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TOTAL SYNTHESES OF LIPHAGAL: A POTENT AND SELECTIVE PHOSPHOINOSITIDE 3-KINASE α (PI3Kα) INHIBITOR FROM THE MARINE SPONGE *AKA CORALLIPHAGA*

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Abstract – Liphagal, isolated from the marine sponge *Aka coralliphaga*, exhibits a potent and selective inhibitory activity against phosphoinositide 3-kinase α (PI3Kα). This marine natural product has attracted significant attention because of its potential as a promising candidate or new lead for the development of novel molecular targeted anticancer agents. In this review, the reported total syntheses of liphagal are presented with a particular focus on the methodologies and strategies employed.

CONTENTS

1. INTRODUCTION

Phosphoinositide 3-kinases (PI3Ks) play crucial roles in the signaling pathways used by various kinds of cell surface receptors on neutrophils.[1] Within the PI3K family, there are four PI3K isoforms (α, β, γ, and δ) that exhibit different expression patterns and pathophysiological functions.[2] PI3Kα is considered to be a potential anticancer target,[3] and PI3Kβ, PI3Kγ, and PI3Kδ are expected to be promising targets for other pathogenic states, such as cardiovascular disorders (PI3Kβ)[4] and inflammation and autoimmune diseases (PI3Kγ and PI3Kδ).[5] Consequently, the potent and selective inhibition of PI3Kα is highly desirable in cancer chemotherapy.

In 2006, Andersen et al. reported the isolation and structural elucidation of a new liphagane type of meroterpenoid, liphagal (**1**, Figure 1), from the marine sponge *Aka coralliphaga* collected from reefs in Prince Rupert Bay, Portsmouth, Dominica.[6] This marine natural product has been shown to have potent inhibitory activity against PI3Kα with an IC_{50} value of 0.1 μM and tenfold greater selectivity for PI3Kα than PI3Kγ.[6] Although a large number of PI3Ks inhibitors have been reported to date,[7] liphagal, which has shown α-isoform selectivity among several isoforms, is one of the most remarkable small-molecule inhibitors.[7a] Molecular docking and molecular dynamics simulations were performed to investigate the

