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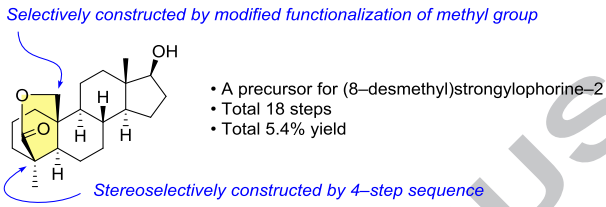

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Synthetic study of strongylophorines: stereoselective construction of the characteristic lactone bridge

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ABSTRACT

Herein, we report an efficient construction of the lactone bridge of strongylophorine–2, which is a meroditerpenoid isolated from *Strongylophora durissima* and an inhibitor for HIF–1 transcriptional pathway. Starting from dehydroepiandrosterone acetate, the characteristic lactone has been constructed in 5.4% over 18 steps by employing, (1) modified oxy radical-mediated C–H functionalization at the C24 methyl group, and (2) four-step manipulation of C4 quaternary carbon stereogenic center. The lactone synthesized here is expected as a precursor for (8–desmethyl)strongylophorine–2 which is of particular interest in terms of structure–activity relationships in the inhibition of HIF–1 transcriptional pathway.

Introduction

Hypoxia inducible factor–1 (HIF–1) upregulates expression of genes and protein such as vascular endothelial growth factor (VEGF) associated with tumor growth and progression.[1] Inhibitor for hypoxia-activated HIF–1 transcriptional pathway often acts as an anticancer agent,[2] and in 2008, strongylophorines–2 (**1**, Fig. 1)[3,4] and –8 (structure not shown)[4] were reported to belong to the class of these inhibitors.[5] Strongylophorine–2 (**1**), first isolated in 1978 from marine sponge,[3,4] *Strongylophora durissima*, is a meroditerpenoid composed of δ–lactone (A'–ring) and hydroxychromane (DE–ring) fused to perhydrophenanthrene core skeleton (ABC–ring). Because of the limited availability from natural resources, the mode of action as the inhibitor for HIF–1 transcription pathway has not been unfortunately clarified. We, therefore, started a program on synthesis of **1** and the analogs. Here, we report our progress toward a synthesis of (8–desmethyl)strongylophorine–2 (**2**). Starting from dehydroepiandrosterone acetate, we have successfully established a route for formation of the unique and characteristic δ–lactone (A'–ring) which has been suggested to be important for the biological activity.[6] This is the first chemical synthesis of the δ–lactone bridge fused to perhydrophenanthrene in the strongylophorine synthesis.[7]

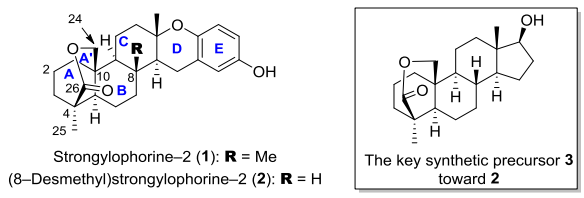
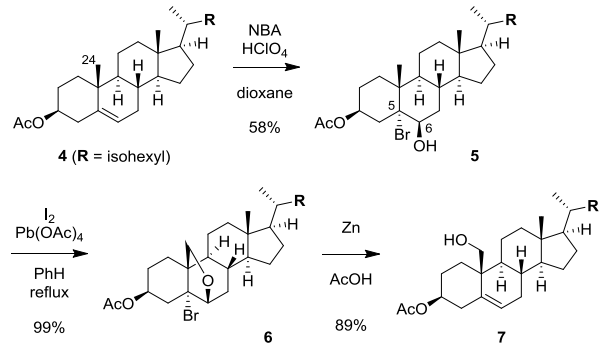


Figure 1. Our design and synthetic strategy for analog of strongylophorine–2. Numbering refers to that for strongylophorine–8.[5]

Results and discussion

As a model study, we first explored oxidation of methyl group at C24 by oxy radical-mediated iodination followed by



Scheme 1. Model study for C–H oxidation of C24 methyl group using cholesterol acetate (**4**).

