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TOTAL SYNTHESIS OF DECAHYDROBENZO[*d*]XANTHENE SESQUITERPENOIDS AUREOL, STRONGYLIN A, AND STACHYFLIN: DEVELOPMENT OF A NEW STRATEGY FOR THE CONSTRUCTION OF A COMMON TETRACYCLIC CORE STRUCTURE

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Abstract – In this article, the total synthesis of rearranged sesquiterpenoid hydroquinones—aureol, strongylin A, and stachyflin—is reviewed with a particular focus on their methodology and strategy.

CONTENTS

1. INTRODUCTION

In recent years, a wide variety of natural products with unique structural features and attractive biological activities have been isolated from marine organism and microorganism.[1] Several of these natural products have received considerable attention owing to their potential for use as new therapeutic agents.[1] In most cases, however, further biological studies, including those focusing on structure–activity relationships (SARs), have been severely restricted probably because of the scarcity of samples and/or the structural

diversity of the natural products derived from natural resources. As a consequence, the development of efficient and flexible methods for the synthesis of bioactive natural products and their analogues is highly desirable and worthwhile from the viewpoint of medicinal/pharmaceutical chemistry.[2]

(+)-Aureol (**1**, Figure 1) was originally isolated from the Caribbean sponge *Smenospongia aurea* by Faulkner et al. in 1980[3] and subsequently in 2000 from a different species of the Caribbean sponge *Verongula gigantea*.[4] This marine natural product was found to exhibit selective antiproliferative activity against human tumor cells, including non-small-cell lung cancer A549 and colon adenocarcinoma HT-29 cells,[5] and anti-influenza A virus activity.[6] (+)-Strongylin A (**2**, Figure 1) was first isolated from the Caribbean sponge *Strongylophora hartmani* by Wright et al. in 1991[7] and subsequently from the Bahamian sponge *Xestospongia wiedenmayeri* by scientists from Schering–Plough Corporation (now Merck & Co., Inc.) in 1995.[8] This marine natural product was found to exhibit antiproliferative activity against P388 murine leukemia cells (IC_{50} = 13 μg/mL) and antiviral activity against the human influenza A/PR/8/34 (H1N1) virus in vitro (IC_{50} = 6.5 μg/mL).[7] (+)-Stachyflin (**3**, Figure 1) was isolated from the culture broth of *Stachybotrys sp*. RF-7260 by scientists from Shionogi & Co., Ltd., Japan, in 1997.[9] This secondary metabolite was found to exhibit potent antiviral activity against the human influenza A/WSN/33 (H1N1) virus in vitro (IC_{50} = 3 nM) with a novel mechanism of action.[9b] The antiviral activity of **3** has been shown to result from interference with a low-pH-induced hemagglutinin conformation change, which is indispensable for the virus-cell membrane fusion process that occurs during influenza

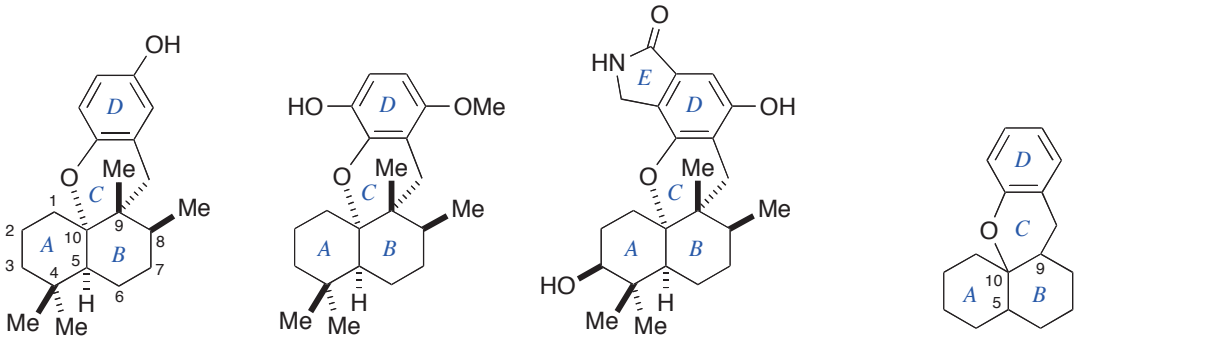


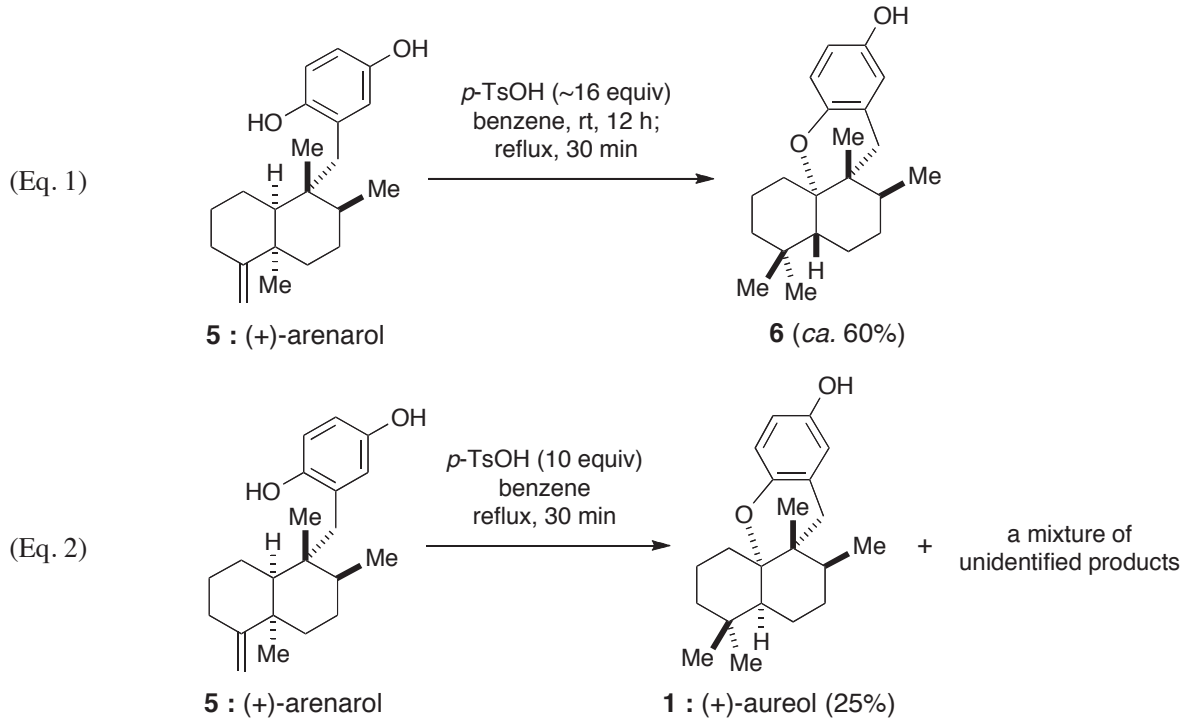
Figure 1. Structures of (+)-aureol (**1**), (+)-strongylin A (**2**), (+)-stachyflin (**3**), and decahydrobenzo[*d*]xanthene (**4**).

viral infection.[10] Structurally, **1**, **2**, and **3** possess a novel tetracyclic decahydrobenzo[*d*]xanthene skeleton (ABCD ring system) that consists of three asymmetric carbons at the C5, C9, and C10 positions, as depicted in structure **4** (Figure 1). Owing to the attractive biological properties and the unique structural features of these molecules, considerable attention has been devoted to the total synthesis of these decahydrobenzo[*d*]xanthene sesquiterpenoids (**1**–**3**).

In 2001, we embarked on a project directed at the total synthesis of this class of natural products. Our efforts culminated in the completion of the enantioselective total synthesis of **1** in 2002,[11] **2** in 2013,[12] and **3** in 2010.[13] The enantioselective total syntheses of **1** and its enantiomer (*ent*-**1**) were also reported by George et al. in 2012[14] and Marcos et al. in 2010,[15] respectively. The total synthesis of racemic (±)-**3** was presented by the Shionogi research group in 1998.[16] Through this synthetic study, the anti-influenza A viral activity of (±)-**3** was about half that of natural (+)-**3**.[16] An enantioselective approach to the tetracyclic core structure (see structure **4**) was published by Cramer et al. in 2010.[17] In the present article, the total syntheses of **1**–**3** are reviewed with a particular focus on synthetic strategy.

2. TOTAL SYNTHESIS OF AUREOL

It is envisaged that **1** might be produced biogenetically by the acid-induced rearrangement of (+)-arenarol (**5**) (Scheme 1), which was first isolated from the marine sponge *Dysidea arenaria* by Schmitz et al. in 1984,[18] and subsequently from a *Fenestrasongia* sp. by Faulkner et al. in 1985.[19] This type of acid-induced rearrangement has been successfully applied to determine the absolute configuration of marine sesquiterpene quinones and hydroquinones.[20,21] So far, to our knowledge, two examples of the acid-induced rearrangement of **5** have appeared in the literature (cf. Equations 1 and 2). In these examples, however, important synthetic chemical issues with respect to stereocontrol and efficiency were not



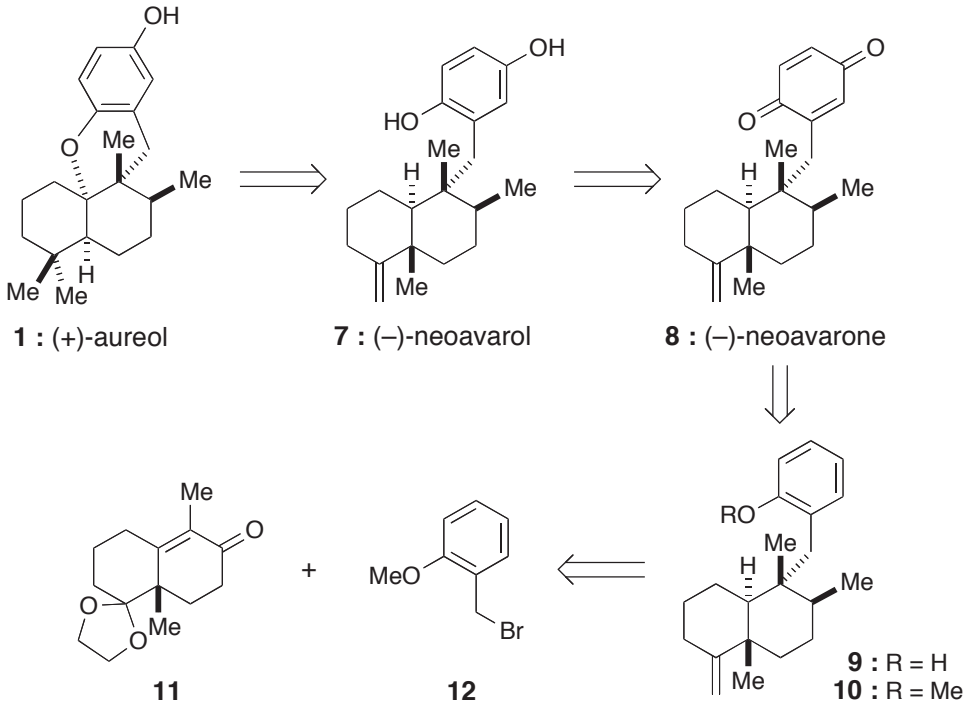
Scheme 1. Previous examples of acid-induced rearrangement of (+)-arenarol (**5**). *p*-TsOH = *p*-toluenesulfonic acid, rt = room temperature.

considered. Thus, in 1990, Schmitz et al. described that the treatment of **5** with a large excess (~16 equiv) of *p*-toluenesulfonic acid (*p*-TsOH) in benzene at room temperature for 12 h followed by reflux for 30 min resulted in the rearrangement/cyclization of product **6** (ca. 60% yield),[22] which corresponds to a stereoisomer of **1** with a *trans*-fused decalin ring system (Equation 1). On the other hand, in 1994, Capon et al. reported that the treatment of **5** in the same acid solution at reflux for 30 minutes provided **1** in 25% yield, along with a mixture of unidentified products (Equation 2).[20a] Considering these results, a more efficient and facile method for preparing **1** with a *cis*-fused decalin junction is highly required that it should provide a reliable and practical source for further biological evaluation.