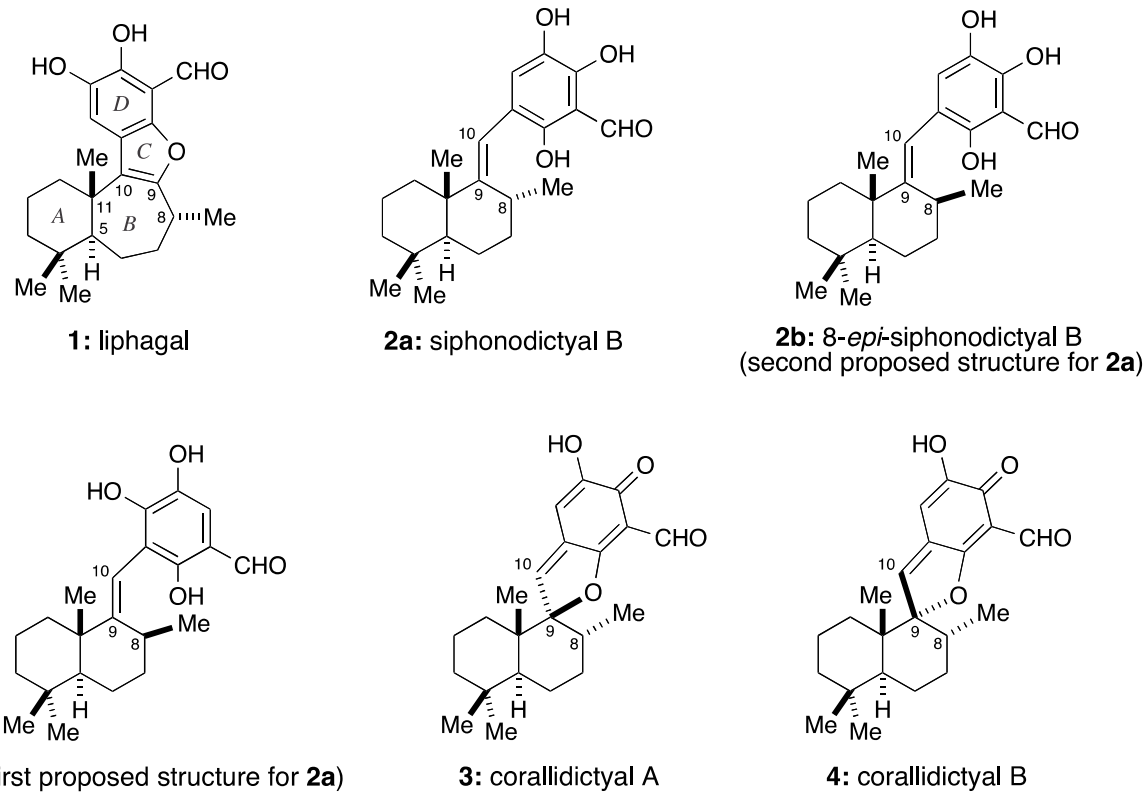


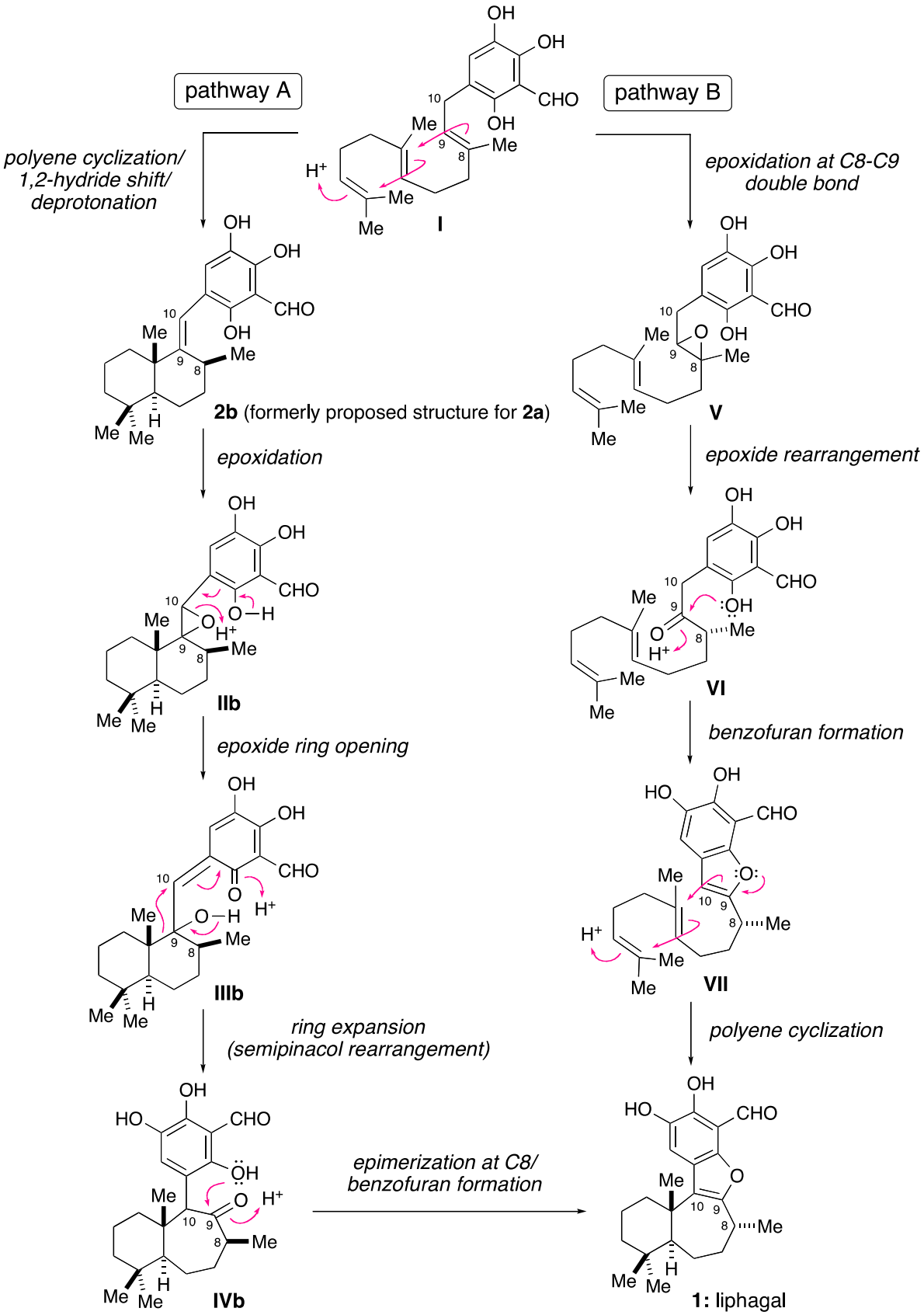
Figure 1. Structures of liphagal (**1**) and siphonodictyal B (**2a**), formerly proposed structures of **2a** (**2b** and **2c**), and structures of corallidictyals A (**3**) and B (**4**)

