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A Practical Synthesis of Cephalostatin 1

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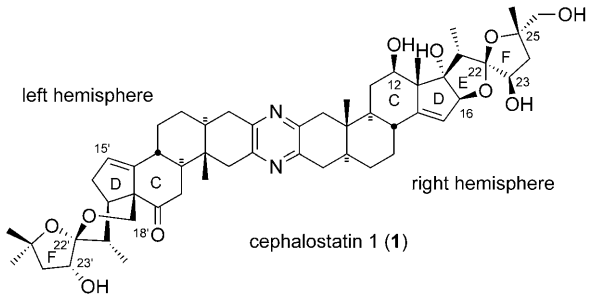
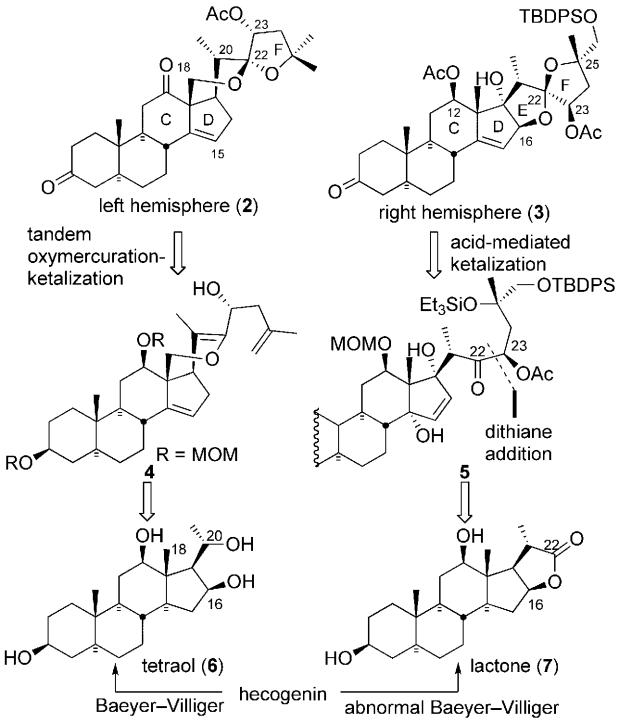
Cephalostatin 1 is among the most powerful anticancer agents ever tested by the National Cancer Institute. It is not only the first discovered but it is also the most potent one out of the 45 structurally related natural pyrazine bis-(steroids) comprised with cephalostatins and ritterazines



(isolated by Pettit et al. and Fusetani et al. from the Indian Ocean marine worm *Cephalodiscus gilchrst* and the tunicate *Ritterella tokio*, respectively).[1] The structure of cephalostatin 1 is characterized by an asymmetric union of two highly oxygenated steroidal spiroketal subunits with a central pyrazine ring. Its unique structure, extremely powerful cytotoxicity (with an IC_{50} value in the low nanomolar range), and natural scarcity have stimulated several synthetic endeavours.[2] Although the research groups of both Fuchs[3] and Shair[4] have completed the synthesis of cephalostatin 1 (**1**), more efficient/practical syntheses of cephalostatin 1 and its analogues are still highly demanded. Herein, we report a practical synthesis of cephalostatin 1.

As retrosynthetic analysis is shown in Scheme 1, cephalostatin 1 could be synthesized by the connection of two substructures, left hemisphere **2** and right hemisphere **3**. The E/F spiroketal ring of **2** would be constructed by a tandem oxymercuration–ketalization of the alkenyl enol ether in **4**. We also believed that a cascade ketalization of **5** could result in the formation of the E/F spiroketal ring of **3**. We envisaged that intermediates **4** and **5** could be prepared from pregnan-(3*S*,12*R*,16*S*,20*S*)-tetraol **6** and steroidal (3*S*,12*R*,16*S*)-triol-22-lactone **7**. Tetraol **6** and lactone **7** were conveniently prepared from hecogenin, a plant-derived ster-



Scheme 1. Retrosynthetic analysis for cephalostatin 1 (**1**).