2.1. Total Synthesis of (+)-Aureol [Katoh et al.]

2.1.1. Synthetic Strategy

We reported the first total synthesis of **1** in 2002[11c] as well as its improved synthesis in 2003.[11b] Our retrosynthetic plan for the improved synthesis is outlined in Scheme 2. The key feature of this plan is the acid-induced rearrangement/cyclization of (–)-neoavarol (**7**) to produce target molecule **1** in one step. We envisioned that this rearrangement/cyclization event would proceed stereoselectively to install the requisite *cis*-fused decalin junction (see **7** → [**I** → **II** → **III**] → **1** in Scheme 4). The advanced key intermediate **7** would be readily derived from (–)-neoavarone (**8**) by the reduction of the quinone moiety. Intermediate **8** would be formed by the strategic salcomine oxidation[23] of phenol **9**, which is accessible

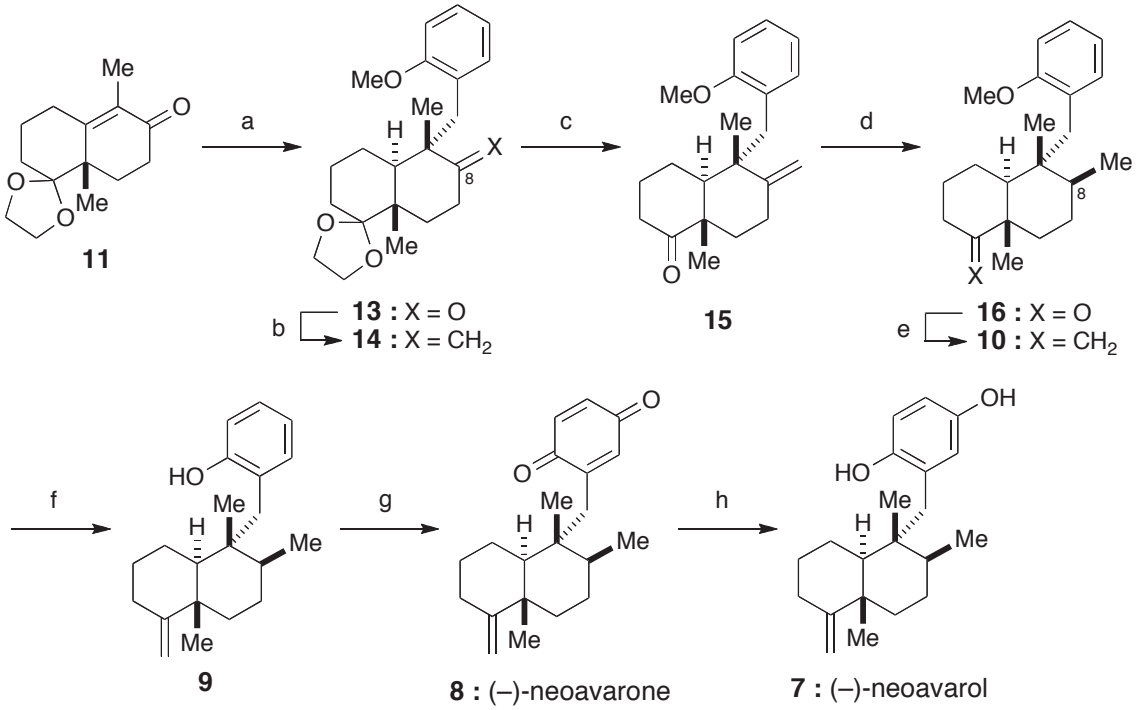


Scheme 2. Retrosynthetic plan for (+)-aureol (**1**) according to Katoh et al.[11]

from methyl ether **10**. Intermediate **10** should, in turn, be derived by the stereocontrolled reductive alkylation of (+)-5-methyl-Wieland–Miescher ketone (**11**)[24] with 2-methoxybenzyl bromide (**12**)[25] by applying protocols previously described in the literature.[26]

2.1.2. Total Synthesis

Initially, we pursued the synthesis of key intermediate **7** [(–)-neoavarol], as shown in Scheme 3. The reductive alkylation of **11**[24] (>99% ee) with **12**[25], readily prepared from commercially available 2-methoxybenzyl alcohol, provided the expected coupling product **13** as a single diastereomer in 74% yield. The subsequent Wittig methylenation[27] of **13** produced *exo*-olefin **14** in 86% yield. To form the C8 stereogenic center, the ethylene acetal moiety in **14** was first removed by acid treatment (97% yield),[28] and the resulting ketone **15** was subjected to hydrogenation, forming the desired product **16** (80% yield) and its C8 epimer (13% yield) after separation by silica-gel column chromatography. The Wittig methylenation of **16** (quantitative yield) followed by the deprotection of the *O*-methyl group in the resulting *exo*-olefin **10**[29] produced phenol **9** (92% yield). To directly construct the quinone system, **9** was

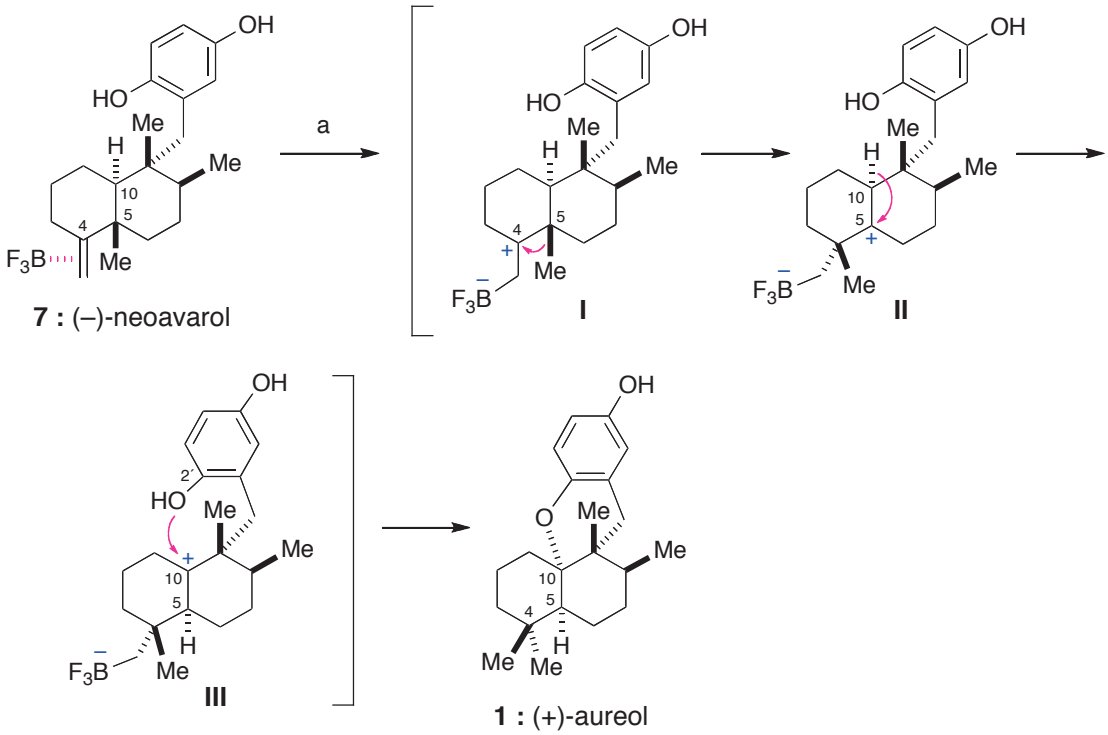


Scheme 3. Synthesis of (–)-neoavarol (**7**), a key precursor of (+)-aureol (**1**). (a) Li, liq. NH_3/THF, –78 to –30 °C, 1 h; add **12**, –30 °C to rt, 2 h, 74%; (b) $Ph_3P^+CH_3Br^-$, *t*-BuOK, benzene, reflux, 24 h, 86%; (c) 4 M HCl, THF, rt, 3 h, 97%; (d) H_2 (1 atm), 10% Pd/C, Et_3N/MeOH 50:1, 17 h, 80% for **16**, 13% for C8 epimer of **16** (e) $Ph_3P^+CH_3Br^-$, *t*-BuOK, benzene, reflux, 12 h, quant.; (f) *n*-BuSLi, HMPA, 110 °C, 3 h, 92%; (g) O_2 (1 atm), salcomine, DMF, rt, 24 h, 91%; (h) $NaBH_4$, THF/H_2O 10:1, 0 °C, 3 min, 86%. HMPA = hexamethylphosphoramide, salcomine = *N*,*N*'-bis(salicylidene)ethylenediaminocobalt(II), DMF = *N*,*N*-dimethylformamide.

subjected to salcomine oxidation,[23] and **8** was formed in 91% yield. Finally, the reduction of **8** with $NaBH_4$ provided **7** in 86% yield.

After obtaining the key intermediate **7**, the crucial acid-induced rearrangement/cyclization was investigated as shown in Scheme 4. Thus, the treatment of **7** with $BF_3{\cdot}Et_2O$ (5 equiv) in CH_2Cl_2 from –50 to –5 °C for 5 h resulted in the formation of **1** in excellent yield (93%). This total synthesis was accomplished with an overall yield of 33.0% in 9 steps from starting material **11**.

This cascade reaction proceeded smoothly and cleanly in a complete stereoselective manner. This can be elaborated via the mechanism shown in Scheme 4. An initial coordination–activation between the Lewis acid and the C4 olefinic double bond in **7** results in the formation of the first intermediate carbocation **I**, which is transformed into the second intermediate carbocation **II** by the migration of the C5 methyl group to the C4 carbocation center. Then, intermediate **II** undergoes a 1,2-hydride shift from the C10 position to the C5 carbocation center on the α-face of the molecule to form the third intermediate carbocation **III**. Finally, the C10 carbocation center in this intermediate is trapped by the C2' hydroxy group in the aromatic moiety to form, after the protonolysis of the C–BF_3 bond, the desired cyclized product **1**. We believe that this cascade sequence proceeds in a stepwise manner under kinetically controlled conditions.

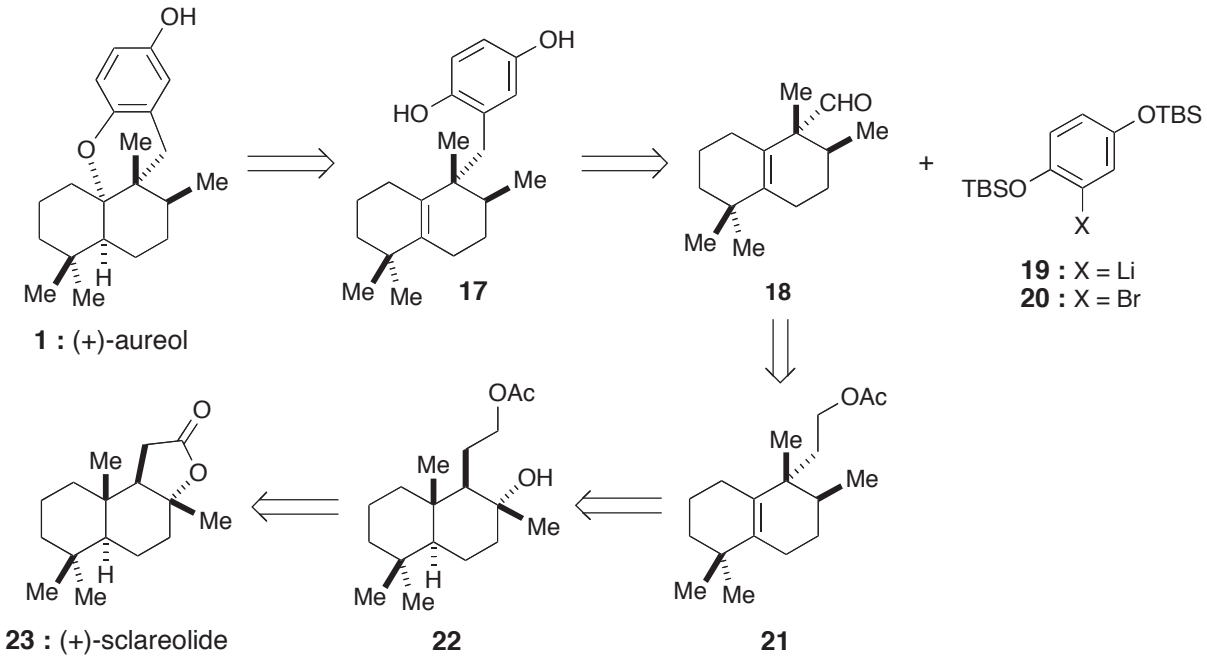


Scheme 4. Synthesis of (+)-aureol (**1**). (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, –50 to –5 °C, 5 h, 93%.

2.2. Total Synthesis of (+)-Aureol [George et al.]

2.2.1. Synthetic Strategy

In 2012, George et al. reported the second total synthesis of **1**.[14] Their synthetic plan is illustrated in Scheme 5. Target molecule **1** should be produced from intermediate **17** by acid-induced ether cyclization, presumably involving an intermediate carbocation (see structure **IV** in Scheme 7). This type of cyclization was previously reported by Marcos et al.[15] in their total synthesis of unnatural (–)-aureol (*ent*-**1**) (vide infra, see section 2.3). Intermediate **17** would be formed by the addition of aryllithium **19** (accessible from known aryl bromide **20**[30]) to aldehyde **18** followed by deoxygenation and deprotection. Intermediate **18** would be obtained from acetate **21** by the one-carbon dehomologation of the side chain. Intermediate **21** would be derived from tertiary alcohol **22** via a biomimetic sequence of 1,2-hydride and methyl shifts. Intermediate **22** would, in turn, be formed by the reduction and the monoprotection of commercially available (+)-sclareolide (**23**).

