27.9, 21.0, 20.8, 15.4, 12.9, 11.6; HRMS-EI (*m/z*): calcd for $C_{30}H_{48}O_9Na^+$: 575.3191, found: 575.3190.

*4.1.7. Aldehyde **64***

To a solution of C22-OH (2.06 g, 4.42 mmol) in CH_2Cl_2 (40 mL) was added Dess–Martin periodinane (2.44 g, 5.74 mmol, 1.3 equiv) and *t*-BuOH (1.2 mL). the reaction mixture was stirred for 10 hours at room temperature, quenched with saturated $Na_2S_2O_3$/saturated $NaHCO_3$ (v/v: 4/1) and diluted with ether (200 mL). The organic layer was separated, washed with brine and dried over Na_2SO_4. Concentration in vacuum afforded the crude aldehyde **64** (2.05 g, 100%). The aldehyde was partially decomposed during flash column chromatography on silica gel to afford a β-elimination product. mp 101–102 °C; $[\alpha]_D^{20}$ +70 (*c* 0.145, CH_2Cl_2); IR (film): 2979, 2927, 2881, 1718, 1456, 1442, 1148, 1102, 1043, 915, 743, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.88 (d, 1H, *J* = 1.8 Hz), 6.44(s, 2H), 4.72, 4.71 (AB, 2H, J_{AB} = 6.9 Hz), 4.68 (s, 2H), 4.08 (dd, 1H, *J* = 12, 4.8 Hz), 3.50 (m, 1H), 3.372 (s, 3H), 3.367 (s, 3H), 3.25 (m, 1H), 1.25 (d, 3H, *J* = 6.9 Hz), 0.94 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 134.1, 133.9, 98.4, 96.3, 94.5, 75.9, 75.4, 64.4, 55.8, 55.1, 45.6, 44.7, 44.0, 36.8, 35.6, 34.9, 33.2, 28.5, 28.4, 27.3, 26.7, 13.1, 11.5, 10.8; HRMS-ESI (*m/z*): calcd for $C_{26}H_{40}O_7Na^+$: 487.2664, found: 487.2666.

*4.1.8. Acid **65***

To a solution of crude aldehyde (4.42 mmol) in *t*-BuOH/H_2O (v/v: 5/1, 78 mL) was added 2-methyl-2-butene (3.28 mL, 31 mmol, 7 equiv), $NaClO_2$ (0.594 g, 5.28 mmol, 1.2 equiv) and NaH_2PO_4•$2H_2O$ (1.373 g, 8.8 mmol, 2.0 equiv) sequentially. The mixture was allowed to stir at room temperature for two hours and diluted with ethyl acetate (300 mL). The organic layer was separated, washed with brine and dried over Na_2SO_4. Filtration, concentration under reduced pressure afforded the acid **65** (2.18 g, 99%) which was used directly in the next step without purification. The analytic sample was obtained by recrystallization with acetone as a white crystal. mp 143–144 °C (acetone); $[\alpha]_D^{20}$ +33.6 (*c* 0.176, $CHCl_3$); IR (film): 3438, 3060, 2942, 2930, 2830, 1740, 1464, 1184, 1149, 1105, 1046, 927, 919 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.66 (d, 1H, *J* = 6.0 Hz), 6.40 (d, 1H, *J* = 6.0 Hz), 4.77 (s, 2H), 4.69 (s, 2H), 4.09 (q, 1H, *J* = 4.8 Hz), 3.46–3.55 (m, 1H), 3.43 (s, 3H), 3.38 (s, 3H), 3.17 (dd, 1H, *J* =10.2, 6.9 Hz), 1.40 (d, 3H, *J* = 6.6 Hz), 0.92 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 134.4, 132.7, 98.4, 96.3, 96.2, 94.4, 75.9, 75.4, 64.6, 55.9, 45.6, 44.0, 37.6, 36.7, 35.6, 34.9, 33.4, 28.5, 28.4, 27.2, 26.6, 14.9, 12.1, 11.5; HRMS-ESI (*m/z*): calcd for $C_{24}H_{40}O_8Na^+$: 503.2615, found: 503.2615.

