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Synthesis of Two Epimeric Secosteroids, Strophasterols A and B

Shuntaro Sato, Yuki Fukuda, Yusuke Ogura, Eunsang Kwon, and Shigefumi Kuwahara*

Abstract: Two epimeric rearranged ergostanes, strophasterols A and B, with an unprecedented carbon skeleton have been synthesized from ergosterol, both in 17 steps via a common secosteroidal intermediate. The conversion of ergosterol into the pivotal intermediate involved an efficient acid-catalyzed double bond migration from ring B to ring D, oxidative cleavage of the double bond, and a completely diastereoselective acyl radical cyclization to form an isolated cyclopentanone ring unique to this recently-discovered family of steroidal compounds produced by mushrooms. The intermediate was transformed stereodivergently into two epimeric cyclopentane derivatives via hydrogenation using two types of catalysts. One of the epimer was elaborated into strophasterol B by utilizing peracid oxidation of an iodide to provide an epoxide directly, and the other epimer into strophasterol A known as a suppressor of endoplasmic reticulum stress.

In the course of screening for ER (endoplasmic reticulum) stress-suppressing and anti-methicillin resistant *Staphylococcus aureus* (MRSA) substances of mushroom origin, Kawagishi and co-workers discovered four novel steroidal compounds in the extract of the fruiting body of *Stropharia rugosoannulata*, an edible mushroom, and named them strophasterols A, B, C, and D.[1] The structures of strophasterols A and B, including their absolute configurations, were determined to be **1** and **2**, respectively, by X-ray crystallographic analysis of the corresponding bis-*p*-bromobenzoates (Figure 1),[1,2] while strophasterols C and D were only given a planar structure represented by **3** that bears an additional keto functionality at the C23 position.[3] Quite recently, Aung and co-workers also isolated strophasterol C from the fruiting body of *Cortinarius glaucopus* along with some novel steroids including glaucoposterol A (**4**) with the same carbon skeleton as the strophasterols, and revealed the absolute configuration of strophasterol C to be the same as that of strophasterol A based mainly on its NOESY spectrum and biosynthetic considerations.[4] The totally unprecedented carbon framework found in strophasterols A–D and glaucoposterol A was hypothesized to be biosynthesized from ergosterol (**5**) via **6**, a suppressor of osteoclast formation also isolated from *S. rugosoannulata*,[5] through its D-ring cleavage followed by bond formation between C15 and C22 to form a new five-membered ring (ring D', see structure **1**) characteristic of this small family of natural products.[1,6] From the viewpoint of biological activity, strophasterol A was shown to exhibit moderate anti-MRSA effect as well as suppress the ER stress-dependent apoptotic neuronal cell death;[1,7] ER stress is considered to be a major cause of neurodegenerative disorders such as Alzheimer's disease.[1,8] Detailed biological evaluation of the strophasterols was, however, precluded due to their limited availability from natural sources.

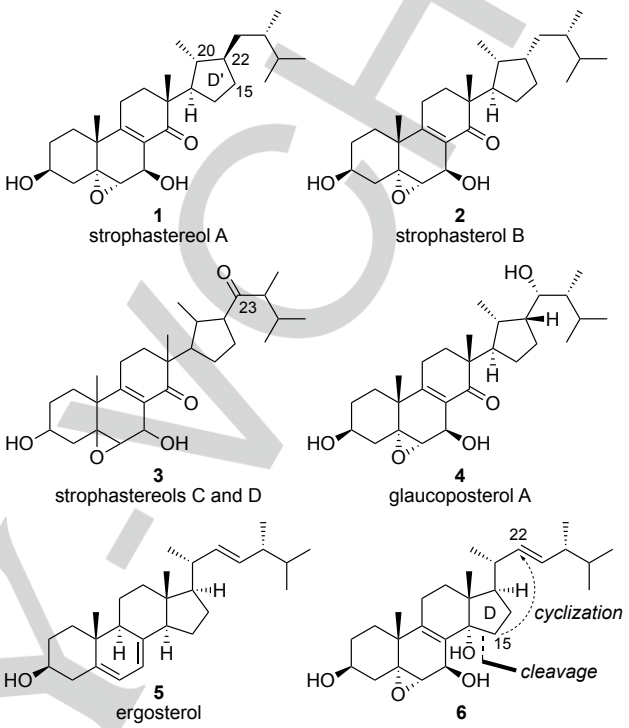

Figure 1. Structures of strophasterols A (**1**), B (**2**), and related natural products.