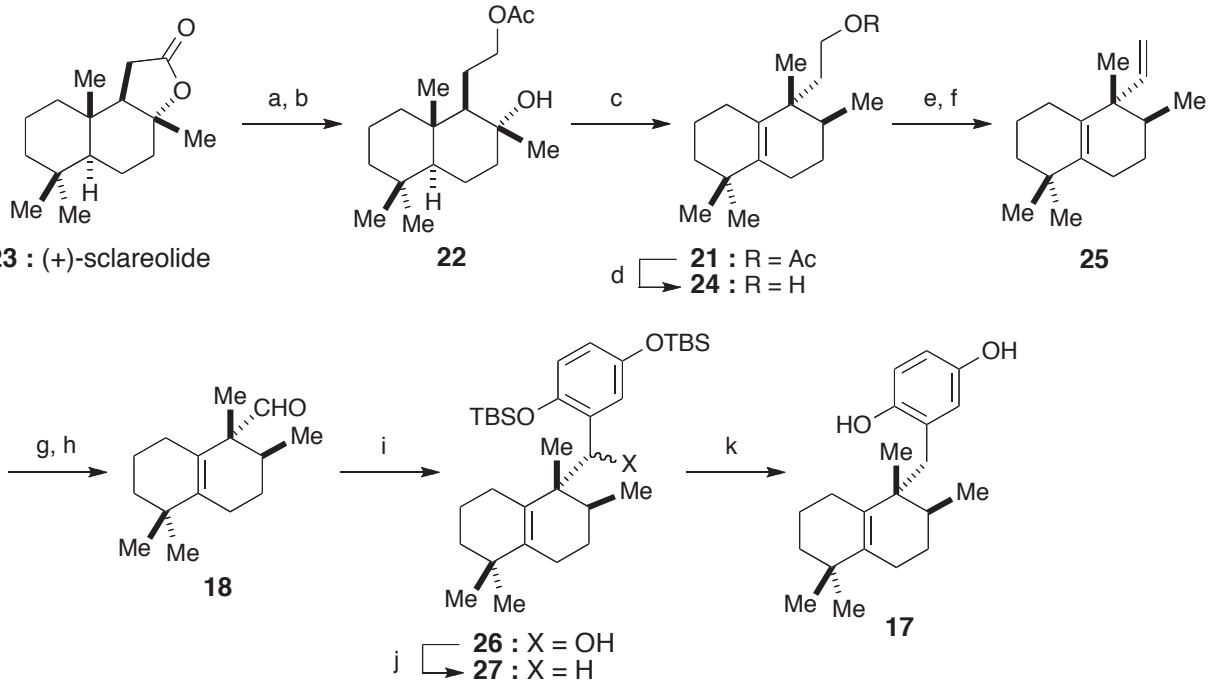


Scheme 5. Retrosynthetic plan for (+)-aureol (**1**) published by George et al.[14] TBS = *tert*-butyldimethylsilyl, Ac = acetyl.

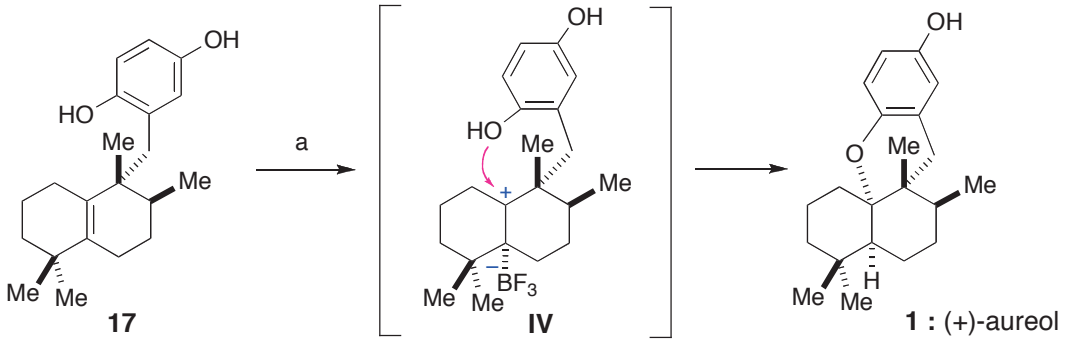
2.2.2. Total Synthesis

As shown in Scheme 6, the synthesis of intermediate **17**, a precursor of the essential acid-induced ether cyclization, was carried out starting from **23** (>99% ee). The reduction of **23** using $LiAlH_4$ generated a diol that was selectively protected at the primary hydroxyl group using Ac_2O in pyridine to produce monoacetate **22** in 84% yield in two steps. The first crucial step was the $BF_3{\cdot}Et_2O$-induced rearrangement of **22**, which occurred via stereospecific 1,2-hydride and methyl shifts to form the desired product **21** as a single stereoisomer in 70% yield. The removal of the acetyl group from **21** produced alcohol **24** in 83% yield. Compound **24** was further converted to key intermediate **18** via a one-carbon dehomologation

sequence involving dehydration using the Grieco–Sharpless protocol[31] (67% yield in two steps) and the subsequent oxidative cleavage of the resulting terminal alkene **25** (45% yield in two steps). The second crucial coupling reaction between **18** with aryllithium **19** (see Scheme 5) was achieved by an initial bromine/lithium exchange of aryl bromide **20**[30] followed by the reaction with **18** from –78 °C to room temperature. The desired coupling product **26** was obtained as a mixture of epimeric alcohols, which,



Scheme 6. Synthesis of intermediate **17**, a key precursor of (+)-aureol (**1**). (a) $LiAlH_4$, THF, pyridine, 0 °C, 1 h; (b) Ac_2O, DMAP, pyridine, rt, 12 h, 84% (2 steps); (c) $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 12 h, 70%; (d) KOH, MeOH, rt, 30 min, 83%; (e) *o*-$NO_2C_6H_4SeCN$, *n*-Bu_3P, THF, rt, 1 h, 88%; (f) 35% aq. H_2O_2, THF, 50 °C, 45 min, 77%; (g) OsO_4 (cat), NMO, acetone/H_2O 9:1, rt, 36 h, 67%; (h) $NaIO_4$, THF/H_2O, rt, 30 min, 68%; (i) aryl bromide **20**, *t*-BuLi, Et_2O, –78 °C, 30 min; at –78 °C, add the formed aryllithium **19** (cf. Scheme 5) to **18**, –78 °C, 30 min, then rising to rt: (j) Li, liq. NH_3/THF, –78 °C, 15 min, 78% (2 steps); (k) TBAF, THF, 0 °C, 20 min, 86%. DMAP = 4-(dimethylamino)pyridine, NMO = *N*-methylmorpholine-*N*-oxide, TBAF = tetrabutylammonium fluoride.



Scheme 7. Synthesis of (+)-aureol (**1**). (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, –60 to –20 °C, 3 h, 66%.

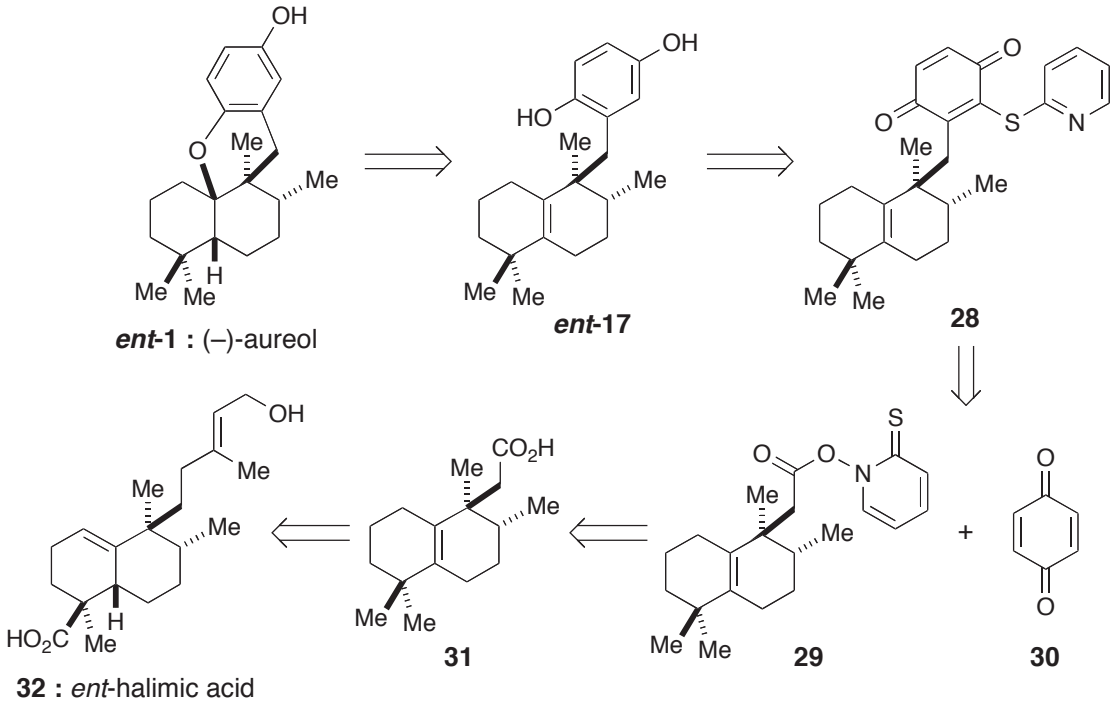
without separation, was then reduced under the Birch conditions to generate deoxygenated product **27** with an overall yield of 78% from **18**. The removal of the two *O*-TBS protecting groups from **27** produced hydroquinone **17** in 86% yield.

After obtaining the key intermediate **17**, the final acid-induced ether cyclization step required to complete the synthesis was performed, as shown in Scheme 7. Thus, the treatment of **17** with $BF_3{\cdot}Et_2O$ (4.5 equiv) in CH_2Cl_2 from –60 to –20 °C for 3 h resulted in the formation of target **1** in 66% yield. In this reaction, the intermediate carbocation **IV** would be involved. This total synthesis was accomplished with an overall yield of 6.7% in 12 steps from starting material **23**.

2.3. Total Synthesis of (–)-Aureol [Marcos et al.]

2.3.1. Synthetic Strategy

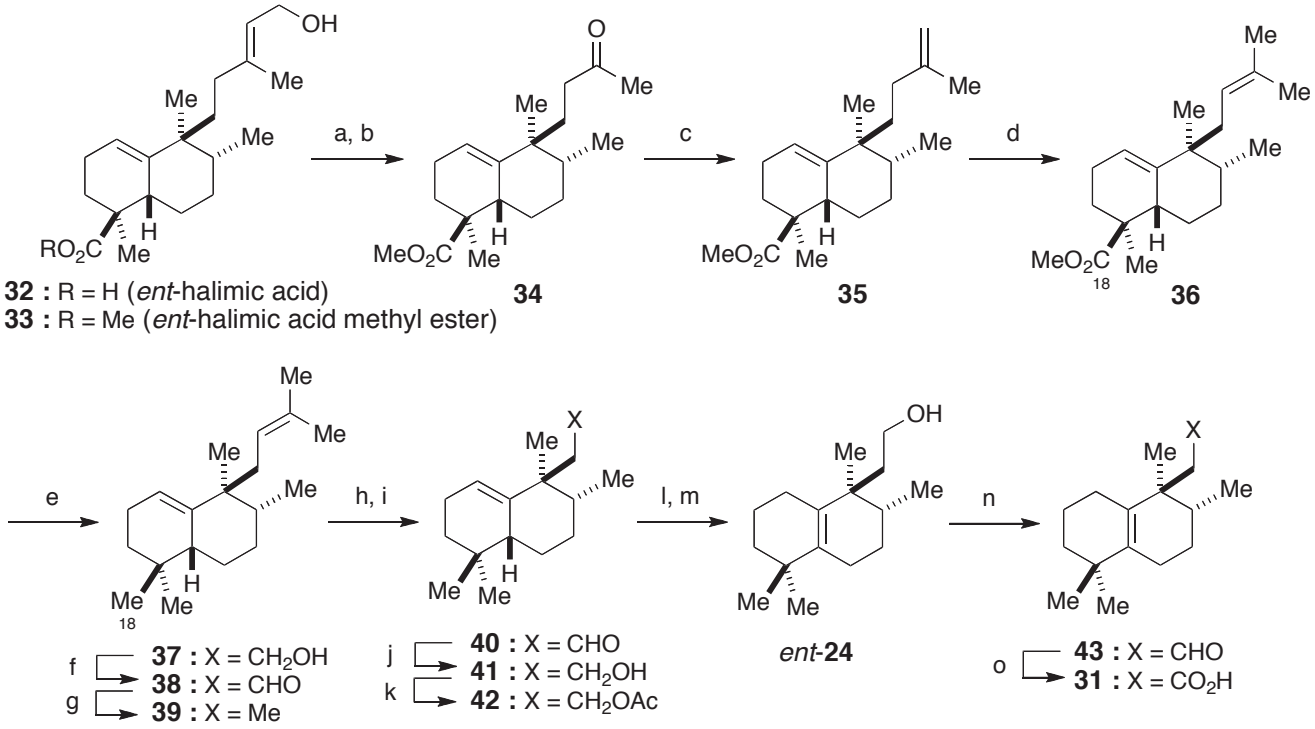
In 2010, Marcos et al. reported the total synthesis of unnatural (–)-aureol (*ent*-**1**).[15] Their retrosynthetic plan is shown in Scheme 8. The first crucial step is expected to be the acid-induced ether cyclization of hydroquinone *ent*-**17** via an intermediate carbocation (see structure *ent*-**IV** in Scheme 11). Intermediate *ent*-**17** would be derived from quinone **28** by reduction with Raney®-nickel. An alternative essential step could be the Barton radical decarboxylation[32]/*p*-benzoquinone addition sequence to form intermediate **28** (**29** + **30** → **28**). This type of radical coupling reaction was originally explored by Theodorakis et al. in their total synthesis of marine sesquiterpenoid quinones and hydroquinones.[33] Intermediate **29**, in turn, would be derived from carboxylic acid **31**, which is accessible from commercially available *ent*-halimic acid (**32**).