*4.1.9. C17-OH lactone **66***

To a solution of acid **65** (1.80 g, 3.75 mmol) in DCM (35 mL) was added acetic acid (1.50 mL, 26.0 mmol, 7 equiv) and zinc powder (1.50 g, 22.5 mmol, 6 equiv). The resulting suspension was warm to reflux for 4 hours until the starting material was fully consumed. The reaction mixture was filtrated through a short pad of silica gel, and diluted with ethyl acetate (150 mL). The organic layer was washed with diluted brine, saturated aqueous $NaHCO_3$ solution, brine, and dried over Na_2SO_4. Filtration, concentration and flash column chromatography on silica gel (PE/EA: 8/1) furnished lactone **66** (1.10 g, 63%) as a wax. The reaction was performed at 50 mg scale to give a yield at 77%. $[\alpha]_D^{20}$ +40 (*c* 0.11, DCM); IR (film): 3459, 2933, 1772, 1715, 1647, 1195, 1147, 1102, 1040, 915, 415 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ 5.43 (s, 1H), 5.00 (s, 1H), 4.72, 4.62(AB, 2H, J_{AB} = 6.0 Hz), 4.66 (s, 2H), 4.28 (s, 1H), 3.84 (dd, 1H, *J* =11.1, 4.8 Hz), 3.44-3.53 (m, 1H), 3.39 (s, 3H), 3.34 (s, 3H), 2.76 (q, 1H, *J* = 7.5 Hz), 1.28 (d, 3H, *J* = 7.5 Hz), 1.09 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 158.9, 117.1, 95.6, 94.5, 91.4, 87.1, 79.5, 75.7, 55.8, 55.2, 55.1, 51.7, 44.3, 42.0, 36.7, 36.0, 34.9, 34.3, 28.8, 28.4, 27.9, 26.4, 15.2, 11.9, 10.8; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{26}H_{40}O_7$: 487.2668, found: 487.2666.

*4.1.10. Addtion of lithium reagent to give adduct **68***

To a solution of iodide **67** (82 mg, 0.32 mmol) in anhydrous pentane/ether (1.5 mL, v/v: 3/2) under argon atmosphere was slowly added *t*-BuLi (1.5 M in pentane, 0.44 mL, 0.66 mmol) at −78 °C. The resulting solution was stirred for another hour, and added slowly a solution of lactone **66** (49 mg, 0.11 mmol) in anhydrous THF. Methanol (0.80 mL) was added to quench the reaction after 15 minutes, and the mixture was diluted with ethyl acetate. The organic layer was washed with saturated aqueous NH_4Cl solution and brine, dried over Na_2SO_4. Filtration, concentration and flash column chromatography on silica gel (PE/EA: 3/1–1/1) furnished the desired adduct **68** (7 mg, 25% brsm) as a pale yellow oil, 20-*epi*-**66** (8 mg), and the starting material **66** (30 mg, 61%). Adduct **68**: $[\alpha]_D^{20}$ +27 (*c* 0.25, CH_2Cl_2); IR (film): 3500, 2933, 1458, 1377,1214, 1148, 1106, 1044, 912, 411 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34 (s, 1H), 4.84 (brs, 1H), 4.76, 4.70 (AB, 2H, J_{AB} = 6.6 Hz), 4.68 (s, 2H), 4.33 (s, 1H), 4.21 (s, 1H), 3.82, 3.71 (AB, 2H, J_{AB} = 8.4 Hz), 3.76–3.84 (m, 1H), 3.43–3.56 (m, 1H), 3.42 (s, 3H), 3.37 (s, 3H), 1.40 (s, 6H), 1.29 (s, 3H), 1.12 (s, 3H), 1.08 (d, 3H, *J* = 6.9 Hz), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 119.7, 109.2, 108.6, 95.6, 94.6, 92.4, 92.1, 80.9, 80.7, 75.9, 74.1, 56.3, 55.2, 54.3, 52.6, 45.9, 44.6, 36.8, 36.2, 35.1, 33.9, 33.2, 31.5, 29.0, 28.6, 28.2, 27.3, 27.0, 26.6, 25.0, 14.5, 12.0, 7.9; HRMS-ESI (*m/z*): calcd for $C_{34}H_{56}O_9Na^+$: 631.3822, found: 631.3817. 20-*epi*-**66**: $[\alpha]_D^{20}$ −9 (*c* 1.00, CH_2Cl_2); IR (film): 3459, 2929, 2859, 1775, 1716, 1558, 1379, 1216, 1189, 1147, 1104, 1041, 991, 966, 915, 820, 757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51 (s, 1H), 4.89 (s, 1H), 4.77 (d, 1H, *J* = 2.7 Hz), 4.71, 4.65 (AB, 2H, J_{AB} = 7.5 Hz), 4.68 (s, 2H), 3.90 (dd, 1H, *J* =11.7, 3.9 Hz), 3.44-3.55 (m, 1H), 3.41 (s, 3H), 3.37 (s, 3H), 3.13 (q, 1H, *J* = 7.2 Hz), 1.44 (d, 3H, *J* = 7.2 Hz), 1.10 (s, 3H), 0.86 (s, 3H); HRMS-ESI (*m/z*): calcd for $C_{26}H_{40}O_7Na^+$: 487.2664, found: 487.2666.