The strikingly unique carbon skeleton of the strophasterols unveiled for the first time in the long history of steroid chemistry coupled with the intriguing biological profiles of **1** prompted synthetic studies on this class of natural products, which recently culminated in the first synthesis of **1** from **5** by the Heretsch group that featured unique base-promoted D-ring cleavage of a steroidal intermediate and 5-*exo*-trigonal radical cyclization of an iodo olefin to form the D'-ring exclusively in a 20,22-*trans* fashion.[9] We were also attracted by the unprecedented carbon framework of the strophasterols and, in addition, took interest in their essential physiological roles in mushrooms per se, which inspired our synthetic efforts to supply them in sufficient amounts for detailed biological evaluation. We describe herein our synthesis of **1** and **2** (22-*epi* form of **1**) from **5** via a common synthetic intermediate.

Scheme 1 outlines our retrosynthetic analysis of **1** and **2**. Compound **1** with 20,22-*trans* configuration would be derived from **7** by its B-ring functionalization using the 14-keto group as the foothold, while 20,22-*cis* isomer **2** (22-*epi*-**1**) from 22-*epi*-**7**. As a common precursor of **7** and 22-*epi*-**7**, we set 20,22-*trans*-substituted cyclopentanone **8** since its stereodivergent transformation into each of the two epimers was considered to be possible by taking advantage of the 15-keto function next to the C22-substituent. The intermediate **8** was then traced back to olefinic carboxylic acid **9** with the expectation that 5-*exo*-trigonal cyclization of an acyl radical species generated from **9** would lead to **8** in a diastereoselective manner due to its higher thermodynamic stability compared to the corresponding 20,22-*cis* cyclization product. Compound **9** would be prepared by Δ^{14}-selective

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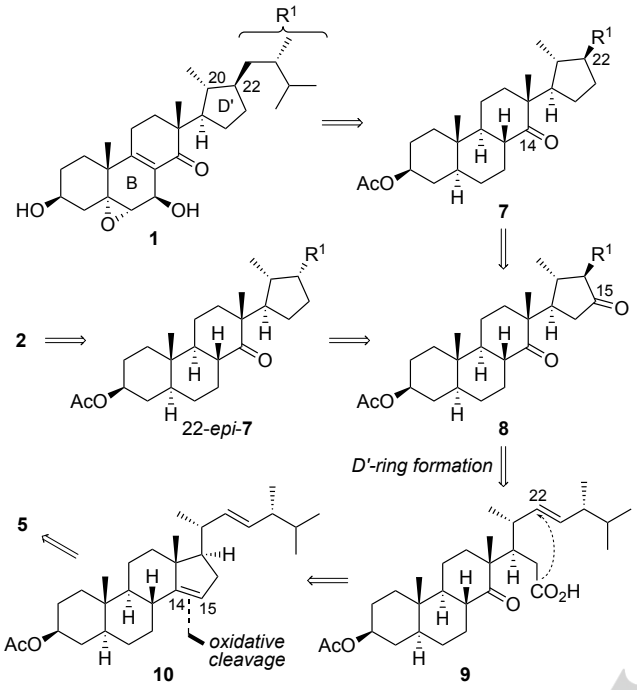
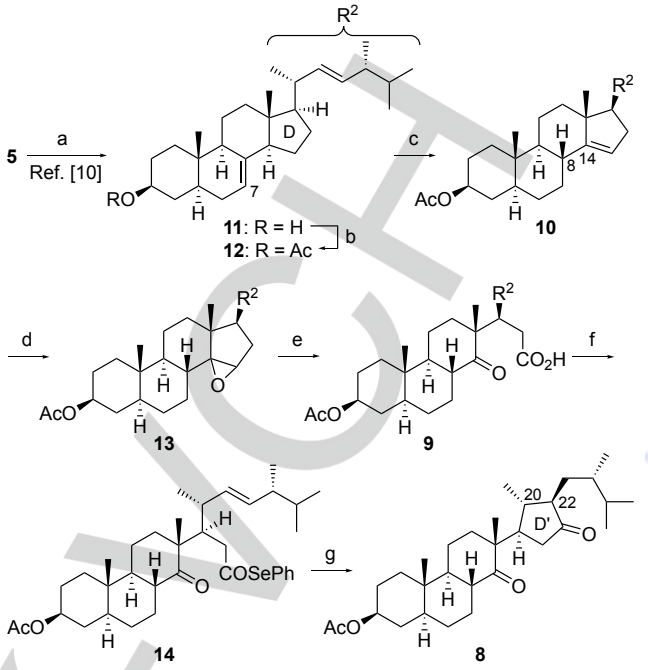
oxidative cleavage of **10**, which, in turn, would be accessible from **5** via double bond migration as the key step.