Scheme 8. Retrosynthetic plan for (–)-aureol (*ent*-**1**) according to Marcos et al.

2.3.2. Total Synthesis

First, intermediate **31** was prepared starting from *ent*-halimic acid methyl ester (**33**), as shown in Scheme 9. The degradation of the side chain of **33** was achieved by OsO_4 oxidation followed by reaction with $Pb(OAc)_4$ to form the desired ketone **34**[34] in 94% yield in two steps. The subsequent Wittig methylenation of **34** (87% yield) and the olefin isomerization of the resulting *exo*-olefin **35** furnished *endo*-olefin **36** (99% yield). The C18 methyl ester function in **36** was efficiently converted to the C18 methyl group in **39** via a three-step sequence including $LiAlH_4$ reduction (97% yield), the tetra-*n*-propylammonium perruthenate (TPAP) oxidation of the resulting alcohol **37** (97% yield), and the Wolff–Kishner reduction of the resulting aldehyde **38** (90% yield). The chemoselective epoxidation of the side-chain double bond in **39** (98% yield) using *m*-chloroperoxybenzoic acid (*m*CPBA) followed by the oxidative cleavage of the resulting epoxide by treatment with H_5IO_6 in H_2O/THF produced aldehyde **40** (94% yield). Compound **40** was further converted to alcohol *ent*-**24** via a four-step sequence including $LiAlH_4$ reduction (99% yield), acetylation of the resulting alcohol **41** (99% yield), isomerization of the olefinic double bond in the resulting acetate **42** with HI (97% yield), and removal of the acetyl group (98% yield). Eventually, the twofold oxidation of *ent*-**24** using pyridinium dichromate (PDC) provided the requisite carboxylic acid **31** (50% overall yield based on recovery of the starting material) via aldehyde **43**.

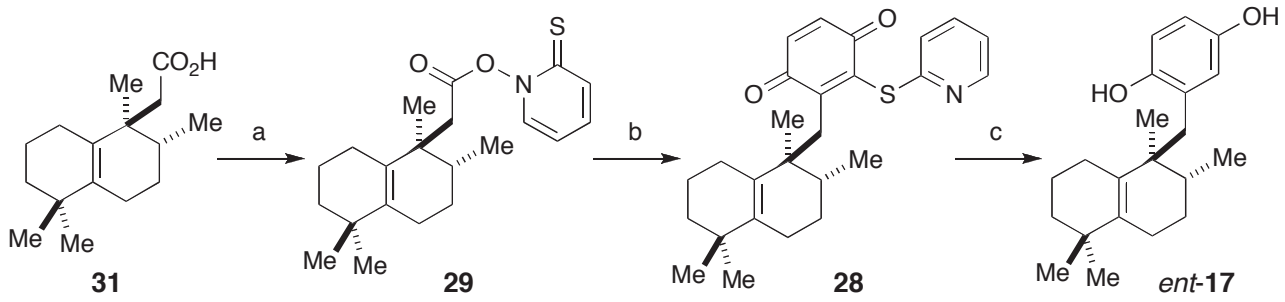


Scheme 9. Synthesis of intermediate **31**. (a) OsO_4, NMO, *t*-BuOH/THF/H_2O 7:2:1, rt, 20 h; (b) $Pb(OAc)_4$, benzene, rt, 20 min, 94% (2 steps); (c) $Ph_3P^+CH_3Br^-$, $NaN(SiMe_3)_2$, THF, –78 °C to rt, 4 h, 87%; (d) *p*-TsOH, benzene, 60 °C, 2 h, 99%; (e) $LiAlH_4$, Et_2O, rt, 35 min, 97%; (f) TPAP, NMO, CH_2Cl_2, rt, 1 h, 97%; (g) $NH_2NH_2{\cdot}H_2O$, KOH, diethylene glycol, 175 °C, 17 h, rising to 230 °C, 3.5 h, 90%; (h) *m*CPBA, CH_2Cl_2, rt, 1.5 h, 98%; (i) H_5IO_6, H_2O/THF 1:3, rt, 2 h, 94%; (j) $LiAlH_4$, Et_2O, rt, 50 min, 99%; (k) Ac_2O, pyridine, rt, 19 h, 99%; (l) HI, benzene, reflux, 35 min, 97%; (m) K_2CO_3, MeOH, rt, 2 h, 98%; (n) PDC,

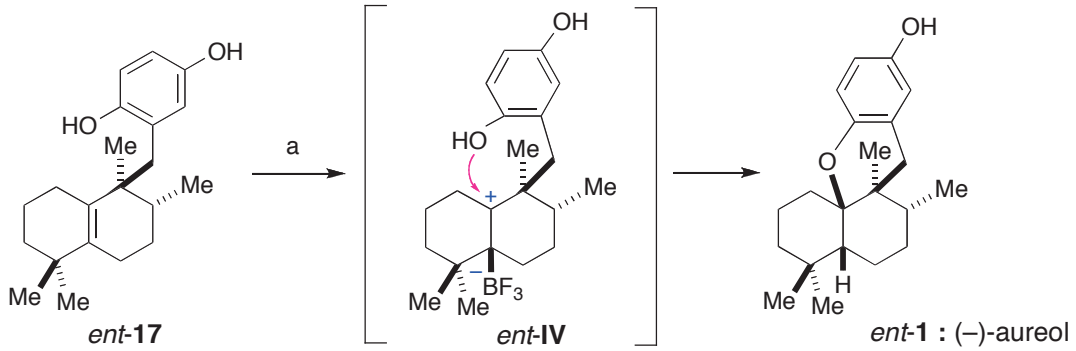
DMF, rt, 7 h, 52% for **43**, 35% for **31**; (o) PDC, DMF, rt, 7 h, 38% (58% recovery of **43**). TPAP = tetra-*n*-propylammonium perruthenate, *m*CPBA = *m*-chloroperoxybenzoic acid, PDC = pyridinium dichromate.

After obtaining intermediate **31**, the synthesis of hydroquinone *ent*-**17**, the key precursor of *ent*-**1**, was carried out as shown in Scheme 10. Treatment of **31** with 2-mercaptopyridine *N*-oxide in the presence of *N*,*N*'-dicyclohexylcarbodiimide (DCC)[32] resulted in the corresponding 2-thiopyridon-1-yl ester **29**. The crucial installation of the quinone moiety was performed by the light-induced decarboxylation of **29** (halogen lamp, 500 W) in the presence of *p*-benzoquinone (**30**), which formed the expected quinone addition product **28** in 65% yield from **31**. The subsequent reduction of **28** with Raney®-nickel in EtOH provided *ent*-**17** in 99% yield.

With the key precursor *ent*-**17** synthesized, the final crucial step was examined as shown in Scheme 11. Thus, the treatment of *ent*-**17** with $BF_3{\cdot}Et_2O$ (4.3 equiv) in CH_2Cl_2 from –50 to –5 °C for 2 h resulted in the formation of target (–)-aureol (*ent*-**1**) in 60% yield via the intermediate carbocation *ent*-**IV**. This total synthesis produced an overall yield of 10.3% in 19 steps from starting material **33**.



Scheme 10. Synthesis of intermediate *ent*-**17**, a key precursor of (–)-aureol (*ent*-**1**). (a) 2-mercaptopyridine *N*-oxide, DCC, CH_2Cl_2, rt, 16 h; (b) *p*-benzoquinone (**30**), CH_2Cl_2, hν (halogen lamp, 500 W), 0 °C, 2 h, 65% (2 steps); (c) Raney®-nickel, EtOH, rt, 5 min, 99%. DCC = *N*,*N*'-dicyclohexylcarbodiimide.

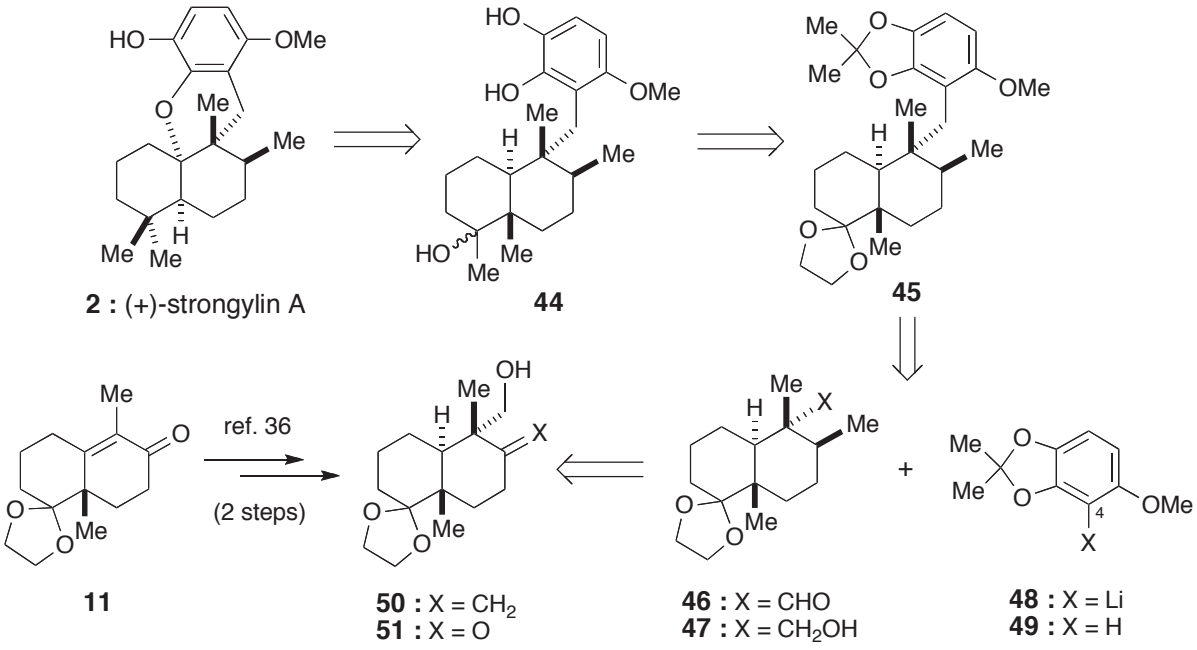


Scheme 11. Synthesis of (–)-aureol (*ent*-**1**). (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, –50 to –5 °C, 2 h, 60%.