*4.1.11. Treatment of **68** with HOAc*

The solution of adduct **68** (26 mg, 0.43 mmol) in HOAc (65% aqueous solution, 2.0 mL) was stirred at room temperature for 3 hours. The reaction was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4. Filtration, concentration and flash column chromatography on silica gel (PE/EA: 10/1) provided **69** (6 mg, 26%), **70** (8 mg, 34%), and **71** (8 mg, 34%). **69**: $[\alpha]_D^{20}$ +19.2 (*c* 0.50, CH_2Cl_2); IR (film): 2451, 2927, 2858, 1462, 1374, 1210, 1147, 1109, 1045, 920 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.31 (d, 1H, *J* = 1.8 Hz), 4.77, 4.67 (AB, 2H, J_{AB} = 6.0 Hz), 4.72 (s, 1H), 4.68 (s, 2H), 3.80 (dd, 1H, *J* = 11.7, 4.8 Hz), 3.60 (d, 1H, *J* = 11.4 Hz), 3.49 (m, 1H), 3.384 (s, 3H), 3.382 (d, 1H, *J* = 11.4 Hz), 3.37 (s, 3H), 1.18 (s, 3H), 1.11 (s, 3H), 1.03 (d, 3H, *J* = 6.9 Hz), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 118.5, 118.1, 96.3, 94.6, 93.2, 91.0, 86.7, 80.4, 76.0, 68.6, 55.9, 55.2, 55.2, 52.1, 44.5, 44.1, 36.8, 36.0, 35.1, 34.4, 34.2, 30.3, 29.2, 28.6, 28.2, 27.7, 23.8, 15.6, 12.0, 7.7; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{31}H_{50}O_8$: 573.3395, found: 573.3395. **70**: $[\alpha]_D^{20}$ +17,5 (*c* 0.50, CH_2Cl_2); IR (film): 3495, 2927, 1701, 1460, 1376, 1149, 1107, 1043, 936 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (s, 1H), 4.78, 4.66 (AB, 2H, J_{AB} = 6.0 Hz), 4.68 (s, 2H), 4.62 (s, 1H), 3.83 (dd, 1H, *J* = 11.5, 8.0 Hz), 3.84 (d, 1H, *J* = 11.5 Hz), 3.49 (m, 1H), 3.39 (d, 1H, *J* = 11.4 Hz), 3.38 (s, 3H), 3.37 (s, 3H), 3.30 (s, 1H), 1.13 (s, 3H), 1.09 (s, 3H), 1.07 (d, 3H, *J* = 7.0 Hz), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 117.7, 107.4, 96.2, 94.6, 93.7, 90.8, 79.7, 76.0, 69.3, 66.6, 58.6, 55.4, 55.2, 51.7, 47.5, 44.4, 36.9, 36.0, 35.1, 34.2, 32.3, 29.3, 28.6, 28.2, 27.7, 27.28, 24.8, 16.2, 12.0, 7.5; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{31}H_{50}O_8$: 573.3395, found: 573.3397. **71**: $[\alpha]_D^{20}$ +79.7 (*c* 0.80, CH_2Cl_2); IR (film): 3450, 2964, 2932, 1692, 1637, 1609, 1376, 1262, 1147, 1102, 1031, 915 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (s, 1H), 4.69, 4.62 (AB, 2H, J_{AB} = 6.3 Hz), 4.68 (s, 2H), 3.42 (m, 4H), 3.37 (s, 3H), 3.36 (s, 3H), 2.18 (s, 3H), 1.41 (s, 3H), 1.18 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.5, 194.6, 185.3, 148.1, 137.8, 125.6, 96.0, 94.6, 82.2, 75.8, 72.2, 69.7, 55.7, 55.2, 51.5, 51.2, 44.1, 36.7, 36.4, 35.4, 35.2, 34.9, 31.5, 29.0, 28.5, 27.8, 27.4, 23.6, 18.0, 15.8, 11.9; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{31}H_{48}O_8$: 571.3242, found: 571.3241.