dynamic behavior of liphagal with the enzyme PI3Kα,[8] which may be beneficial for the discovery of more potent liphagal analogs targeting PI3Kα. It has also been shown that liphagal exhibits antiproliferative activities against several human cancer cell lines in the submicromolar to low micromolar range [e.g., LoVo (human colon): IC_{50} = 0.58 μM, CaCo (human colon): IC_{50} = 0.67 μM, MDA-468 (human breast): IC_{50} = 1.58 μM].[6] Liphagal, therefore, is strongly anticipated to be a promising candidate or new lead for the development of novel molecular targeted anticancer agents. However, further biological studies of this marine natural product are severely limited by the scarcity of samples available from the sponge *Aka coralliphaga* (0.0019% isolated yield).[6]

Structurally, liphagal possesses an unprecedented fused 6,7,5,6-tetracyclic skeleton (ABCD ring system) containing three asymmetric carbon centers (C5, C8, and C11 positions, liphagal numbering) with the characteristic feature of a highly substituted aromatic portion (D-ring). The absolute configuration of liphagal was established later by three independent research groups (i.e., the Andersen, George, and Alvarez-Manzaneda groups) at almost the same time (2010) through the enantioselective total synthesis of naturally occurring (+)-**1** (vide infra, sections 3-1–3-3). Closely related natural products possessing the same carbon framework and substitution patterns on the aromatic ring have previously been isolated from the same marine sponge *Aka coralliphaga*. These include siphonodictyal B (**2a**)[9] and corallidictyals A (**3**) and B (**4**),[10] all of which were reported to exhibit antimicrobial and antiproliferative activities.[9a,9c,10]