3. TOTAL SYNTHESIS OF (+)-STRONGYLIN A [Katoh et al.]

3.1. Synthetic Strategy

Recently, we accomplished the first total synthesis of naturally occurring (+)-strongylin A (**2**), which led to the determination of the absolute configuration of natural **2**.[12] Our retrosynthetic plan is outlined in Scheme 12. The key element of this approach is the acid-induced dehydroxylation/rearrangement/ cyclization of tertiary alcohol **44** to form the target molecule in one step. We believed that this cascade reaction would stereoselectively proceed to construct the requisite *cis*-fused decalin ring junction (see **44** → [**V** → **VI** → **VII**] → **2** in Scheme 14). The second crucial step was considered to be a coupling reaction of *trans*-decalin **46** (accessible from alcohol **47**) with aryllithium **48** (accessible from known trioxybenzene derivative **49**[35]) to form intermediate **45**, which could be converted to **44** by deprotection and functional group manipulation. Intermediate **47** would be formed by the stereoselective hydrogenation of *exo*-olefin **50**, which is accessible from known *trans*-decalone **51**.[36] As a starting material, **51** was readily prepared from **11** in two steps by applying the method reported by Smith et al.[36]



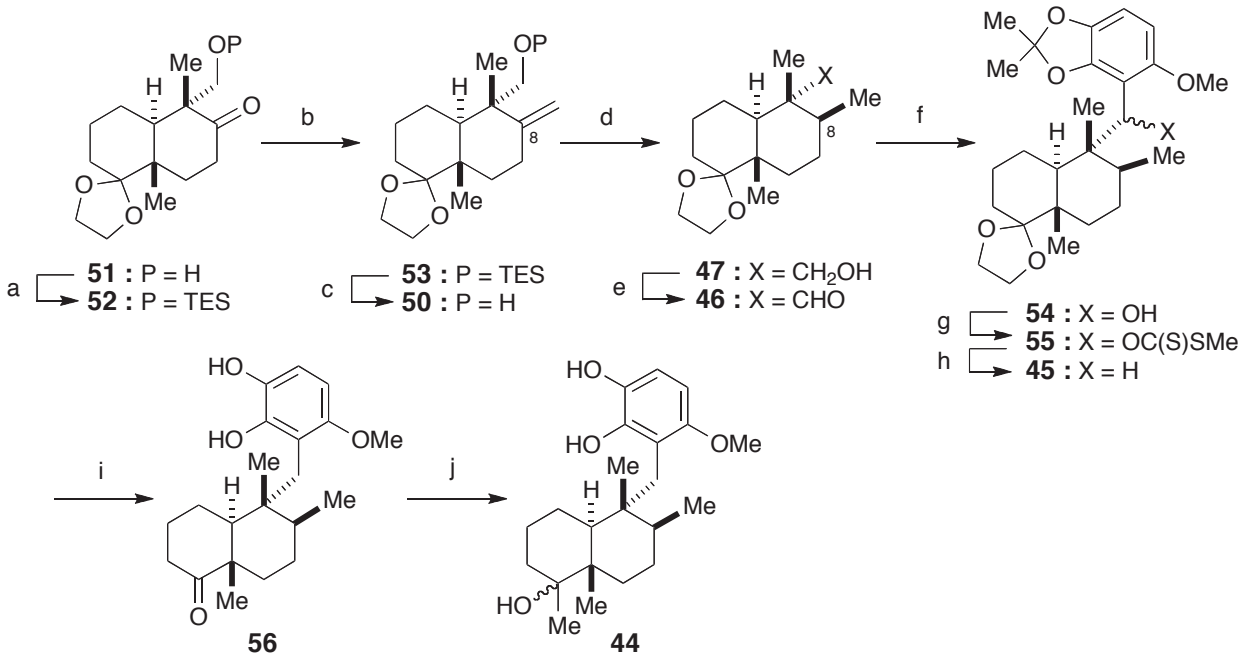
Scheme 12. Retrosynthetic plan for (+)-strongylin A (**2**) according to Katoh et al.[12]

3.2. Total Synthesis

In Scheme 13, we initially pursued the synthesis of intermediate **44**, a precursor of the key cascade reaction, starting from **51**[36] (>99% ee). The protection of the hydroxy group in **51** followed by the Wittig methylenation of the resulting triethylsilyl (TES) ether **52** and the deprotection of the TES group in the resulting *exo*-olefin **53** provided the desired alcohol **50** in 69% yield in three steps. To establish the C8 stereogenic center, **50** was subjected to hydroxyl-group-directed hydrogenation using Crabtree's catalyst

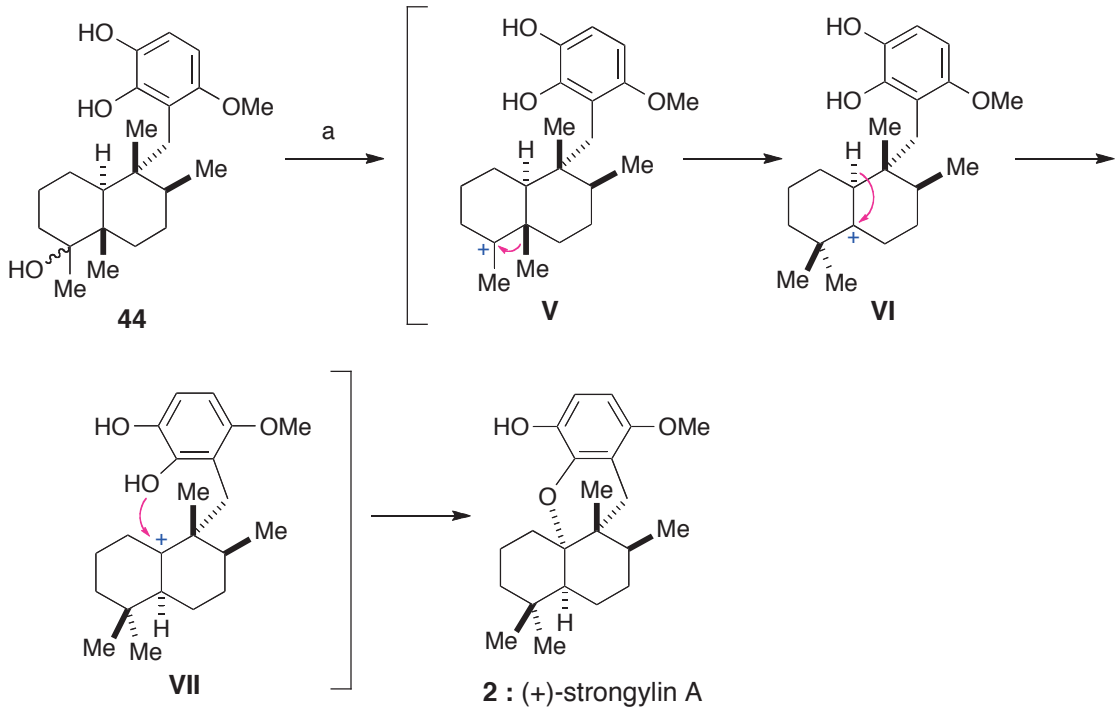
{[Ir(COD)(PCy_3)(py)]$^+$[PF_6]$^-$}[37] (2.5 mol%), which produced the requisite product **47** with complete stereoselectivity in almost quantitative yield (98%). The oxidation of **47** with TPAP then generated decalin aldehyde **46** in 94% yield.

The crucial coupling reaction between the decalin and aromatic portions was efficiently achieved by site-selective lithiation at the C4 position in **49** (see Scheme 12) using *t*-BuLi in THF at 0 °C followed by the treatment of aryllithium **48**, generated in situ with aldehyde **46** at 0 °C to room temperature for 1 h. The expected coupling product **54** was obtained in excellent yield (94%) as an inseparable mixture of epimeric alcohols (ca. 4:1). The hydroxyl group of **54** was removed by applying the Barton–McCombie procedure,[38] and the desired deoxygenated product **45** was formed with an overall yield of 78% via methyl xanthate **55**. The exposure of **45** to concentrated hydrochloric acid in refluxing EtOH caused the simultaneous deprotection of the acetonide and ethylene acetal moieties, resulting in the formation of the desired ketone **56** in 71% yield. Finally, the reaction of **56** with MeMgBr (5 equiv) in THF from 0 °C to room temperature for 1 h, formed the requisite intermediate **44** in 70% yield as an inseparable mixture of epimeric alcohols (ca. 1.7:1).



Scheme 13. Synthesis of intermediate **44**, a key precursor of (+)-strongylin A (**2**). (a) TESCl, imidazole, CH_2Cl_2, rt, 1 h; (b) $Ph_3P^+CH_3Br^-$, *t*-BuOK, benzene, reflux, 1 h; (c) TBAF, THF, rt, 1 h, 69% (3 steps); (d) H_2 (1 atm), Crabtree's catalyst (2.5 mol%), CH_2Cl_2, rt, 1 h, 98%; (e) TPAP, NMO, CH_2Cl_2/MeCN, 4Å MS, rt, 1 h, 94%; (f) 5-methoxy-2,2-dimethylbenzo[*d*][1,3]dioxole (**49**), *t*-BuLi, THF, 0 °C, 30 min; at 0 °C, add **46**, 0 °C to rt, 1 h, 94%; (g) $NaN(SiMe_3)_2$, CS_2, MeI, THF, –78 to –65 °C, 3 h; (h) *n*-Bu_3SnH, AIBN, benzene, reflux, 5 h, 78% (2 steps); (i) 12 M HCl, EtOH, reflux, 5 h, 71%; (j) MeMgBr, THF, 0 °C to rt, 1 h, 70%. TES = triethylsilyl, Crabtree's catalyst = [Ir(COD)(PCy_3)(py)]$^+$[PF_6]$^-$ (COD = 1,5-cyclooctadiene, Cy = cyclohexyl, py = pyridine), MS = molecular sieves, AIBN = 2,2'-azobis(isobutyronitrile).

With the key intermediate **44** in hand, we then investigated the crucial acid-induced cascade of dehydroxylation/rearrangement/cyclization to complete the projected synthesis (Scheme 14). The desired cascade event was successfully achieved by treating **44** with excess of $BF_3{\cdot}Et_2O$ (10 equiv) in CH_2Cl_2 from –78 to 0 °C for 3 h, which resulted in the formation of **2** as a single stereoisomer in high yield (84%). The optical rotation of synthetic **2** {$[\alpha]^{23}_D$ = +83.3} was in good agreement with that of natural **2** {$[\alpha]^{20}_D$ = +72}, verifying the absolute configuration of **2**. We believe that this cascade sequence would involve intermediate carbocations such as **V**, **VI**, and **VII** in a manner similar to that described in section 2.1 (see **7** → [**I** → **II** → **III**] → **1** in Scheme 4). This total synthesis was accomplished with an overall yield of 19.0% in 11 steps from starting material **11**.



Scheme 14. Synthesis of (+)-strongylin A (**2**). (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, –78 to 0 °C, 3 h, 84%.

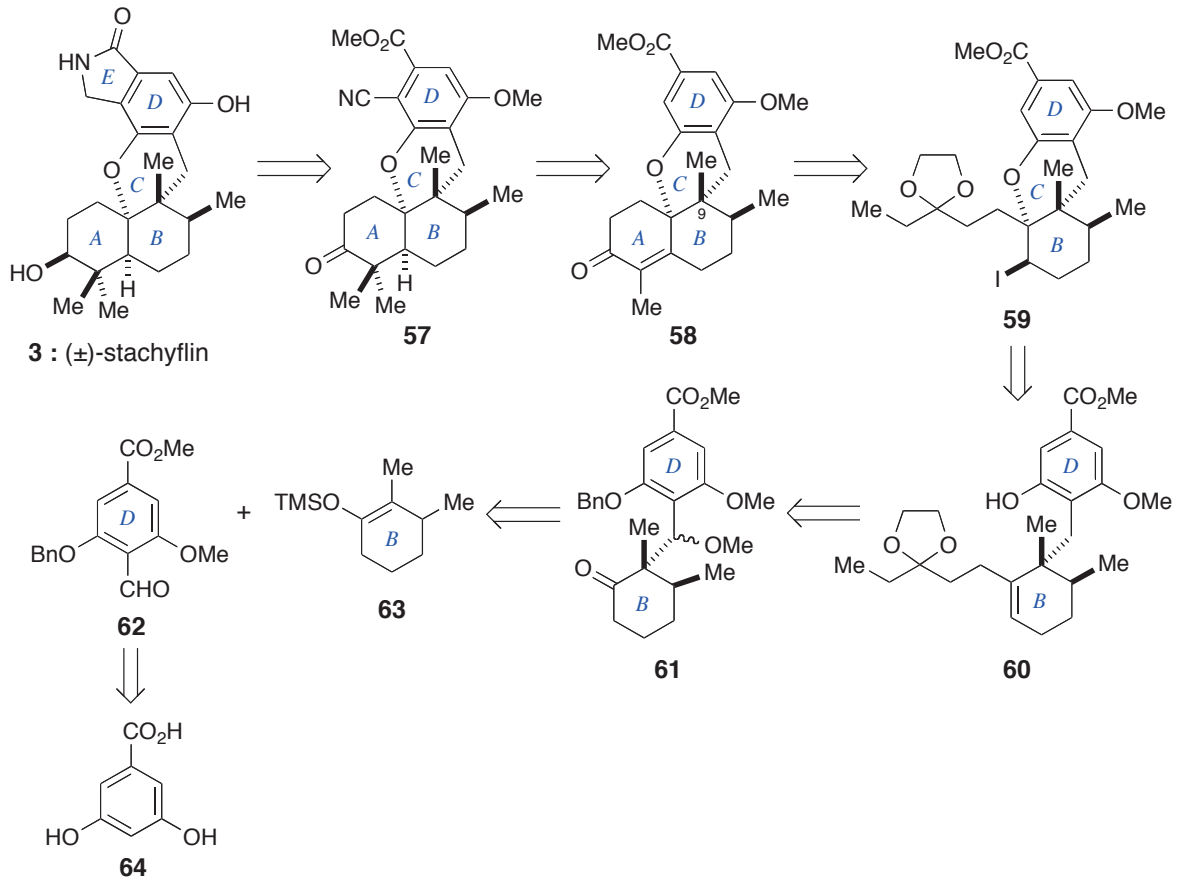
4. TOTAL SYNTHESIS OF STACHYFLIN

4.1. Total Synthesis of (±)-Stachyflin [Shionogi & Co., Ltd.]

4.1.1. Synthetic Strategy

In 1998, scientists from the Shionogi research group reported the first total synthesis of racemic (±)-**3**.[16] Through their synthetic study, they discovered that the anti-influenza A virus activity of (±)-**3** is approximately half that of natural (+)-**3**.[16] Their retrosynthetic plan for (±)-**3** is illustrated in Scheme 15. The first crucial transformation in this contemplated scheme is expected to be the construction of the tetracyclic intermediate **57** (ABCD ring system) from the tricyclic intermediate **59** (BCD ring system) via enone **58** (see **59** → **58** → **57**). Hydrogenation of **58** would stereoselectively produce the desired *cis*-fused