*4.1.12. Adduct **73***

To a solution of **72** (372 mg, 1.5 mmol) in HMPA/THF (0.15 mL/2.5 mL) at -70 °C was slowly added a solution of *t*-BuLi in pentane (1.50 M, 1.10 mL, 1.65 mmol) under argon. The mixture was stirred at -70 °C and a solution of aldehyde **64** (348 mg, 0.75 mmol) in THF was added slowly. After one hour, a saturated aqueous NH_4Cl solution was added to quench the reaction and the mixture was allowed to warm to ambient temperature. The mixture was diluted with ethyl acetate and separated; the organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure. Purification through flash column chromatography on silica gel (PE/EA: 25/1 to 6/1) afforded **73** (250 mg, 51%) as a wax. $[\alpha]_D^{20}$ + 35.7 (*c* 0.66, $CHCl_3$); IR (KBr film) 3464, 2982, 2931, 2863, 1466, 1374, 1105, 1043, 914 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (d, 1H, *J* = 6.0 Hz), 6.31 (d, 1H, *J* = 5.7 Hz), 4.77 (s, 2H), 4.67 (s, 2H), 4.38 (s, 1H), 4.18 (d, 1H, *J* = 4.2 Hz), 4.11 (dd, 1H, *J* =11.4, 4.2Hz), 3.88 (d, 1H, *J* = 8.1 Hz), 3.83 (d, 1H, *J* =8.1 Hz), 3.50 (m, 1H), 3.37 (s, 3H), 3.35 (s, 3H), 3.06-2.65 (m, 6H), 1.08 (s, 3H), 0.80 (s, 3H); LRMS-ESI (*m/z*): 735.4 ($[M+Na]^+$); Anal. Calcd for $C_{37}H_{60}O_9S_2$: C, 62.33; H, 8.48. Found: C, 62.22; H, 8.61.

*4.1.13. Adduct **74***

At -70 °C, to a solution of (*S*)-4-(2-iodoethyl)-2,2,4-trimethyl-1,3-dioxolane (**67**, 209 mg, 0.77 mmol) in ether/pentane (0.64 mL/0.96 mL) was added a solution of *t*-BuLi in pentane (1.50 M, 1.0 mL, 1. 5 mmol) under argon. After 30 min, to the resulting white suspension was added a solution of **64** (232 mg, 0.50 mmol) in THF (4.0 mL). After TLC showed complete consumption of **64**, a saturated aqueous NH_4Cl solution was added to quench the reaction and the mixture was allowed to warm to ambient temperature. The mixture was diluted with ethyl acetate and separated; the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification through flash column chromatography on silica gel (PE/EA: 5/1) afforded **74** (145 mg, 48%) as a wax. IR (KBr film) 3437, 2934, 1380, 1260, 1211, 1148, 1039, 897; cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (1H, d, *J* = 6.0 Hz), 6.33 (1H, d, *J* = 5.7 Hz), 4.69 (s, 2H), 4.68 (s, 2H), 4.05 (m, 1H), 3.78 (s, 2H), 3.51 (m, 1H), 3.39 (s, 3H), 3.36 (s, 3H), 1.11 (d, 3H, *J* = 6.9 Hz), 1.07 (s, 3H), 0.83 (s, 3H); HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{34}H_{54}O_9$: 631.3817, found: 631.3817.