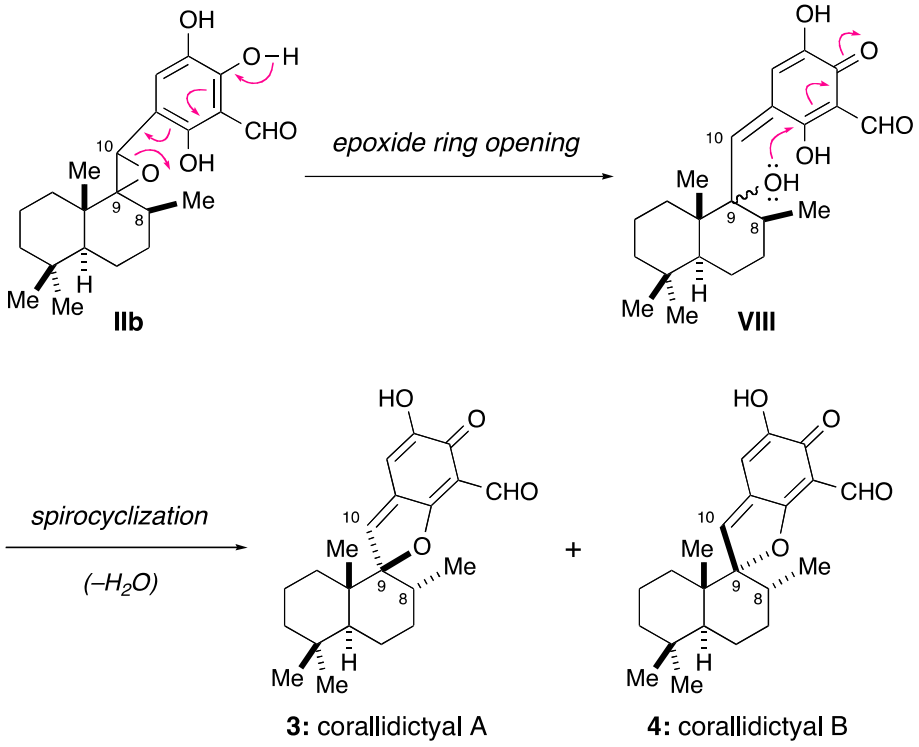
There is a checkered history of structural determination for siphonoductyal B. This substance was originally isolated in 1981 by Faulkner et al. from the marine sponge *Aka coralliphaga* (also known as *Siphonodictyon coralliphagum*), and the structure shown in formula **2c** was proposed by the same researchers.[9c] Subsequently, the first proposed structure **2c** was revised to structure **2b** (8-*epi*-siphonodictyal B) by Faulkner and Clardy et al. in 1986.[9b] Recently, the second proposed structure **2b** was revised again to structure **2a**, the true structure (C8 epimer of **2b**), by George et al. (2015) through the total synthesis of this marine natural product.[11] Indeed, it took more than thirty years to establish the true structure of siphonodictyal B (**2a**) since it was first isolated.

During the period in which formula **2b** was considered a possible stereostructure for siphonodictyal B, two alternative biosynthetic pathways to liphagal (**1**: pathways A and B in Scheme 1) were proposed by Andersen et al.[6] In pathway A, the more likely biogenesis, proton-initiated polyene cyclization of farnesylated trihydroxybenzaldehyde **I** could produce 8-*epi*-siphonodictyal B (**2b**) following a 1,2-hydride shift from C9-H to the resulting C8 carbocation and deprotonation from C10-H. Compound **2b** could then be transformed into intermediate **IVb**, possessing a fused 6,7-ring system, through epoxidation followed by epoxide ring opening of intermediate **IIb** and ring expansion (semipinacol rearrangement) of the resulting *o*-quinone methide **IIIb**. Epimerization at C8 in **IVb** followed by benzofuran formation could produce **1**. Alternatively, as shown in pathway B, epoxidation at the C8–C9



Scheme 1. Biosynthetic pathways to liphagal (**1**) proposed by Andersen et al.[6]

double bond in the farnesyl side chain of **I** followed by epoxide rearrangement of the resulting epoxide **V** could form ketone **VI**, which could induce formation of benzofuran **VII**. Finally, polyene cyclization of the dienyl side chain in benzofuran **VII** could deliver **1**. More interestingly, as shown in Scheme 2, George et al. proposed that corallidictyals A (**3**) and B (**4**) might be produced biosynthetically from the same intermediate **IIb** through epoxide ring opening followed by 5-*exo*-*trig*-type spirocyclization of the *p*-quinone methide intermediate **VIII**.[12]



Scheme 2. Biosynthesis of corallidictyals A (**3**) and B (**4**) proposed by George et al.[12]