decalin (AB ring) due to the steric hindrance caused by the C9 methyl group (see **58** → **57**). Advanced key intermediate **57** would be converted to target (±)-**3** via lactam (E ring) formation. The second critical step is believed to involve the iodoetherification of intermediate **60** to construct tricyclic intermediate **59**. Intermediate **60** would be derived from intermediate **61** by functional group manipulation. Intermediate **61**, in turn, would be formed by the coupling reaction of the D-ring portion **62** [accessible from commercially available 3,5-dihydroxybenzoic acid (**64**)] with the B-ring portion **63**.

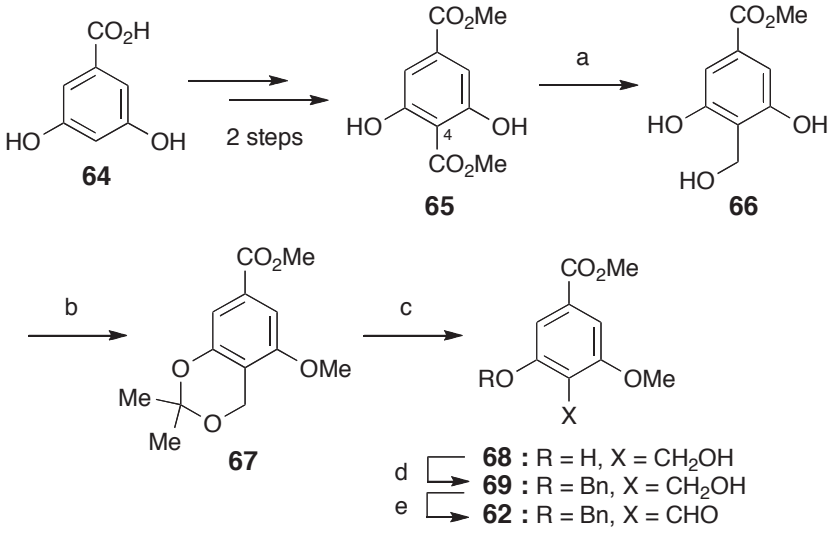


Scheme 15. Retrosynthetic plan for (±)-stachyflin (**3**) according to the Shionogi group.[16]

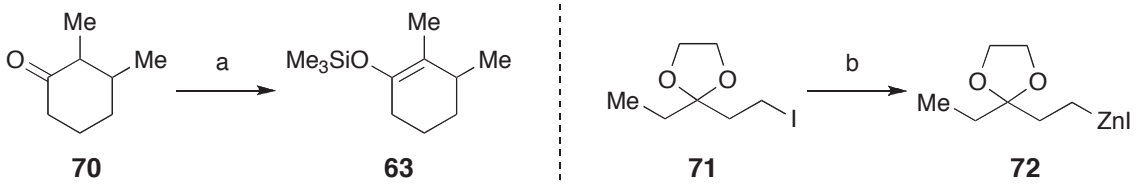
4.4.2. Total Synthesis

As shown in Scheme 16, the synthesis of intermediate **62**, the coupling partner of **63**, was carried out starting from **65**, which was pr epared from **64** in two steps. Thus, the chemoselective reduction of the C4 methyl ester function in **65** using $NaBH_4$ provided the corresponding triol **66**, which was subjected to acetonide formation followed by methyl etherification to generate acetonide **67** with an overall yield of 61% from **65**. Compound **67** was then converted to the requisite intermediate **62** with an overall yield of 74% via a three-step procedure including the removal of the acetonide moiety, the selective *O*-benzylation of the resulting diol **68**, and the pyridinium chlorochromate (PCC) oxidation of the resulting alcohol **69**.

Scheme 17 shows the synthesis of trimethylsilyl enol ether **63** and alkylzinc reagent **72**[39], both of which are necessary for the following synthesis of key intermediate **59** (see Scheme 18). Compounds **63** and **72** were prepared from 2,3-dimethylcyclohexanone (**70**) and alkyl iodide **71**, respectively (the yields were not described in the literature[16]).



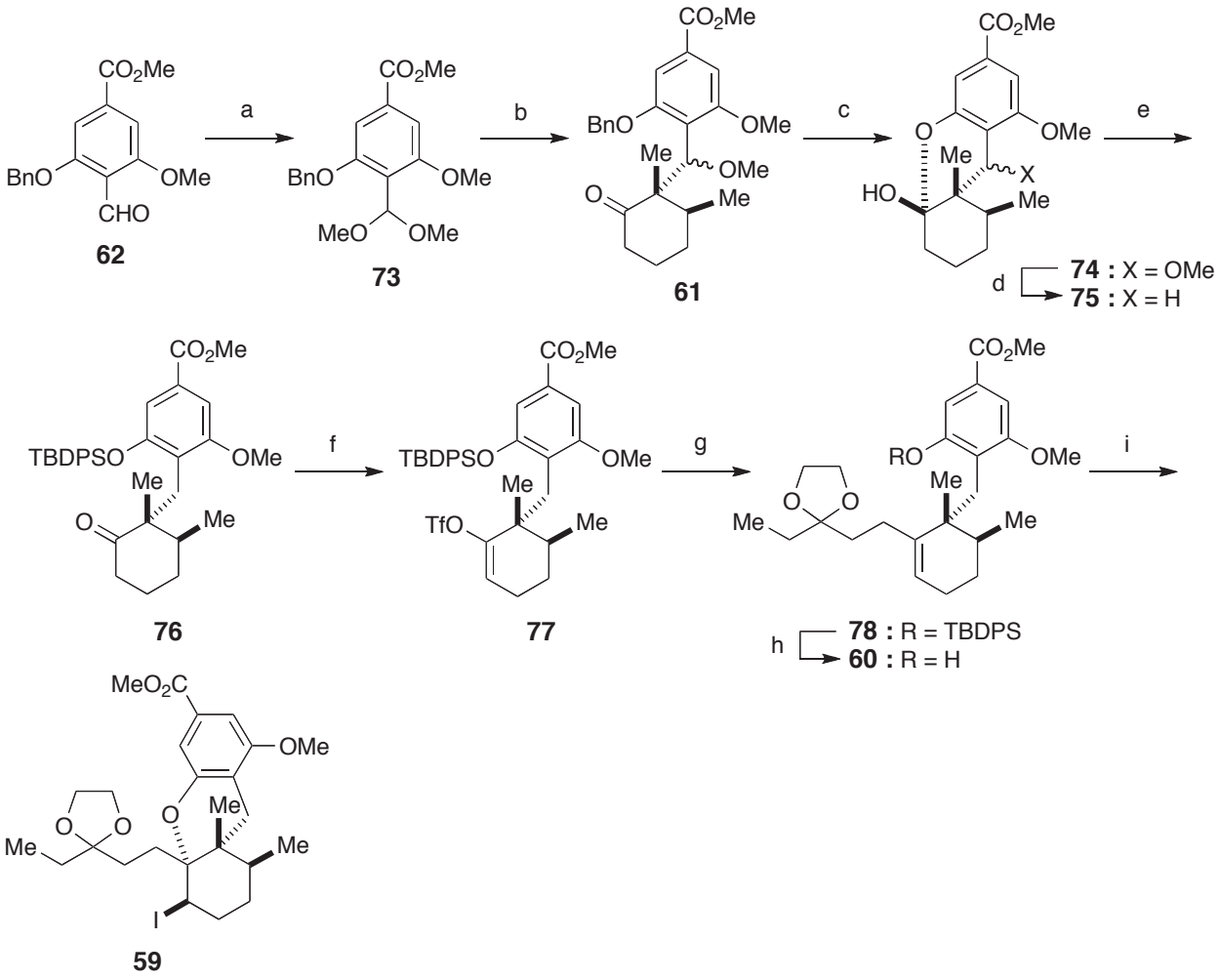
Scheme 16. Synthesis of intermediate **62**. (a) $NaBH_4$, THF; (b) *p*-TsOH, acetone; $(MeO)_2SO_2$, K_2CO_3, 61% (3 steps); (c) 1 M HCl, MeOH/THF; (d) BnBr, K_2CO_3, acetone; (e) PCC, CH_2Cl_2, 74% (3 steps). PCC = pyridinium chlorochromate.



Scheme 17. Synthesis of trimethylsilyl enol ether **63** and alkylzinc reagent **72**. (a) Me_3SiCl, $HN(SiMe_3)_2$, NaI, MeCN; (b) Zn, Me_3SiCl, THF.

Key intermediate **59** was synthesized as shown in Scheme 18. After the dimethylacetal formation of **62**, Noyori's aldol condensation[40] of the resulting dimethyl acetal **73** with silyl enol ether **63** (see Scheme 17) was achieved to produce the expected coupling product **61** as a 1:1 diastereomixture. The subsequent deprotection of the benzyl group in **61** and the removal of the benzylic methoxy group from the resulting hemiacetal **74** formed deoxygenated hemiacetal **75** with an overall yield of 65% from **62**. Compound **75** was then converted to phenolic alkene **60**, a precursor for the key iodoetherification step, via a four-step sequence including the protection of the masked phenolic hydroxy group in **75** as its

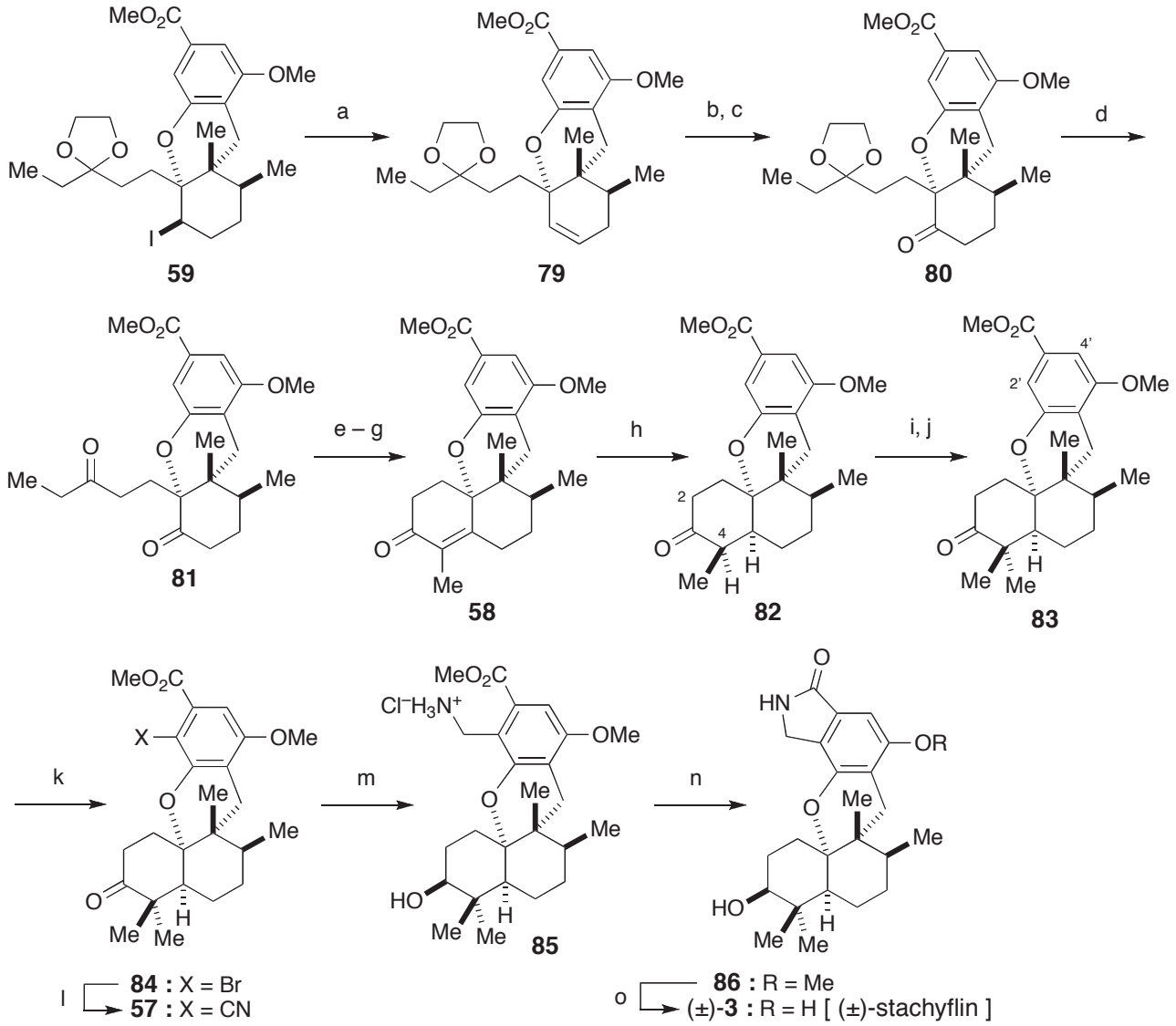
tert-butyldiphenylsilyl (TBDPS) ether (81% yield), the enol triflate formation of the resulting ketone **76** using Comins' reagent[41] (82% yield), the palladium-catalyzed coupling reaction[42] of the resulting enol triflate **77** with alkylzinc reagent **72** (cf. Scheme 17) (85% yield), and the deprotection of the *O*-TBDPS group in the resulting coupling product **78** (91% yield). The crucial iodoetherification of **60** was efficiently achieved by treatment with I_2 in THF in the presence of propylene oxide as an HI scavenger. The desired cyclization product **59** was formed in high yield (87%).