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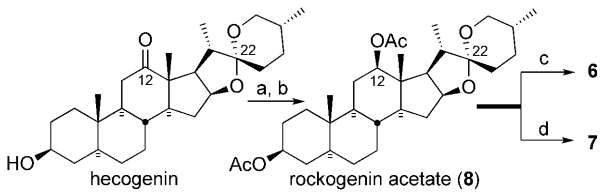
oidal sapogenin, which is available in large quantities at rather low cost (ca. $100–150/kg) in China, following two methods we have developed to degradate the steroidal sapogenins.[5]

Tetraol **6** and lactone **7** were prepared as illustrated in Scheme 2. Hecogenin was converted into rockogenin acetate (**8**) by reduction ($NaBH_4$, THF/MeOH, 12β/12α: 7.2–8.4/1) and acetylation (recrystallization from ethanol removed the



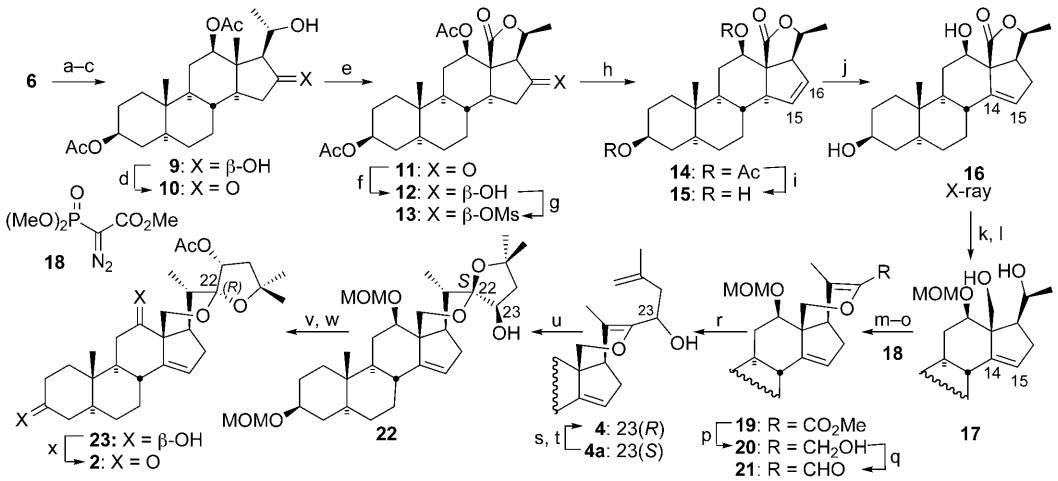
Scheme 2. Preparation of tetraol **6** and lactone **7**: a) $NaBH_4$, MeOH, THF, 0 °C, 2 h; b) Ac_2O, pyridine, 80 °C, 3 h, recrystallization from EtOH, 76% over two steps; c) HCOOH, 30% H_2O_2, 50 °C, 3 h; KOH, EtOH, reflux, 2 h, 93%; d) AcOOH, I_2 (10 mol%), cat. H_2SO_4, 5 h; KOH, EtOH, reflux, 5 h, 84%.

undesired 12α isomer) on large scale. Baeyer–Villiger oxidation of **8** with performic acid (generated in situ from commercially available 30% H_2O_2 and formic acid) followed by saponification provided tetraol **6** in 93% yield. In contrast, **8** reacted with peracetic acid in the presence of a catalytic amount of iodine to afford the abnormal Baeyer–Villiger oxidation product, steroidal lactone **7** in 84% yield. Both tetraol **6** and lactone **7** could be prepared on large scale (> 200 g in our laboratory), and the degradation methods worked well on other steroidal sapogenins (diosgenin and tigogenin).

With adequate amounts of **6** and **7** in hand, we turned our attention to their reactions and applications for the syntheses of **2** and **3**. The synthesis of the left hemisphere **2** involved three challenging transformations: (1) functionalization of the C18 angular methyl group, (2) introduction of the C14–C15 double bond, and (3) construction of the E/F-ring spiroketal. Our synthetic route for the left hemisphere is shown in Scheme 3.