*4.1.14. Adduct **75***

To a solution of 1,3-dithiane (716 mg, 5.97 mmol) in anhydrous THF (30 mL) under argon atmosphere was added *n*-BuLi (3.50 mL, 1.60 M in hexane, 5.60 mmol) at −78 °C. The resulting mixture was stirred for additional 40 min, then added a

solution of aldehyde **64** (crude product from Dess–Martin oxidation, 1.58 g, 3.29 mmol) in THF. The reaction was kept at −78 °C until the aldehyde was completely consumed (by TLC), and saturated NH_4Cl aqueous solution was added to quench the reaction. Brine (30 mL) was added to the mixture at room temperature and the solution was extracted with ethyl acetate for three times, the combined organic layer was dried over Na_2SO_4. Filtration, concentration, and flash column chromatography on silica gel (PE/EA: 4/1) afforded **75** (1.534 g, 78% from C22-OH) as a white foam. $[\alpha]_D^{20}$ + 40.0 (*c* 0.45, $CHCl_3$); IR (KBr film) 2936, 2857, 1466, 1449, 1388, 1245, 1147, 1103, 1033, 913 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.63 (d, 1H, *J* = 6.0 Hz), 6.30 (d, *J* = 6.0 Hz), 4.74 (d like, 2H, *J* = 2.1 Hz), 4.68 (s, 2H), 4.32 (d, 1H, *J* = 10.5 Hz), 4.07 (dd, 1H, *J* = 10.4, 4.5 Hz), 3.73 (d, 1H, *J* = 10.2 Hz), 3.46-3.57 (m, 1H), 3.36 (s, 3H), 3.35 (s, 3H), 1.12 (s, 3H), 1.05 (d, 3H, *J* = 7.2 Hz), 0.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 131.3, 99.6, 98.3, 96.9, 94.6, 76.5, 76.0, 68.1, 64.2, 55.5, 55.1, 47.8, 45.8, 44.1, 36.8, 35.7, 35.0, 33.2, 33.1, 28.7, 28.5, 27.3, 27.0, 26.6, 25.9, 25.2, 13.0, 11.6, 8.6; LRMS-ESI (*m/z*): 607.0 ($[M+Na]^+$); Anal. Calcd for $C_{30}H_{48}O_7S_2$: C, 61.61; H, 8.27. Found: C, 61.55; H, 8.01.

*4.1.15. Triol **76***

To a solution of peroxide **75** (1.534 g, 2.62 mmol) in THF (35 mL) embedded in an ice/water bath was added Zn powder (not activated, 1.712 g, 26.3 mmol) and acetic acid (4.50 mL, 4.68 g, 78 mmol). The reaction was aged for 2 h to consume the starting material completely. The mixture was filtered through a short pad of silica gel and washed with ethyl acetate (160 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ solution (2 × 100 mL) and brine, dried over Na_2SO_4. Filtration, concentration, and flash column chromatography on silica gel (PE/EA: 3/1) afforded the desired 14,17,22-triol **76** (1.433 g, 93%) as a white foam. $[\alpha]_D^{20}$ + 37.8 (*c* 0.40, $CHCl_3$); IR (KBr film) 3415, 2934, 2862, 1468, 1415, 1385, 1148, 1104, 1042, 961, 934, 913 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.29 (d, 1H, *J* = 5.7 Hz), 6.23 (d, *J* = 6.0 Hz), 4.68 (s, 2H, *J* = 2.1 Hz), 4.78 (d, 1H, *J* = 6.0 Hz), 4.62 (d, 1H, *J* = 6.0 Hz), 4.37-4.41 (m, 3H), 3.90 (d, 1H, *J* = 10.2 Hz), 3.44-3.55 (m, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 2.84-3.02 (m, 2H), 2.69-2.76 (m, 2H), 2.32 (qu., 1H, *J* = 7.0 Hz), 1.16 (s, 3H), 0.92 (d, 3H, *J* = 7.2 Hz), 0.87 (s, 3H); LRMS-ESI (*m/z*): 609.0 ($[M+Na]^+$); Anal. Calcd for $C_{30}H_{50}O_7S_2$: C, 61.40; H, 8.59. Found: C, 61.42; H, 8.41.