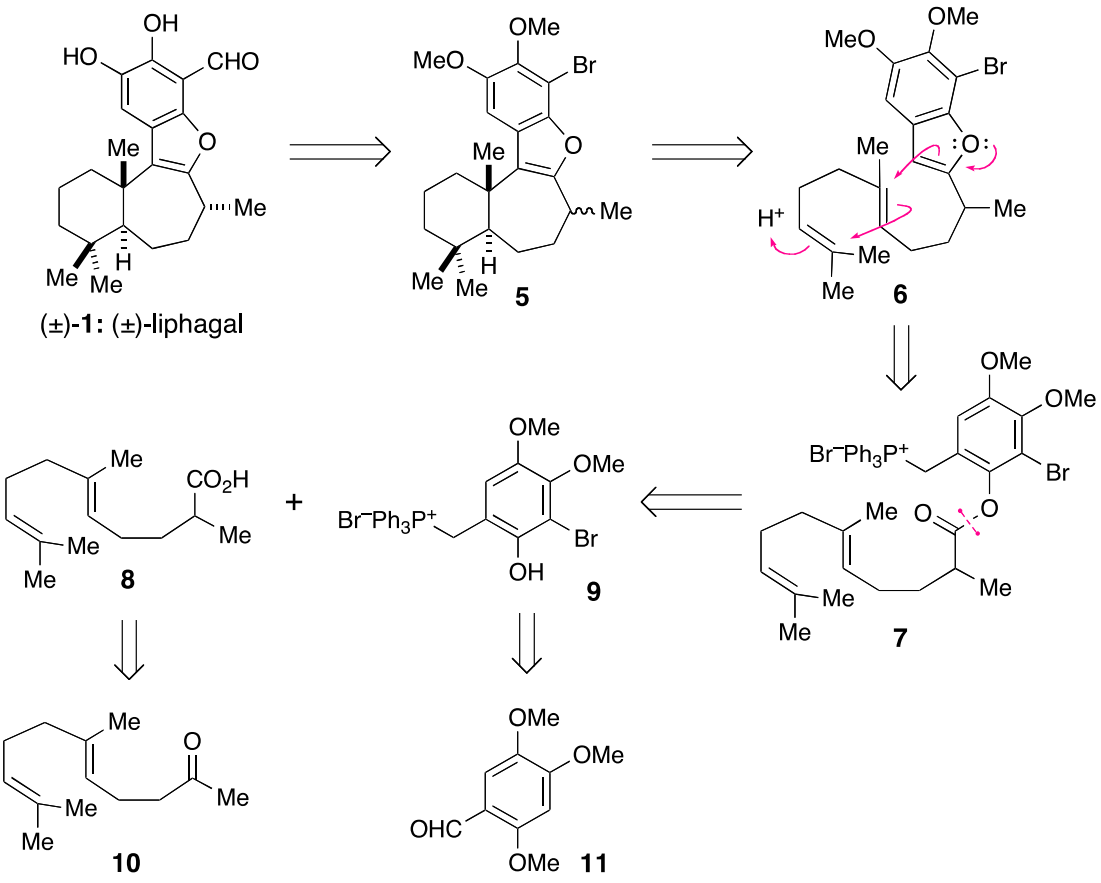
The unique structural features, attractive biological activities, limited availability from natural resources, and plausible biosynthetic pathway have made liphagal (**1**) an exceptionally intriguing and timely target for total synthesis. In 2006, the first total synthesis of racemic (±)-**1** was presented by Andersen et al.[6] Subsequently, the formal total syntheses of (±)-**1** were reported by Mehta et al. (2009)[13] and Kumar et al. (2011).[14] Enantioselective total syntheses of naturally occurring (+)-**1** were separately achieved by Andersen et al. (2010),[15] George et al. (2010[12] and 2015[11]), Alvarez-Manzaneda et al. (2010),[16] Stoltz et al. (2011),[17] and our group (2014).[18] Recently, the formal total synthesis of (±)-**1** was reported by Ferreira et al. (2017).[19] Related synthetic studies have also been reported by several other research groups.[20] The syntheses and biological evaluation of liphagal analogs were performed by Andersen et al.[15,21] In this article, the total syntheses of **1** are reviewed with a particular focus on the synthetic strategies employed.