There have been many reports about the remote intramolecular free radical functionalizations of (20*R*)-pregnanols. However, few examples for the (20*S*)-pregnanols, particularly for those with a substituted group in the D ring, are known.[6] To avoid the side reactions during the functionalization of the C18–CH_3 in **6**, selective protection of its hydroxy groups at C3, C12, and C16 was necessary. Tetraol **6** was subjected to acetonization (in acetone), acetylation (in acetic anhydride/pyridine), and deacetonization (in aqueous acetic acid) to afford diol **9**. Regioselective oxidation of the C16–OH in **9** was achieved under Dess–Martin conditions to afford **10**. Proximal funtionalization of the C18–CH_3 group in **10** was accomplished by using Meystre's hypoiodite method[7] (lead tetraacetate (LTA)/I_2, *hv*), which conveniently provided lactone **11** in 73% yield after Jones oxidation. Further investigation of this reaction demonstrated that C20(*S*)–OH is more suitable for C18–CH_3 functionalization than its C20(*R*)–OH isomer, owing to the faster reaction rate and higher yield, and in addition to the facile preparation of the substrate.

Preparation of compound **14** from **10** by the Shapiro reaction was not feasible because of the difficulty in gaining



Scheme 3. Synthesis of left hemisphere 2: a) acetone, TsOH, RT; b) Ac_2O, pyridine, DMAP, 80 °C, 2 h, 98% over 2 steps; c) 80% AcOH, 60 °C, 3.5 h, 86% (98% brsm); d) Dess–Martin periodinane, CH_2Cl_2, RT, 3 h, 82% (96% brsm); e) $Pb(OAc)_4$, I_2, cyclohexane, *hv*, reflux, 4 h; then Jones oxidation, 73%; f) $NaBH_4$, THF/MeOH (4:1), 0 °C, 20 min; g) MsCl, pyridine, DMAP, CH_2Cl_2, RT, 18 h; h) NaI, HMPA, 120 °C, 92% over three steps; i) K_2CO_3, MeOH, RT, 4.5 h, 99%; j) $RhCl_3{\cdot}3H_2O$, EtOH, 70 °C, 24 h, 82%; k) MOMCl, *i*Pr_2NEt, KI, CH_2Cl_2, reflux, 87%; l) $LiAlH_4$, THF, 40 °C, 96%; m) $Rh_2(OAc)_4$, **18**, benzene, reflux, 7 h, 80%; n) Jones oxidation, 97%; o) *t*BuOK, THF, 0 °C, 1 h, 87%; p) $LiAlH_4$, THF, RT, 1 h; q) Dess–Martin periodinane, CH_2Cl_2, RT, 97% over 2 steps; r) $CH_2C(CH_3)CH_2MgCl$, THF, 0 °C, 99% (52% for **4**, 47% for **4a**); s) Dess–Martin periodinane, CH_2Cl_2, RT; t) $NaBH_4$, THF/MeOH, 0 °C, 99% (43% for **4**, 56% for **4a**); u) $Hg(OAc)_2$, THF/H_2O (1:1), RT, 40 min; then $NaBH_4$, aq. NaOH, 93%; v) Ac_2O, pyridine, DMAP, CH_2Cl_2, RT, 99%; w) $LiBF_4$, CH_3CN/H_2O, reflux, 4 h, 93%, **23**: 22-*epi*-**23** = 3:1; x) Jones oxidation, 90% (65% for **2**, 25% for 22-*epi*-**2**). DMAP = 4-dimethylaminopyridine. brsm = based on recovered starting material.

access to the C16 of the tosylhydrazone of **10**. Stereoselective reduction of **11** with $NaBH_4$ afforded the C16(*S*)-hydroxy lactone **12**, which after subsequent conversion into mesylate **13** underwent iodination (or bromination)-elimination to provide the Δ^{15} compound **14** in 92% yield over three steps.

Surprisingly, the $RhCl_3$-catalyzed double bond migration[8] did not work when the C3−OH was protected as either an acetate or as a *tert*-butyldiphenylsilyl (TBDPS) ether. However, the reaction was dramatically accelerated when a catalytic amount of progesterone-3-ol was added. This result indicated that the rhodium(I) (generated by oxidating the substrate) might be the real active catalyst for this transformation. For this reason, compound **14** was hydrolyzed to afford **15** (without increasing the overall number of steps of the synthesis because the C3,12-acetates needed to be converted into methoxymethyl (MOM) ethers anyway). Gratifying, **15** was treated with 10 mol% $RhCl_3$ (EtOH, 70°C, 24 h) to afford the desired 3,12-dihydoxy-Δ14-lactone **16** (X-ray structure available)[9] in 82% yield, along with a small amount of the 3-oxo byproduct (about 5%). Compound **16** was reprotected as MOM ethers and treated with $LiAlH_4$ to afford (18,20*S*)-diol **17** in high yield.