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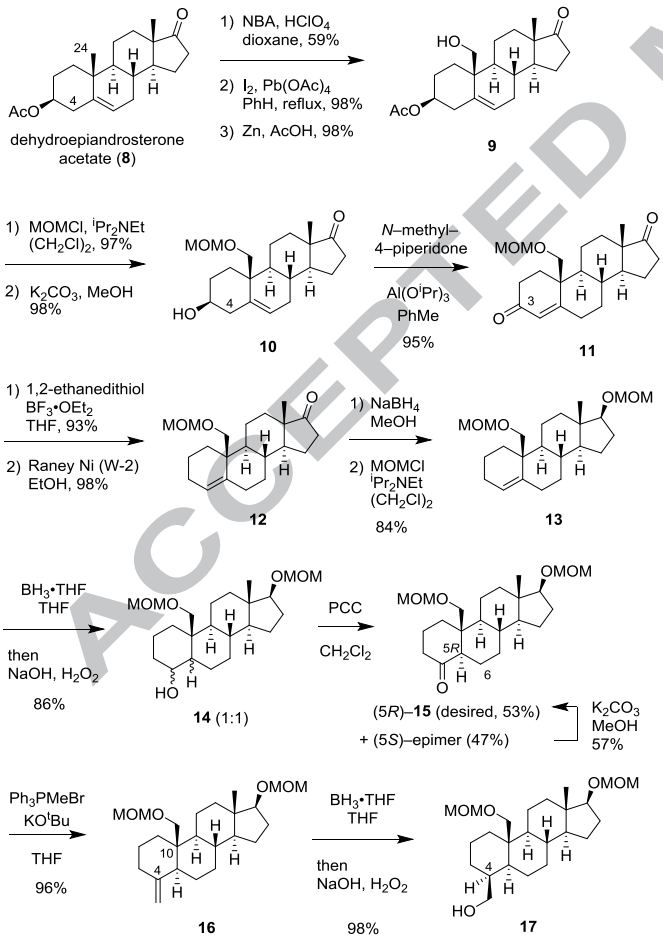
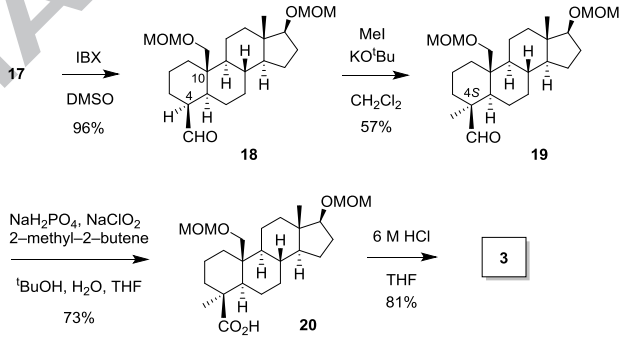
etherification using cholesterol as a model compound (Scheme 1). In 1985, Sucrow *et al* have reported the 3-step synthesis of alcohol **7** from cholesterol acetate (**4**) (50% total yield),[8] and we decided to improve the reactions in the present study. Thus, hypobromous acid (BrOH)-mediated bromination of cholesterol acetate (**4**) readily provided bromohydrin **5** in 58% with the diastereomer (17%, structure not shown).[9] We next attempted to improve the procedure for construction of tetrahydrofuran **6** by $Pb(OAc)_4$-mediated unfunctionalized C–H iodination and spontaneous ether formation. As mentioned above, the same reaction had been reported by Sucrow *et al* in 1985 under irradiation conditions with 500 W lamp.[8] Here we found the reaction proceeded without irradiation to give rise to **6** quantitatively, when the reagents were added to a solution of the substrate **5** in refluxing benzene to drive the reaction smoothly. It should be noted that other reaction conditions employing $PhI(OAc)_2$ and I_2 under ultrasonication[10] gave 5,6–β–epoxide in 42% yield (structure not shown), and the yield for desired **6** was quite low (18%). Reductive opening of bromo ether **6** readily provided homoallylic alcohol **7** in 89% yield. While our total yield (51% for 3 steps) for alcohol **7** from cholesterol acetate (**4**) is only comparable to that in Sucrow's procedure (50% for 3 steps),[8] our irradiation-free procedure significantly simplified the oxy radical-mediated remote functionalization of methyl group.

With the improved procedure shown in Scheme 1 in hand, we started our synthetic study of **2** from dehydroepiandrosterone acetate (**8**). The quaternary carbon stereogenic center at C4 was planned to be constructed in a stepwise manner, and Scheme 2 shows the synthesis of hydroxymethylated intermediate **17**. First, homoallylic alcohol **9** was synthesized over 3 steps from **8** according to the procedure shown in Scheme 1. The yield (57% for 3 steps) was higher than that reported previously (36%).[11] Protecting group manipulation of **9** gave secondary alcohol **10** in 95% yield for 2 steps. Oppenauer oxidation[12] provided enone **11** with concomitant migration of the olefin in good yield (95%). The C3 carbonyl group was then selectively removed to give rise to **12** via dithiane (structure not shown),[13] which was subjected to stereoselective reduction[14] followed by protection (MOMCl, $^iPr_2NEt$). Hydroboration of trisubstituted olefin **13** furnished alcohol **14** after work-up with NaOH and H_2O_2. Although alcohol **14** was an inseparable diastereomeric mixture (1:1), the desired (5*R*)–isomer was isolated after oxidation in 53% yield. The structure was determined on the basis of NMR analysis ($^3J_{H5,H6}$ = 12.0, 4.0 Hz). It should be also noted here that the conversion yield for the desired (5*R*)–isomer **15** from olefin **13** is actually much higher, since the undesired epimer, (5*S*)–**15**, can be thermodynamically epimerized under alkaline conditions (K_2CO_3, MeOH) to give desired (5*R*)–**15** in 57% yield. Toward elaboration of C4 quaternary carbon center, Wittig reaction (Ph_3PMeBr, KO^tBu) and hydroboration (BH_3 · THF; NaOH, H_2O_2) were successively carried out here to furnish alcohol **17** in 94% yield for 2 steps.[15,16]