Scheme 1. Retrosynthetic analysis of **1** and **2**.



Scheme 2. Preparation of intermediate **8** with the D'-ring installed. Reagents and conditions: a) Li, 2-methyl-2-butanol, THF, liq. NH_3, –78 °C, 99%; b) AcCl, pyridine, RT, 98%; c) HCl, CH_2Cl_2, –78 °C, 71% (85%, based on a single separation/re-equilibration cycle); d) MMPP, EtOH/CH_2Cl_2, RT, 82%; e) CrO_3, H_2SO_4, acetone, RT, 77%; f) PhSeCl, *n*Bu_3P, Et_3N, THF, RT, 94%; g) *n*Bu_3SnH, AIBN, C_6H_6, 80 °C, 65%. MMPP = magnesium monoperoxyphthalate, AIBN = 2,2'-azobis(isobutyronitrile).

The preparation of the common intermediate **8** began with the acetylation of known sterol **11** obtained by the Birch reduction of **5** (Scheme 2).[10] Treatment of the resulting acetate **12** with hydrogen chloride in CH_2Cl_2 at –78 °C brought about the migration of the Δ^7 double bond, furnishing quantitatively a ca. 5:2 mixture of **10** (Δ^{14}-isomer) and its $\Delta^{8(14)}$-isomer, from which the two positional isomers could be isolated in yields of 71% and 28%, respectively, by column chromatography on SiO_2/$AgNO_3$. Re-exposure of the latter isomer to the same reaction conditions effected re-equilibration of the $\Delta^{8(14)}$ double bond, furnishing an additional amount of **10** in 14% yield (total yield: 85%).[11,12] The double bond positions in **10** and its $\Delta^{8(14)}$-isomer were assigned by comparison of their ^{13}C NMR data with those reported for analogous steroids.[13] Compound **10** was then exposed to magnesium monoperoxyphthalate to regioselectively give epoxide **13**,[14] the oxidative cleavage of which under Jones' oxidation conditions afforded keto carboxylic acid **9**.[15] Compound **9** was converted into the corresponding selenoester **14**,[16] the exposure of which to Boger's acyl radical cyclization conditions furnished the pivotal intermediate **8** with 20,22-*trans* configuration as a single diastereomer.[17] The stereochemical assignment of **8** was performed on the basis of diagnostic NOE correlations observed among some protons around the newly formed D'-ring (see the Supporting Information).

With the key intermediate **8** in hand, we set about its stereodivergent transformation into **7** and 22-*epi*-**7** (Scheme 3), which have the same configuration in their D'-ring units as **1** and **2**, respectively. With the intention of obtaining **7** by desulfurization of dithiane derivative **15**, compound **8** was treated with 1,3-propanedithiol and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature for 2 h. The dithioacetalization proceeded regioselectively at the keto function on the D'-ring, but unexpectedly, the product obtained quantitatively was a ca. 2:1 mixture of **15** and its C22-epimer (22-*epi*-**15**). Fortunately, SiO_2 column chromatography enabled the separation of the two epimers, providing **15** and 22-*epi*-**15** in isolated yields of 60% and 31% respectively. Each epimer was subjected to Raney nickel desulfurization to afford **7** (66% yield) and 22-*epi*-**7** (65% yield); the relative configuration of **7** was determined by X-ray crystallographic analysis.[18] The generation of 22-*epi*-**15** would be explainable by the intervention of a thioenol ether intermediate prior to the dithiane ring formation (cf. structure **16**). Interestingly, this epimerization was suppressed when the reaction was conducted at –40 to –20 °C, affording **15** as virtually a single isomer in 94% yield and thereby establishing a diasteroselective two-step route from **8** to **7** in 62% overall yield. Although 22-*epi*-**7**, which we set as a precursor to **2**, could also be secured (20% yield through 2 steps from **8**) by conducting the dithioacetalization at room temperature, we sought a better way to give 22-*epi*-**7** preferentially and examined stereoselectivity in the hydrogenation of trisubstituted cyclopentene **17** prepared from **8** via thioenol ether **16**.[19] After considerable experimentation, we found that exposure of **17** to hydrogen in the