*4.1.16. Cyclization Product **77***

To a solution of diol **76** (234 mg, 0.40 mmol) in dry CH_2Cl_2 (20 mL) immersed in an ice/water bath was added TMSCl (50.0 μL, 0.40 mmol). The mixture was quenched with saturated aqueous $NaHCO_3$ solution after TLC indicated that the diol was completely consumed. The solution was diluted with ethyl acetate (160 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Filtration, concentration, and flash column chromatography on silica gel (PE/EA: 3/1) afforded the cyclized product **77** (164 mg, 72%) as a white foam. The C22 configuration was assigned as *R* through ^1H-^1H COSY and 2D NOESY. $[\alpha]_D^{20}$ + 33.9 (*c* 0.86, $CHCl_3$); IR (KBr film) 3513, 2932, 1466, 1449, 1375, 1147, 1103, 1044, 1027, 974 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.30 (s, 1H), 4.75 (d, 1H, *J* = 6.3 Hz), 4.65 (d, 1H, *J* = 6.3 Hz), 4.70 (s, 1H), 4.68 (s, 2H), 4.37 (d, 1H, *J* = 10.2 Hz), 3.95 (dd, 1H, *J* = 10.2, 5.4 Hz), 3.90 (dd, 1H, *J* =5.7, 4.8 Hz), 3.44-3.54 (m, 1H), 3.40 (s, 3H), 3.37 (s, 3H), 2.79-2.92 (m, 4H), 2.48-2.53 (m or dq, 1H), 1.14 (s, 3H), 1.12 (d, 3H, *J* = 7.2 Hz), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 118.5, 95.7, 94.5, 93.4, 91.6, 81.9, 81.1, 75.9, 56.0, 56.0, 55.1, 51.4, 47.4, 44.3, 42.2, 36.8, 35.97, 34.98, 34.1, 29.4, 29.2, 29.0, 28.5, 28.1, 26.9, 25.9, 15.4, 11.99, 9.2; LRMS-ESI (*m/z*): 591.0 ($[M+Na]^+$); Anal. Calcd for $C_{30}H_{48}O_6S_2$: C, 63.34; H, 8.51. Found: C, 61.24; H, 8.34.

*4.1.17. Aldehyde **78***

To a suspension of red HgO (65.2 mg, 0.30 mmol) in THF/water (3.0 mL/3.0 mL) was added BF_3•Et_2O (27.5 μL, 0.305 mmol) at room temperature. The mixture was stirred for 10 min, then added a solution of dithiane **77** (56.9 mg, 0.10 mmol) in THF (3.0 mL) and the system was warmed to reflux for 2 h. The solid was filtered, the filtrate was quenched with saturated $NaHCO_3$ solution and extracted with ethyl ether for several times. The combined organic layer was washed with brine and dried over Na_2SO_4. Filtration, concentration, and flash column chromatography on silica gel (PE/EA: 3/1) provided the desired aldehyde **78** (45.6 mg, 95%) as a white foam. $[\alpha]_D^{20}$ + 60.7 (*c* 0.52, $CHCl_3$); IR (KBr film) 3511, 2930, 1721, 1648, 1467, 1450, 1385, 1311, 1149, 1103, 1037, 951, 937, 915 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.76 (d, 1H, *J* = 3.0 Hz), 5.40 (s, 1H), 5.05 (s, 1H), 4.75 (d, 1H, *J* = 6.6 Hz), 4.67 (d, 1H, *J* = 6.6 Hz), 4.68 (s, 2H, *J* = 2.1 Hz), 4.21 (dd, 1H, *J* = 3.0, 5.4 Hz), 3.79 (dd, 1H, *J* = 5.1, 7.8 Hz), 3.43-3.55 (m, 1H), 3.40 (s, 3H), 3.37 (s, 3H), 2.61 (qui., 1H), 1.16 (s, 3H), 1.07 (d, 3H, *J* = 7.2 Hz), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.95, 154.2, 119.8, 95.6, 95.5, 94.6, 91.2, 87.7, 75.9, 56.2, 55.1, 54.0, 52.6, 44.5, 44.2, 36.8, 36.2, 35.0, 33.98, 28.9, 28.5, 28.1, 26.5, 13.9, 12.0, 7.5; LRMS-ESI (*m/z*): 501.2 ($[M+Na]^+$), 533.3 ($[M+MeOH+Na]^+$); Anal. Calcd for $C_{27}H_{42}O_7$: C, 67.76; H, 8.84. Found: C, 67.65; H, 8.68.