Scheme 2. Functionalization at C4 and C24 positions starting from dehydroepiandrosterone acetate (**8**).



Scheme 3. Elaboration of the C4 stereogenic center and the lactone bridge toward **3**.

Introduction of methyl group at C4 was next investigated (Scheme 3). We expected that electrophilic substitution would deliver quaternary carbon stereogenic center at C4 stereoselectively under kinetic conditions.[16,17] Indeed, we were gratified to find that aldehyde **18**, prepared by IBX oxidation[18] of **17** in 96% yield, underwent deprotonation followed by stereoselective methylation to give rise to carboxylic acid **20** in 42% yield as a sole product after Pinnick oxidation.[19] The 4*S*–stereochemistry was determined after formation of the lactone bridge (see below). The low yield was due to the inherent instability of the substrate **18** and the product **19**, which suffer decomposition in one day even at 0 °C. Finally, acidic hydrolysis (6 M HCl, THF) induced concomitant deprotection of MOM groups of **20** and lactonization to furnish desired lactone **3** in 81% yield.

The structure of lactone **3** was unequivocally determined by de novo NMR spectroscopic analysis, which also supported 4*S*–stereoselectivity in the methylation (**18**→**19**). In addition, we were gratified to find that the ^{13}C NMR chemical shift values of synthetic **3** around A– and A'–rings are nearly identical to those of natural **1**[3,4] (Table 1), to indicate their identical configuration and conformation.

Conclusion

In conclusion, we have successfully established construction of the characteristic lactone bridge of strongylophorine–2 for the first time,[7] which is suggested to be important for the inhibitory activity for HIF–1 transcriptional pathway.[6] The synthesis of the key segment **3** was achieved in 5.4% yield over 18 steps starting from dehydroepiandrosterone acetate (**8**) by developing improved oxidative C–H functionalization at the C24 methyl group, followed by stereoselective construction of the C4 quaternary carbon stereogenic center in a stepwise manner. Current efforts are now focused on the synthesis of (8–desmethyl)strongylophorine–2 (**2**), which would be achieved in an additional 7–9 steps from **3** and the inhibitory activity is of particular interest in terms of the structure–activity relationships to develop more efficient inhibitor, and the results will be reported in due course.[20]

Table 1. Comparison of the ^{13}C NMR spectroscopic data for natural **1**[3,4] and synthetic **3**.

position	δc (natural, ppm)[a]	δc (**3**, ppm)[b]	Δδ (ppm)
1	38	38.4	-0.4
2	22.6	23.5	-0.9
3	40.3	40.1	0.2
4	43.2	43.5	-0.3
5	50	49.3	0.7
10	36.5	35.9	0.6
24	73.4	74.3	-0.9
25	23.5	23.6	-0.1
26	176	176.1	-0.1

a) Extracted from Faulkner paper (pyridine–d_5).[4]
b) Collected in pyridine–d_5 at 100 MHz.

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Supplementary data

Supplementary data (experimental procedures, ^{1}H and ^{13}C NMR spectra, and NOESY analysis of **17**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/.

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15. The hydroboration is highly α–selective. In a related example,[16] the hydroboration of exo-methylene at C4 has been reported to selectively take place from the α–side. Our observation is consistent with the report and the selectivity can be attributed to the presence of the sterically demanding axial $MOMOCH_2$– group at C10. See reference 16.
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20. Our future work will also focus on methylation of **3** at C8 position by C–H functionalization technology toward synthesis of **1**.

Highlights

Strongylophorine-2 is a meroditerpenoid isolated from marine sponge, *Strongylophora durissima.*

This compound is an inhibitor for HIF–1 transcriptional pathway.

Oxidative C–H functionalization at the C24 methyl group proceeded smoothly.

Construction of the C4 quaternary carbon stereogenic center was accomplished.

The characteristic lactone bridge was constructed in a stepwise manner.