Scheme 18. Synthesis of intermediate **59**. (a) $HC(OMe)_3$, *p*-TsOH, MeOH; (b) **63**, Me_3SiOTf, CH_2Cl_2; (c) H_2, 10% Pd/C, 1 M HCl, acetone; (d) H_2, 10% Pd/C, CH_3CO_2H, 65% (4 steps); (e) TBDPSCl, *t*-BuOK, THF, 81%; (f) Comins' reagent, $KN(SiMe_3)_2$, THF, 82%; (g) **73**, $Pd(PPh_3)_4$, HMPA, THF, 85%; (h) TBAF, THF, 91%; (i) I_2, propylene oxide, THF, 87%. Tf = trifluoromethanesulfonyl, TBDPS = *tert*-butyldiphenylsilyl, Comins' reagent = *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonamide).

Completion of the total synthesis of (±)-**3** is outlined in Scheme 19. The β-elimination of HI from **59** afforded alkene **79** (92% yield), which was then subjected to hydroboration and subsequent PCC oxidation to form ketone **80** with an overall yield of 45%. After the deprotection of the ethylene acetal moiety in **80** (90% yield), the resulting diketone **81** was converted to enone **58** with an overall yield of

75% via a three-step sequence including intramolecular aldol cyclization, the dehydration of the cyclized aldol product, and the base-induced isomerization of the resulting mixture of α,β- and β,γ-unsaturated ketones to the thermodynamically more stable enone **58**. The critical stereoselective hydrogenation of **58** was best achieved under the optimized conditions [H_2 (1 atm), 5% Rh/C, acetone]. The desired *cis*-fused decalin **82** was formed in 52% yield as the major stereoisomer (*cis*/*trans* 1.6:1). After the construction of the *cis*-fused decalin system, the regioselective introduction of a methyl group at the C4 position over the



Scheme 19. Synthesis of (±)-stachyflin [(±)-**3**]. (a) DBU, DMSO, 92%; (b) BH_3·THF; H_2O_2, NaOH; (c) PCC, CH_2Cl_2, 45% (3 steps); (d) 0.5 M HCl, acetone, 90%; (e) NaOMe, MeOH/THF; (f) $SOCl_2$, pyridine, CH_2Cl_2; (g) NaOMe, MeOH, 75% (3 steps); (h) H_2, 5% Rh/C, acetone, 52%; (i) Me_3SiCl, $HN(SiMe_3)_2$, MeCN, 80 °C; NaI; (j) MeI, tris(diethylamino)sulfur(trimethylsilyl)difluoride, CH_2Cl_2, 75% (2 steps); (k) NBS, DMF, 76% (based on recovery of byproducts); (l) CuCN, DMF, 80%; (m) H_2, PtO_2, EtOH/$CHCl_3$; (n) NaOMe, MeOH, 87% (2 steps); (o) *n*-BuSLi, HMPA, 83%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMSO = dimethylsulfoxide, NBS = *N*-bromosuccinimide.

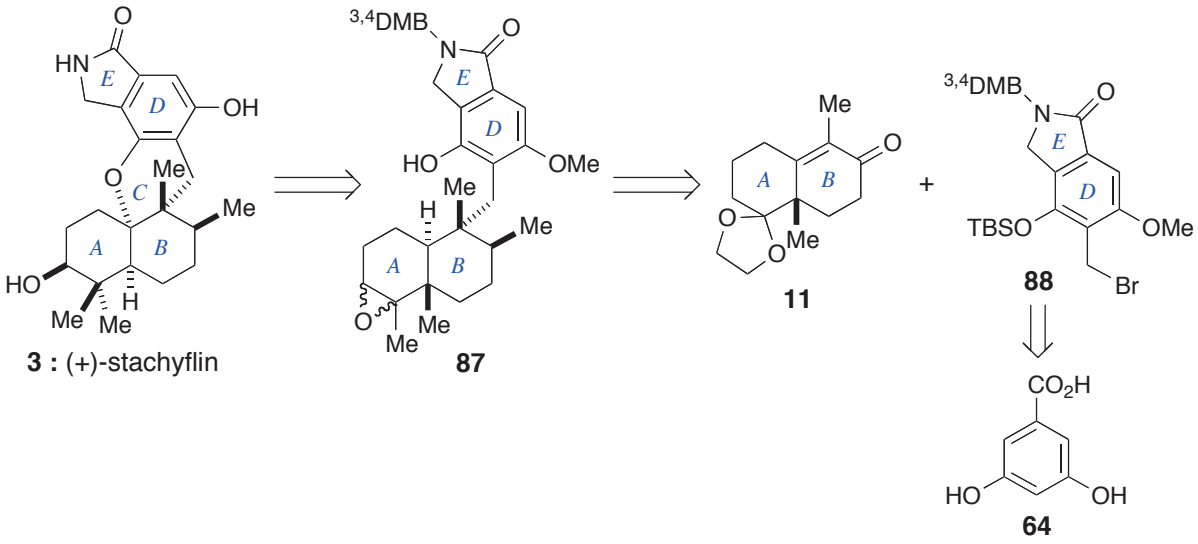
C2 position in **82** was performed by the methylation of the thermodynamically more stable trimethylsilyl enol ether of **83** to form geminal dimethyl ketone **83** in 75% yield in two steps.

In the last stage of the synthesis, γ-lactam (E ring) formation was investigated as follows.[43] The bromination of the C2' position of the aromatic ring in **83** generated bromide **84** in 76% yield based on the recovery of the undesired regioisomer (the C4'-brominated product) and dibromide. These byproducts were efficiently reduced to reusable compound **83** by treatment with $Pd(PPh_3)_4$ and HCO_2Na in DMF.[44] The subsequent cyanation of **84** with CuCN produced nitrile **57** in 80% yield. The hydrogenation of the nitrile function of **57** delivered ammonium salt **85**, which was then exposed to a MeOH solution of NaOMe at room temperature, resulting in the formation of γ-lactam **86** in 87% yield in two steps. In the hydrogenation step, the carbonyl group in **57** was simultaneously reduced to form the requisite β-alcohol in a highly stereoselective manner. Finally, the removal of the phenolic *O*-methyl moiety from **86** (*n*-BuSLi, HMPA)[29] generated target (±)-**3** in 83% yield. This total synthesis was completed with an overall yield of 0.9% in 31 steps from starting material **64**.

4.2. Total Synthesis of (−)-Stachyflin [Katoh et al.]

4.2.1. Synthetic Strategy

We accomplished the first enantioselective total synthesis of naturally occurring **3** in 2010.[13] Our retrosynthetic plan is outlined in Scheme 20. We envisioned that target molecule **3** would be derived from epoxide **87** through an acid-induced cascade reaction (see **87** → [**VIII** → **IX** → **X**] → **103a** and **103b** in Scheme 23), which was devised based on our previous studies described earlier.[11] Key intermediate **87** would be prepared through the coupling reaction of **11** with bromide **88** (accessible from **64**).

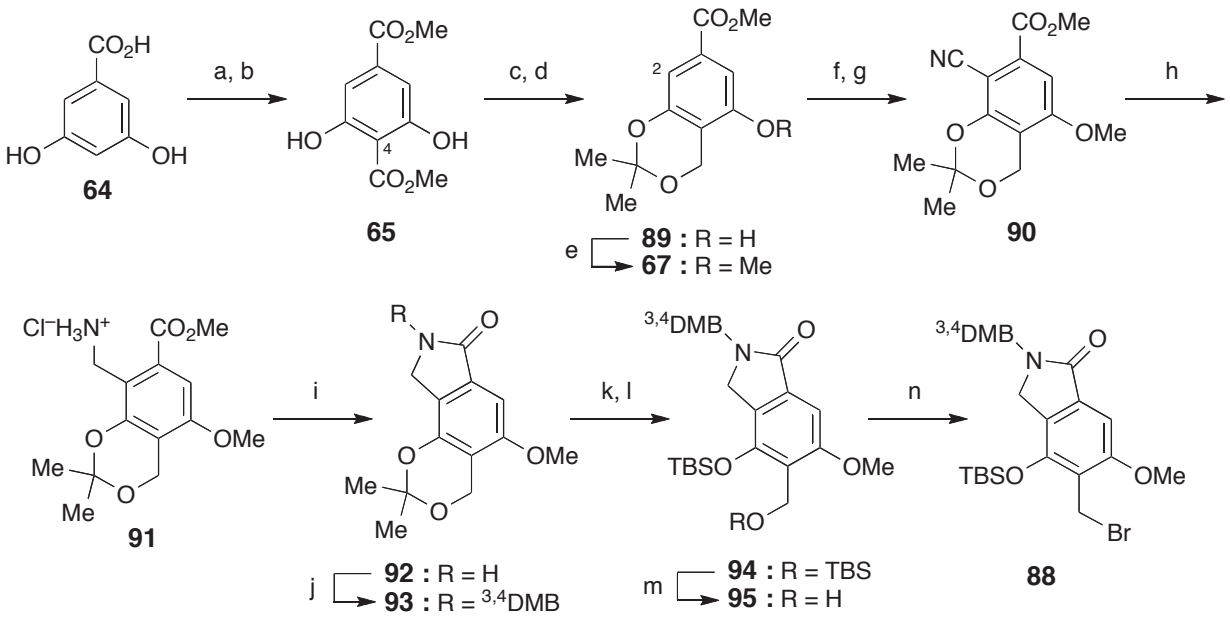


Scheme 20. Retrosynthetic plan for (+)-stachyflin (**3**) according to Katoh et al.[13] ^{3,4}DMB = 3,4-dimethoxybenzyl.