*4.1.18. Methylallylation of aldehyde giving the acetates of **79** and 23-epi-**79***

To a suspension of aldehyde **78** (95.7 mg, 0.20 mmol) and $MgBr_2$•Et_2O (153 mg, 0.60 mmol) in dry CH_2Cl_2 (10 mL) was added trimethyl(2-methylallyl)stannane. The mixture was stirred at ambient temperature for two hours and quenched with 1N HCl aqueous solution, diluted with ether. The organic layer was separated and washed with brine, dried over Na_2SO_4. Filtration, concentration, and flash column chromatography on silica gel (PE/EA: 2/1-1/1) provided **79** (101 mg, 95%) as a colorless oil. NMR indicated that the aldehyde was completely converted and no 23-epimer formed. $[\alpha]_D^{20}$ + 33.7 (c 1.00, $CHCl_3$); IR (KBr film) 3383, 2931, 1467, 1454, 1145, 1108, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.36 (s, 1H), 4.90 (s, 1H), 4.84 (br s, 2H), 4.72 (s, 2H), 4.67 (s, 2H), 4.62 (br s, 1H), 4.08 (br s, 1H), 4.10 (d, 1H, *J* = 8.1 Hz), 3.75-3.82 (m, 2H), 3.42-3.56 (m, 1H), 3.38 (s, 3H), 3.36 (s, 3H), 2.54 (p like, 1H, *J* = 7.5 Hz), 2.42 (dd, 1H, *J* = 8.1, 13.8 Hz, $C_{24}\mathbf{H_a}$), 2.24 (dd, 1H, *J* = 5.1, 13.8 Hz, $C_{24}\mathbf{H_b}$), 1.78 (s, 3H), 1.17 (s, 3H), 1.10 (d, 3H, *J* = 6.9 Hz), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 143.0, 120.4, 112.9, 95.6, 95.0, 94.6, 91.5, 85.2, 81.0, 75.9, 68.1, 56.1, 55.2, 54.8, 52.4, 44.5, 42.3, 41.7, 36.7, 36.1, 35.0, 33.8, 28.9, 28.5, 28.1, 27.0, 22.6, 14.2, 12.0, 8.7; LRMS-ESI (*m/z*): 557.3 ($[M+Na]^+$); HRMS-MALDI (*m/z*): calcd for $C_{31}H_{50}O_7Na^+$: 557.3449. Found: 557.3460.

The crude product of aldehyde **78** (216 mg, 0.452 mmol) with (2-methylallyl)magnesium chloride (prepared from 3-chloro-2-methylprop-1-ene) was dissolved in dry CH_2Cl_2 (10 mL). To the resulting solution were added AC_2O (0.16 mL, 1.7 mmol), Et_3N (0.30 mL, 2.14 mmol) and DMAP (26.0 mg, 0.21 mmol), and the mixture was stirred until the disappearance of the starting material. The mixture was directly concentrated and purified through flash column chromatography on silica gel (PE/EA: 5/1–4/1) to provide 23*R*-acetate (60.4 mg, 25%, white foam) and 23*S*-acetate (146 mg, 59%, white foam). Acetate of **79** (23*R*-epimer): ^1H NMR (400 MHz, $CDCl_3$) δ 5.32 (s, 1H, $C_{15}\mathbf{H}$), 5.18-5.25 (m, 1H, $C_{23}\mathbf{H}$), 4.77-4.82 (2H, $C_{26}\mathbf{H}$), 4.76 (s, 1H, $C_{16}\mathbf{H}$), 4.73, 4.65 (AB, 2H, *J* = 6.3Hz, 12-O**M**OM), 4.68 (s, 2H, 3-O**M**OM), 3.99