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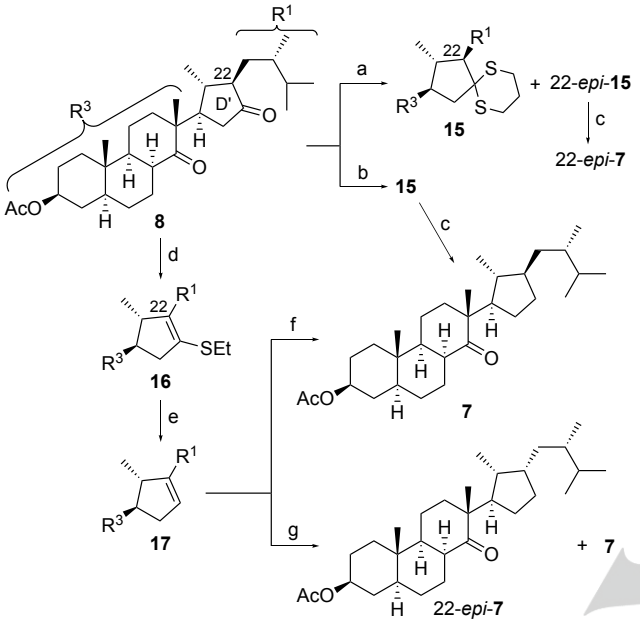
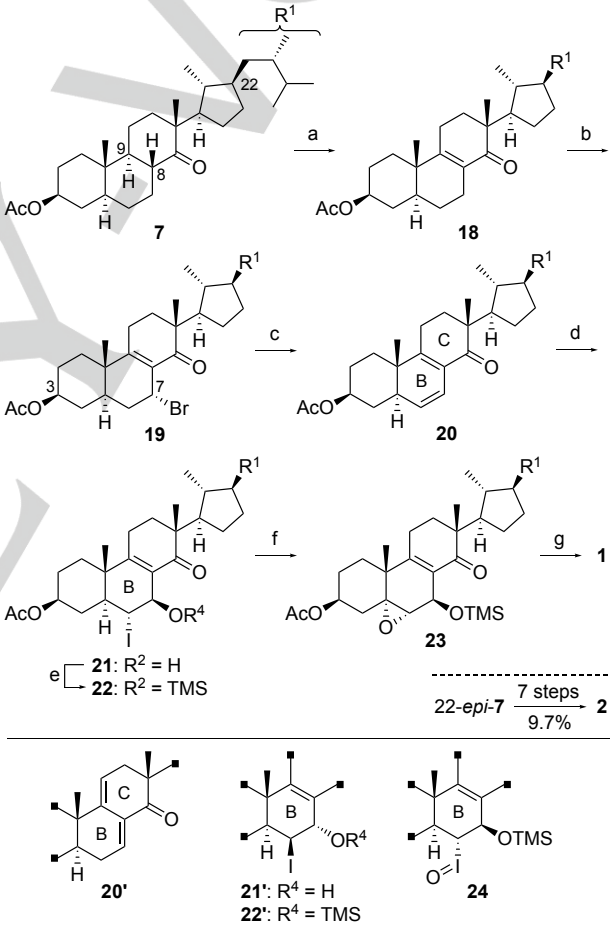
presence of palladium on carbon in hexane gave **7** exclusively (95% isolated yield),[20] while hydrogenation with Crabtree's catalyst in CH_2Cl_2 afforded a separable 1.7:1 mixture of 22-*epi*-**7** and **7**, favoring the former isomer.[21] Chromatographic separation of the mixture provided 22-*epi*-**7** in 58% yield (and **7** in 34%), thus realizing the preferential formation of 22-*epi*-**7** from the common intermediate **8**.



Scheme 3. Stereodivergent transformation of **8** into **7** and 22-*epi*-**7**. Reagents and conditions: a) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, RT, **15**: 60%, 22-*epi*-**15**: 31%; b) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –40 to –20 °C, 94%; c) H_2, Raney Ni, THF, EtOH, RT, 66% for **7**, 65% for 22-*epi*-**7**; d) EtSH, TMSCl, CH_2Cl_2, RT, 88%; e) H_2, Raney Ni, EtOH, 60 °C, 83%; f) H_2, Pd/C, hexane, RT, 95%; g) H_2, Crabtree's catalyst, CH_2Cl_2, RT, 22-*epi*-**7**: 58%, **7**: 34%. TMSCl = trimethylsilyl chloride.