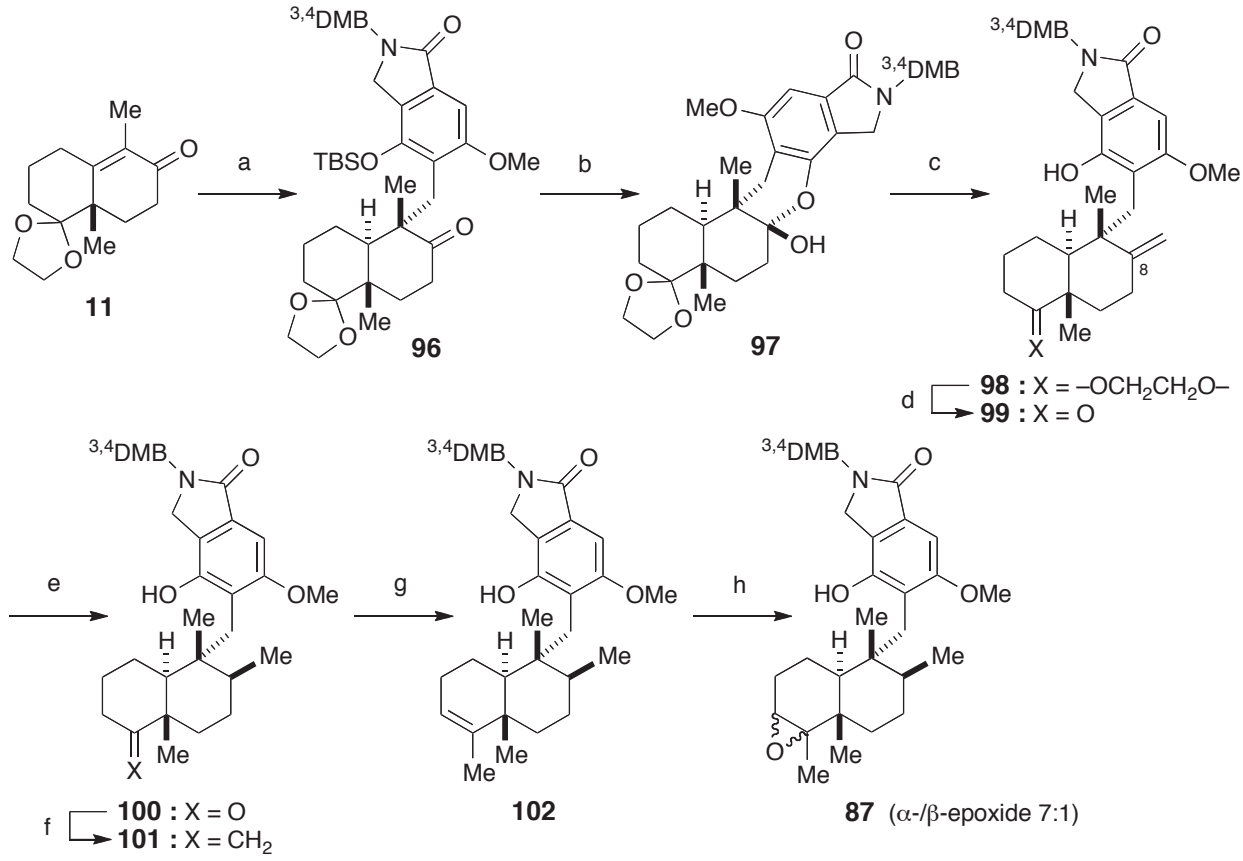
4.2.2. Total Synthesis

We initially pursued the synthesis of intermediate **88**, the coupling partner of **11**, starting from **64** (Scheme 21). The Kolbe–Schmitt reaction[45] of **64** followed by methyl esterification provided dimethyl ester **65** in 64% yield in two steps. Compound **65** was then converted to acetonide **67** with an overall yield of 79% via methyl ester **89** by the selective reduction of the C4 methyl ester function to its corresponding hydroxymethyl congener followed by acetonide formation and methyl etherification. The subsequent regioselective bromination at C2 in **67** and cyanation with CuCN provided nitrile **90** in 66% yield in two steps. Isoindolinone **92** was formed with an overall yield of 98% from **90** by the hydrogenation [H_2 (1 atm), PtO_2, EtOH/$CHCl_3$, rt] and subsequent lactamization of the resulting ammonium salt **91** following treatment with NaOMe in MeOH at room temperature. After the protection of the lactam amide moiety in **92** with a 3,4-dimethoxybenzyl (^{3,4}DMB) group (78% yield), the resulting lactam **93** was transformed into bis-TBS ether **94** with an overall yield of 75% by the cleavage of the acetonide moiety and silylation of the liberated hydroxyl groups. Finally, the regioselective desilylation of **94** (48% aq. HF, MeCN, 0 °C) followed by the bromination of the resulting benzyl alcohol **95** formed the requisite intermediate **88** in 86% yield in two steps.

With the requisite intermediate **88** in hand, we next synthesized intermediate **87**, the precursor of the key



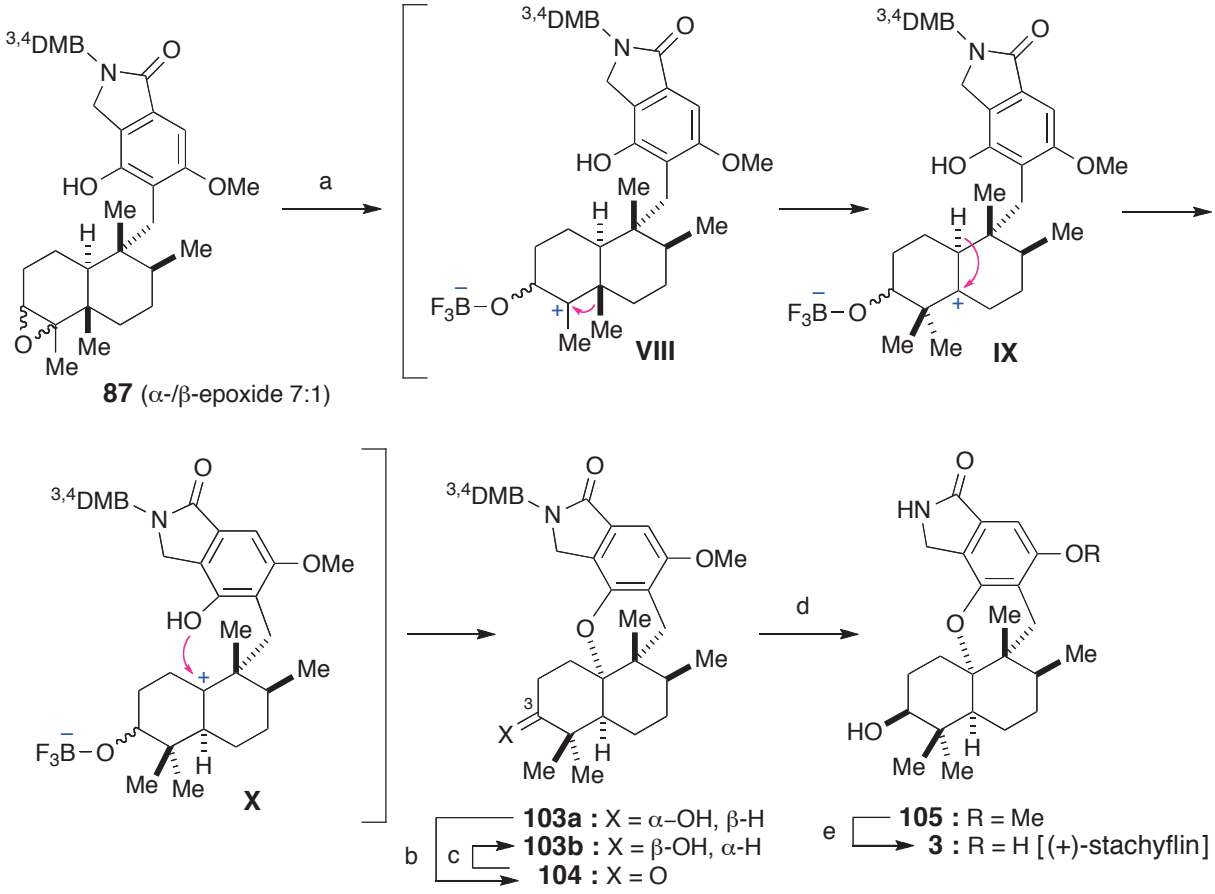
Scheme 21. Synthesis of intermediate **88**. (a) CO_2, $KHCO_3$, glycerol, 180 °C; (b) Me_2SO_4, $KHCO_3$, acetone, reflux, 64% (2 steps); (c) $NaBH_4$, THF/H_2O, rt; (d) 2,2-dimethoxypropane, *p*-TsOH, rt; (e) MeI, K_2CO_3, acetone, rt, 79% (3 steps); (f) NBS, MeCN, 0 °C; (g) CuCN, DMF, 120 °C, 66% (2 steps); (h) H_2 (1 atm), PtO_2, EtOH/$CHCl_3$, rt; (i) NaOMe, MeOH, rt, 98% (2 steps); (j) ^{3,4}DMBCl, $NaN(SiMe_3)_2$, *n*-Bu_4NI, THF, 0 °C to rt, 78%; (k) 1 M HCl, THF, rt; (l) TBSCl, imidazole, DMF, rt, 75% (2 steps); (m) 48% aq. HF, MeCN, 0 °C; (n) CBr_4, PPh_3, CH_2Cl_2, rt, 86% (2 steps).



Scheme 22. Synthesis of intermediate **87**. (a) Li, liq. NH_3/THF, –78 to –30 °C, 1 h; H_2O, isoprene, –78 to –30 °C, 2 h; add **88**, –30 °C to rt, 5 h, 76%; (b) TBAF, THF, 0 °C to rt, 88%; (c) $Ph_3P^+CH_3Br^-$, *t*-BuOK, benzene, reflux, 86%; (d) 4 M HCl, THF, rt, 98%; (e) H_2 (1 atm), 10% Pd/C, Et_3N/MeOH 50:1, rt, 96%; (f) $Ph_3P^+CH_3Br^-$, *t*-BuOK, benzene, reflux, 74%; (g) $RhCl_3 \cdot 3H_2O$, EtOH, reflux, 100%; (h) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 86% (α-/β-epoxide 7:1).

cascade reaction, as shown in Scheme 22. Thus, the crucial reductive alkylation of **11** (>99% ee) with **88** under the Birch conditions proceeded smoothly and cleanly, forming the expected coupling product **96** in 76% yield as a single diastereomer. Cleavage of the TBS group in **96** followed by the Wittig methylenation of the resulting hemiacetal **97** produced *exo*-olefin **98** in 79% yield in two steps.

In order to establish the C8 stereochemistry, the ethyleneacetal moiety in **98** was first removed (98% yield), and the resulting ketone **99** was subjected to stereoselective hydrogenation, forming the desired product **100** in 96% yield as a single stereoisomer. The subsequent Wittig methylenation of **100** (74% yield) followed by the isomerization of double bond in the resulting olefin **101** provided *endo*-olefin **102** (quantitative yield). Epoxidation of **102** with *m*CPBA afforded the desired intermediate **87** in 86% yield as an inseparable mixture of α- and β-epoxides (7:1).



Scheme 23. Synthesis of (+)-stachyflin (**3**). (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, –40 °C to rt, 66% for **103a**, 9% for **103b**; (b) Dess–Martin periodinane, CH_2Cl_2, rt, 94%; (c) LiAlH(*t*-BuO)$_3$, THF, –20 °C, 96%; (d) PIFA, CH_2Cl_2, rt, 54%; (e) *n*-BuSLi, HMPA, 110 °C, 80%. PIFA = phenyliodine(III) bis(trifluoroacetate).

After synthesizing **87**, our efforts were directed toward the completion of total synthesis of (+)-**3**. To this end, as shown in Scheme 23, the key acid-induced cascade epoxide-opening/rearrangement/cyclization of **87** (α-/β-epoxide, 7:1) was investigated under the conditions similar to those described above (see Scheme 4 in section 2.1 and Scheme 14 in section 3). The desired products **103a** (C3 α-OH) and **103b** (C3 β-OH) were obtained in 66% and 9% yields, respectively, after separation by silica-gel column chromatography. In this cascade reaction, intermediate carbocations such as **VIII**, **IX**, and **X** would be involved in a manner similar to that described in section 3.2 (see **44** → [**V** → **VI** → **VII**] → **2** in Scheme 14). The subsequent inversion of the configuration at C3 of **103a** was achieved by Dess–Martin oxidation (94% yield) followed by the LiAlH(*t*-BuO)$_3$ reduction of the resulting ketone **104** (96% yield). Finally, compound **103b** was successfully converted to target (+)-**3** by the removal of the *N*-^{3,4}DMB group with PIFA[46] (54% yield) and the cleavage of the *O*-methyl moiety[29] in the resulting lactam **105** (80% yield). This total synthesis was accomplished with an overall yield of 1.6% in 27 steps from **64** or with an overall yield of 10.0% in 13 steps from **11**.

5. CONCLUSION

In this article, the total synthesis of three biologically attractive sesquiterpenoid natural products—aureol (**1**), strongylin A (**2**), and stachyflin (**3**)—has been summarized with particular focus on their synthetic strategies. It is of great interest to look at each respective methodology devised for constructing the requisite tetracyclic skeleton (ABCD ring system) and the whole carbon framework by controlling the correct stereochemistry. The key element of our approach is the $BF_3{\cdot}Et_2O$-induced sequential carbocation rearrangement/ether cyclization reaction to stereoselectively construct the desired tetracyclic core structure, comprising *cis*-fused AB- and BC-ring junctions, in one step (**7** → **1** in Scheme 4, **44** → **2** in Scheme 14, and **87** → **103a,b** in Scheme 23). These synthetic studies hold promise for preparing additional analogues of **1**–**3** with the aim of exploring their SARs, which will be useful for the development of novel therapeutic agents.

ACKNOWLEDGEMENTS

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