(dd, 1H, *J* = 4.5, 7.2 Hz, C_{22}**H**), 3.87 (dd, 1H, *J* = 4.5, 11.7 Hz, C_{12}**H**), 3.43-3.56 (m, 1H, C_3**H**), 3.53 (s, 1H), 3.38 (s, 3H, 12-OMO**M**), 3.36 (s, 3H, 3-OMO**M**), 2.48 (p like, 1H, *J* = 7.2 Hz, C_{20}**H**), 2.24-2.38 (m, 1H, C_{24}**H**), 2.04 (s, 3H, 23-**Ac**), 1.77 (s, 3H, 27-**Me**), 1.13 (s, 3H, 18-**Me**), 1.02 (d, 3H, *J* = 7.2 Hz, 21-**Me**), 0.86 (s, 3H, 19-**Me**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 155.5, 141.5, 119.3, 113.7, 95.5, 94.6, 94.3, 91.6, 83.4, 80.7, 76.0, 70.3, 56.0, 55.1, 51.8, 44.5, 41.5, 40.8, 36.9, 36.0, 35.0, 34.1, 29.3, 28.5, 28.2, 26.8, 22.4, 21.4, 15.3, 12.0, 9.0; Acetate of 23-*epi*-**79** (23*S*-epimer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (dt, "m" like, 1H, *J* = 2.7, 8.4 Hz, C_{23}**H**), 5.28 (s, 1H, C_{15}**H**), 4.63-4.77 (7H, C_{26}**H,** C_{16}**H**, 3/12-O**M**OM), 3.95 (t, 1H, *J* = 7.2 Hz, C_{22}**H**), 3.84 (dd, 1H, *J* = 4.5, 8.2 Hz, C_{12}**H**), 3.64 (s, 1H), 3.41-3.55 (m, 1H, C_3**H**), 3.38 (s, 3H, 12-OMO**M**), 3.36 (s, 3H, 3-OMO**M**), 2.47 (p-like, 1H, *J* = 7.2 Hz, C_{20}**H**), 2.49-2.56 (1H, C_{24}**H$_a$**), 2.22 (dd, 1H, *J* = 9.6, 14.1 Hz, C_{24}**H$_b$**), 2.00 (s, 3H, 23-**Ac**), 1.77 (s, 3H, 27-**Me**), 1.13 (s, 3H, 18-**Me**), 1.00 (d, 3H, *J* = 7.2 Hz, 21-**Me**), 0.86 (s, 3H, 19-**Me**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 155.6, 142.1, 119.0, 113.3, 95.6, 94.6, 93.6, 91.7, 83.0, 75.9, 70.9, 56.0, 55.6, 55.1, 51.9, 44.4, 41.8, 40.4, 36.8, 36.0, 35.0, 34.0, 29.6, 28.5, 28.2, 26.8, 22.5, 21.1, 15.0, 12.0, 8.7; LRMS-ESI (*m/z*): 599.2 ([M+Na]$^+$).

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Highlights

1. Mercuric acetate promotes cyclic enol ethers with alkenyl side chain at 2-position to form spiroketals.
2. Iodide-catalyzed abnormal Baeyer-Villiger oxidation of a steroidal sapogenin deliveres the corresponding dinorcholanic lactone.
3. β-Adduct of D-ring diene with singlet oxygen would rearrange to form an unprecedented tricyclic structure.
4. When a leaving group present at C14, C14–C15 double bond tends to undergo S_N2' reaction inter- or intramolecularly.
5. Both spiroketals of cephalostatin 1 are thermodynamically favorable.