The direct introduction of the side chain to **17** by selective oxidation (C20−OH) and an inter- or intramolecular Horner–Wadsworth–Emmons (HWE) reaction was unsuccessful. Referring to Fuchs' procedure,[10] diol **17** was conveniently transformed into pentacyclic ester **19** in 67% overall yield, although it has a different structure to that of the one reported by Fuchs, in which the C14−C15 double bond was saturated. This highly efficient sequence involved regioselective rhodium-mediated C18−OH insertion reaction of α-diazophosphate ester **18** ($Rh_2(OAc)_4$, PhH, reflux), Jones oxidation of the C20−OH, and an intramolecular HWE reaction between the C18 phosphonate ester and the C20 ketone (*t*BuOK, tetrahydofuran (THF), 87%).

Reduction of **19** with $LiAlH_4$ followed by Dess–Martin oxidation afforded the corresponding aldehyde at C23 in 97% overall yield. Aldehyde **21** was subjected to various methylallylation conditions, among which treatment with methylallylmagnesium chloride at 0°C exhibited the best selectivity, thus affording **4** and **4a** as a 1.1:1 mixture in nearly quantitative yield.[11] The minor 23(*S*) isomer **4a** was further converted into **4** by an oxidation–reduction protocol in 43% yield (with **4a** recovered in 56%).

With key intermediate **4** in hand, we next turned our attention to the construction of the spiroketal moiety by utilizing the enol ether and alkene in **4**.[12] Treatment of **4** with 2.2 equivalents of $Hg(OAc)_2$ in a solution of deoxygened THF followed by reduction with $NaBH_4$ directly provided **22** with the E/F spiroketal moiety in 93% yield.[13] The stereochemical outcome at C20 and C22 of this transformation was similar to those previously reported (acid-mediated cyclization by Fuchs,[14] and bromoetherification/reductive debromination sequence by Shair).[4] This transformation was considered as a tandem oxymercuration–ketalization protocol. It is noteworthy that the oxomecuration of enol ether in **4** differs from that of the alkene; the former afforded abnormal *cis*-addition product, while the latter provided the *trans*-addition product.

Although the *S* stereochemistry at C22 of **22** was undesired, it can be easily transformed into its natural stereoisomer under suitable reaction conditions. Acetylation of **22** gave its C23 acetate. Removal of the MOM protecting groups with $LiBF_4$ in refluxing aqueous acetonitrile[15] resulted in isomerization at C22, thereby leading to an inseparable equilibrium mixture (3:1) of the C22(*R*) (**23**) and C22(*S*) (22-*epi*-**23**) spiroketals, as expected. The resulting mixture was then subjected to Jones oxidation to yield the known diketone **2** and its 22-epimer in 65% and 24% yield, respectively. The new strategy for the construction of the E/F spiroketal rings of **2** from **4** required only four reaction steps, which is much shorter than 10 steps, as previously reported for comparable transformations from similar synthetic precursors.

The right hemisphere **3** is not only the most common unit in the cephalostatin family, but is also strongly associated with the most potent antitumor activity based on the research results of their structure–activity relationship.[2] Therefore, a highly efficient synthesis is very important, not only for cephalostatin 1 but also for all the pyrazine bis(steroids).

The synthesis of the right hemisphere is depicted in Scheme 4 and 5. To minimize the unnnecessary redox manipulations, various conditions have been investigated to open the lactone ring directly, however, all of which met with failure. Therefore, lactone **7** was protected as C3,C12-MOM ethers and reduced with $LiAH_4$. The resulting diol underwent selective acetylation of the primary C22−OH and mesylation–elimination of C16−OH in one pot to afford steroid-16-en-22-ol **24** in 60–76% overall yield. Treatment of **24** with *N*-bromosuccinimide (NBS) and azobisisobutyronitrile (AIBN) in refluxing tetrachloromethane for 10 hours resulted in direct formation of the conjugated double bond in the D ring by allylic bromination–elimination to give diene-22-acetate in 87% yield. Solvolysis of acetate, followed by oxidation with Dess–Martin reagent formed C22 aldehyde, which was further converted to the corresponding thioketal **26** by treating it with propanedithiol and 10 mol% of TsOH at 0°C.