2. TOTAL SYNTHESIS OF (±)-LIPHAGAL

2-1. Andersen's Total Synthesis (2006)

2-1-1. Synthetic Strategy

In 2006, Andersen et al. reported the first total synthesis of racemic (±)-**1**.[6] Their retrosynthetic plan is illustrated in Scheme 3. The most crucial step in this plan is the biomimetic polyene cyclization of brominated dienylbenzofuran **6** to produce the requisite tetracyclic ring system (i.e., **6** → **5**), which relies on the proposed biosynthetic pathway (see pathway B in Scheme 1). The cyclized product **5** can be converted into target molecule (±)-**1** by formylation and deprotection. The polyene cyclization precursor **6** can be prepared by the intramolecular Wittig reaction of phosphonium salt **7**. Intermediate **7** can be formed by ester bond formation between carboxylic acid **8** and phenol **9**. Intermediates **8** and **9** can be accessed from commercially available geranylacetone (**10**) and 2,4,5-trimethoxybenzaldehyde (**11**), respectively.

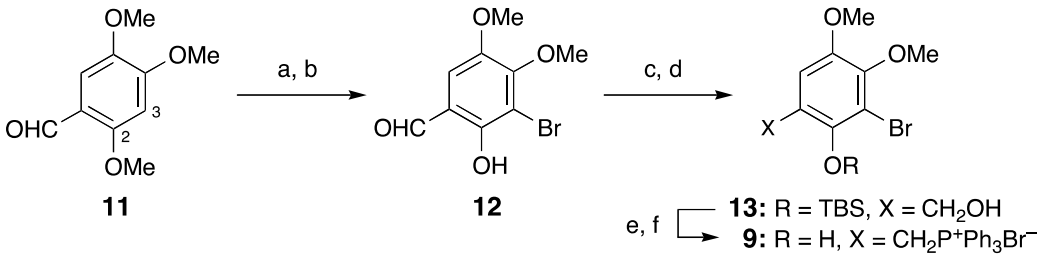


Scheme 3. Retrosynthetic plan for (±)-liphagal [(±)-**1**] according to Andersen et al.[6]

2-1-2. Total Synthesis

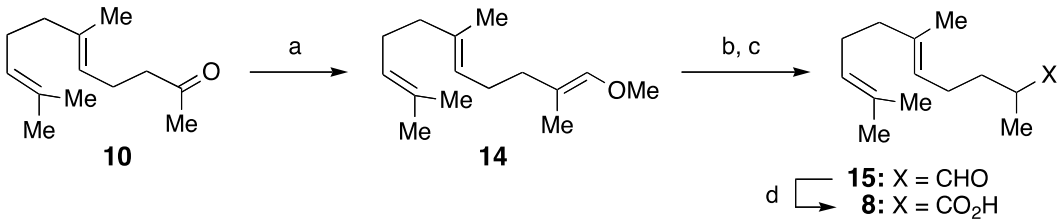
As shown in Scheme 4, the synthesis of intermediate **9** was carried out starting from **11**. Site-selective demethylation of the C2 *O*-methyl group in **11** (87% yield) followed by site-selective bromination at the

C3 position in the resulting phenol afforded bromophenol **12** (54% yield). Silyl protection of **12** (80% yield) followed by formyl reduction provided benzyl alcohol **13** (94% yield). Treatment of **13** with $PPh_3 \cdot HBr$ and subsequent removal of the silyl protecting group furnished the requisite intermediate **9** in 94% yield in two steps.