The B-ring functionalization of **7** and 22-*epi*-**7** leading to the target molecules **1** and **2**, respectively, is shown in Scheme 4. Installation of a double bond at the C8/C9-position of **7** was effected in one pot by α-bromination of the ketone followed by in-situ dehydrobromination to afford **18**.[22] Allylic bromination of **18** with *N*-bromosuccinimide and 2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile) gave 7α-bromo derivative **19** in 50% yield together with a small amount of a 7,11-dibrominated product.[23,24] The structure of **19** was assigned on the basis of a ^{1}H coupling sequence from H3 to H7 observed in its TOCSY spectrum as well as small coupling constants between H7 and the two adjacent protons at the C6 position.[25] Dehydrobromination of **19** to diene **20** was first attempted by its treatment with DBU in THF, but the product obtained was a ca. 1:4 mixture of **20** and undesired $\Delta^{7,9(11)}$-diene **20'**. This problem could be circumvented by prior conversion of **19** into a selenide intermediate and subsequent oxidative elimination in one pot, furnishing **20** in 74% yield, which set the stage for the installation of the epoxy alcohol unit on the B-ring. This challenging task was accomplished by a four-step sequence beginning with regio- and disasterselective iodohydroxylation of **20** with NIS in aq THF, which delivered a ca. 5.5:1 mixture of **21** and its diastereomer **21'**. The inseparable mixture was treated with TMSOTf in 2,6-lutidine to give **22** and **22'** in isolated yields of 48% and 9.7%, respectively, for the two steps. Exposure of the iodide **22** to *m*-chloroperbenzoic acid in CH_2Cl_2 in the presence of $NaHCO_3$ at room temperature elicited three consecutive reactions: (1) oxidation of **22** to iodoso compound **24**; (2) *syn*-elimination of **24** to form an olefinic intermediate bearing a Δ^5-double bond; and (3) epoxidation of the double bond by excess *m*CPBA from its less hindered α face to produce **23** in 78% yield.[26] Finally, removal of the two protecting groups at the C3 and C7 positions in one pot completed the synthesis of **1**, which showed good agreement with natural strophasterol A in NMR, melting point, and specific rotation. Application of essentially the same 7-step sequence of reactions to 22-*epi*-**7** afforded **2** (see the Supporting Information), the physical data of which were also identical with those reported for natural strophasterol B.



Scheme 4. Completion of the synthesis of **1** and **2**. Reagents and conditions: a) $PhNMe_3{\cdot}Br_3$, THF, 50 °C, then DBU, 50 °C, 89%; b) NBS, V-70, CCl_4, 40 °C 50%; c) PhSeSePh, $NaBH_4$, THF, RT, then 30% H_2O_2, RT, 74%; d) NIS, H_2O, acetone, RT; e) TMSOTf, 2,6-lutidine, RT, 48% (2 steps) (**21'**: 9.7%); f) *m*CPBA, $NaHCO_3$, CH_2Cl_2, RT, 78%; g) KOH, MeOH, RT, 80%. DBU = 1,8-diazabicyclo[5.4.0]-7-undecene; NBS = *N*-bromosuccinimide, V-70 = 2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile), NIS = *N*-iodosuccinimide, TMSOTf = trimethylsilyl trifluoromethanesulfonate, *m*CPBA = *meta*-chloroperbenzoic aicd.

In conclusion, strophesterol A (**1**) has been synthesized in 1.8% overall yield from ergosterol (**5**) by a 17-step sequence via **17** (or in

1.6% overall yield via **15** through 16 steps). The new synthesis featured: (1) efficient HCl-mediated double bond migration from ring B to ring D (**12** → **10**); (2) acyl radical cyclization to form exclusively the D'-ring with 20,22-*trans* configuration (**14** → **8**); (3) completely selective palladium-catalyzed hydrogenation to establish the 20,22-*trans*-relationship (**17** → **7**); and (4) *m*CPBA oxidation of protected iodohydrin **22** to deliver epoxide **23** in one pot. The first synthesis of strophasterol B (**2**) has also been achieved from **5** in 17 steps (1.1% overall yield) involving 20,22-*cis*-selective iridium-catalyzed hydrogenation as the pivotal transformation (**17** → 22-*epi*-**7**).

Acknowledgements

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Keywords: hydrogenation • radical reactions • steroids • strophasterol • total synthesis

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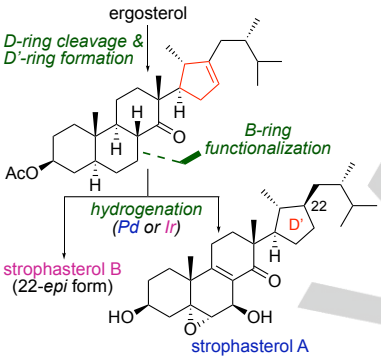
COMMUNICATION

Two from one: Two epimeric secosteroids of mushroom origin, strophasterols A and B, have been synthesized from ergosterol in a stereodivergent manner by using two types of hydrogenation. An isolated cyclopentane ring unit unique to the strophastane family of natural products was installed via an acyl radical cyclization and the B-ring functionalization was achieved through peracid oxidation of an iodide to deliver an epoxide directly.



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