With thioketal **26** and aldehyde **27**[16] in hand, we were set to achieve their union. The metalation of thioketal **26** proved to be quite difficult because of the bulkiness of the steroid skeleton. After screening several anion-generating conditions (*n*BuLi; *t*BuLi, hexamethyl phosphoramide (HMPA)/THF; *n*BuLi/*t*BuOK; *n*BuLi/nBu_2Mg,[17] etc), we found that generation of the desired lithio derivative of **26** was short-lived and it was necessary to be quickly trapped. After treatment of **26** with *n*BuLi at 0°C for 10 minutes, the resulting anion was immediately trapped with **27** at −78°C to afford an inseparable mixture of isomers (5–6:1), favoring the desired 23(*R*)-stereoisomer **28** in 68% yield (91% based on recovered starting material). The C23(*R*) stereochemistry of **28** was proposed according to the transition state of the

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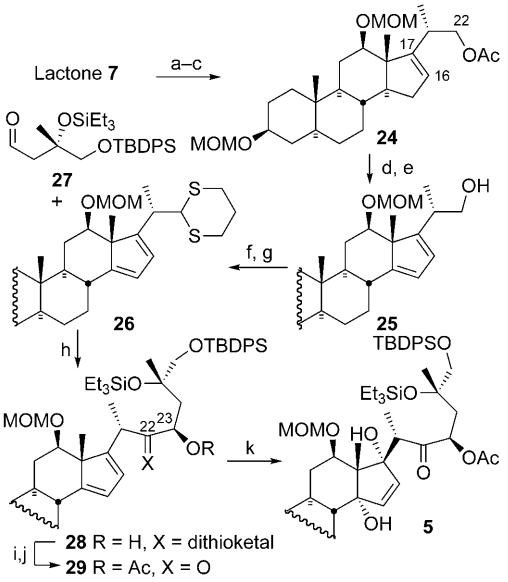
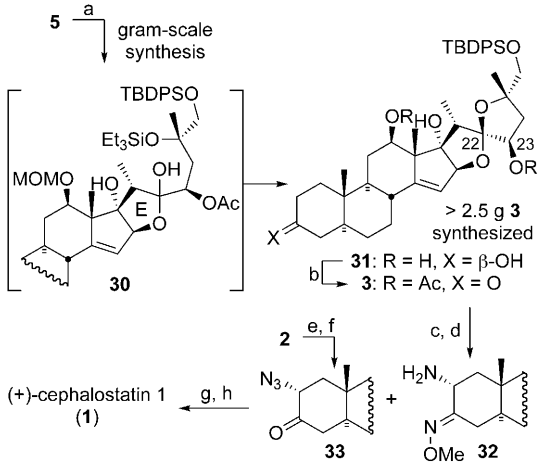


Scheme 4. Synthesis of dithiane **8** and aldehyde **7**: a) MOMCl, *i*Pr_2NEt, Bu_4NI, CH_2Cl_2, reflux, 6 h, 95%; b) $LiAlH_4$, THF, RT, 2 h, 99%; c) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0°C; MsCl, pyridine, 55°C, 4 h, 60–76%; d) NBS, AIBN, cyclohexene oxide, CCl_4, reflux, 87%; e) K_2CO_3, MeOH, RT, 97%; f) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 91%; h) 1,3-propanedithiol, cat. TsOH, CH_2Cl_2, 0°C, 4 h, 87%; h) *n*BuLi, THF, 0°C, 25 min; then −78°C, **27**, 2 h, 68% (91% brsm); i) $PhI(OCOCF_3)_2$, $CaCO_3$, CH_3CN/water, 0°C, 10 min; j) Ac_2O, Et_3N, DMAP, CH_2Cl_2, RT, 97%; k) O_2, TPP, CH_2Cl_2, −78°C, sunlamp, 2 h; then Zn, AcOH, THF, 4 h, 62% (68.4% brsm). TPP = 5,10,15,20-tetraphenyl-21H,23H-porphine.