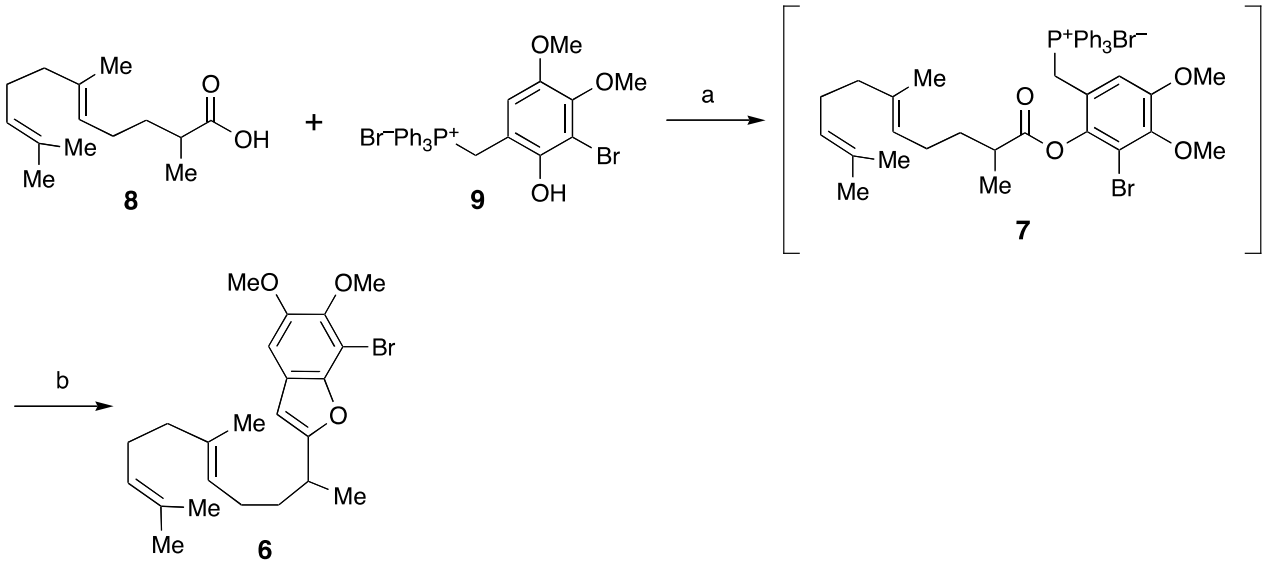
Scheme 4. Synthesis of intermediate **9**. (a) BBr_3, CH_2Cl_2, 0 °C to rt, 87%; (b) Br_2, AcONa, AcOH, rt, 54%; (c) TBSCl, imidazole, CH_2Cl_2, rt, 80%; (d) $NaBH_4$, MeOH, 0 °C, 94%; (e) $Ph_3P \cdot HBr$, MeCN, reflux; (f) HF·pyridine, THF, rt, 94% (2 steps). rt = room temperature, Ac = acetyl, TBS = *tert*-butyldimethylsilyl.

The synthesis of intermediate **8** (a coupling partner of **9**) commenced with a Wittig reaction on geranylacetone (**10**) (Scheme 5), which provided methyl enol ether **14** in quantitative yield. The two-step acid hydrolysis of **14** furnished aldehyde **15** in 76% yield in two steps. Oxidation of **15** with $NaClO_2$ gave **8** in 60% yield.