Scheme 5. Synthesis of right hemisphere **3** and completion of the synthesis of cephalostatin 1: a) 1 M HCl/THF (1:10), RT, 2 h, 90% **30**; or 1 M HCl/THF (1:10), 45°C, 45 h, 59–68% **31**; b) Ag_2CO_3 on Celite, toluene, Dean–Stark Trap, reflux, 4 h; then Ac_2O, DMAP, Et_3N, CH_2Cl_2, 92%; c) $PhNMe_3Br_3$, THF, 15 min, 91%; d) NaN_3, DMF, 0°C, 2 h; $MeONH_2$·HCl, pyridine, CH_2Cl_2, RT, 4 h; PPh_3, THF/water, RT, 20 h, 50–70%; e) $PhNMe_3Br_3$, THF, 0°C, 10 min, 87%; f) TMGA, $MeNO_2$, RT, 4 h, 86%; g) PVP, Bu_2SnCl_2, benzene, Dean–Stark trap, 6 h, 67%; h) TBAF, THF, reflux, 2 h; then K_2CO_3, MeOH, 3 h, reflux, 86%. TMGA = tetramethylguanidinium azide; PVP = polyvinylpyridine; TBAF = tetrabutylammonium fluoride.

Cram–Reetz model.[18] It was further confirmed in subsequent transformations.

It was desirable to convert **28** into **31** in one pot.[19] However, the attempt was unsuccessful because the reaction was too complex. For this reason, we first transformed **28** into **29** through oxidative dethioketalization[20] and acetylation. The cycloaddition reaction of **29** with singlet oxygen, which occurred with moderate stereoselectivity (α/β: 2.5–4.5:1 measured by NMR spectroscopy on the crude product), followed by reduction with Zn/HOAc in tetrahydrofuran afforded **5** in 62% yield (d.r.: 10:1). Using tetrahydrofuran as a solvent for this reduction is crucial to obtain compound **5**.

Treatment of **5** with 1 M HCl in tetrahydrofuran at room temperature for two hours led to **30** in 90% yield.[21] However, conducting this reaction at 45°C for two days provided the expected product **31** in 68% yield (C22(*S*),C23(*R*)/C22(*S*),C23(*S*): 12–15:1), along with another inseparable mixture of two isomers (C22(*R*),C23(*R*) and C22(*R*),C23(*S*): 4:5) in 15–21% yield. This highly efficient transformation involved the removal of protecting groups at C3,C12,C23, and C25 in **5** and the construction of the E/F-ring spiroketal in one operation.

Efforts on selective hydrolysis of the C3 acetate in triacetate of **31** were met with failure due to the competition of the C23 acetate. Selective oxidation of the C3−OH in **31** with Ag_2CO_3/Celite (known as Fétizon's reagent)[22] followed by acetylation provided the right hemisphere **3** in 92% yield. A significant amount of **3** has been prepared by this route (>2.5 g in total, with largest run harvests 698 mg) in our laboratory. The synthesis of **3** from steroidal lactone **7** was achieved in 13 steps in 18% overall yield.

With the left hemisphere **2** and the right hemisphere **3** in hand, the synthesis of cephalostatin 1 (**1**) was completed as illustrated in Scheme 5. The coupling partners, azidoketone **33** and aminomethoxime **32**, were obtained by known protocols.[3a,23] Condensation of **33** (1.1 equiv) with **32** in benzene delivered the protected cephalostatin 1 in 67% yield. The global deprotection resulted in (+)-cephalostatin 1 (**1**) in 86% yield (ca. 250 mg of **1** prepared in this laboratory). The spectroscopic properties of our compound **1** are consistent with those reported in the literature.

In conclusion, a new synthetic strategy for natural sterols is illustrated through the synthesis of (+)-cephalostatin 1, which features: 1) using pregnan-(3*S*,12*R*,16*S*,20*S*)-tetraol (**6**) and steroid-16(*S*),22-lactone (**7**) instead of the traditional prognenolone or epiandrostenone as a starting point for sterols synthesis for the first time; 2) the construction of chiral centers of target molecules by using either substrate control or chiral starting materials, with an emphasis on excluding expensive reagents and difficult operations; 3) the successful application of cascade reactions (the construction of spiroketals in **22** and **31**) and one-pot reactions made our synthesis convenient, simple, and practical. This practical synthesis of (+)-cephalostatin 1 also represents an excellent example for the rational utilization of readily available resource compounds (resource chemistry). Utilizing such syn-

thetic strategies for the synthesis of pyrazine bis(steroids) and other marine natural steroids are in progress.

Acknowledgements

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Keywords: cephalostatin 1 · natural products · spiroketal · steroids · synthesis design

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