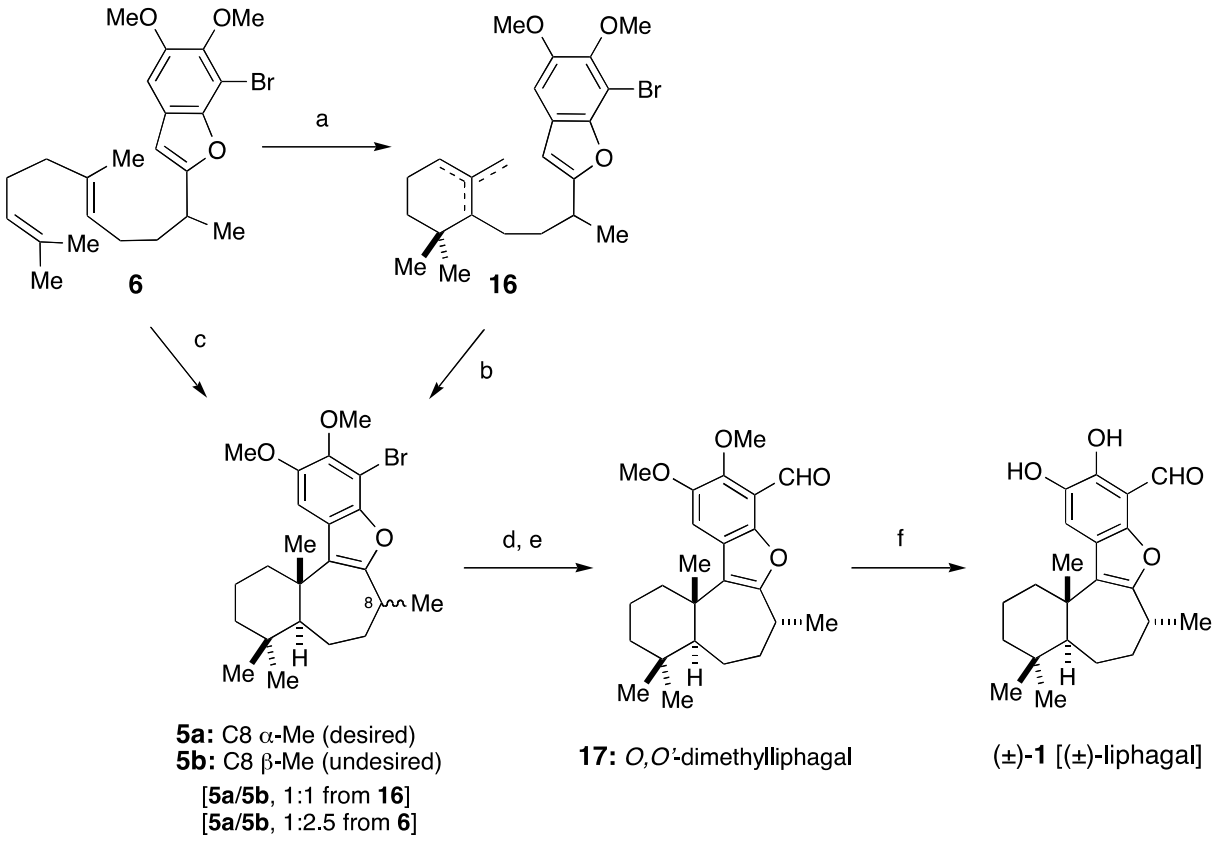
Scheme 5. Synthesis of intermediate **8**. (a) $MeOCH_2P^+Ph_3Cl^-$, *t*-BuOK, THF, rt, 100%; (b) PPTS, MeOH, reflux, 90%; (c) PPTS, acetone/H_2O 4:1, rt, 84%; (d) $NaClO_2$, NaH_2PO_4, acetone/H_2O/amylene 12:6:1, rt, 60%. *t*-Bu = *tert*-butyl, PPTS = pyridinium *p*-toluenesulfonate.

A coupling reaction between **8** and **9** was efficiently achieved via ester bond formation using dicyclohexylcarbodiimide (DCC) to produce the corresponding ester **7** (Scheme 6), which was not isolated. Subsequent treatment of **7** with Et_3N in refluxing THF brought about an intramolecular Wittig reaction to produce the expected benzofuran **6** in 80% yield in two steps.



Scheme 6. Synthesis of intermediate **6**. (a) DCC, DMAP, CH_2Cl_2, rt; (b) Et_3N, THF, reflux, 80% (2 steps). DCC = dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine.

The crucial polyene cyclization of dienylbenzofuran **6** to construct the requisite tetracyclic ring system was intensively investigated as shown in Scheme 7. The cyclization step was first effected by refluxing **6** in a biphasic system of HCO_2H and cyclohexane for 14 days, resulting in the formation of a mixture of partially cyclized alkenes **16** along with a mixture of tetracyclic products **5a** and **5b** (C8 epimers, 1:2.5; reagents, reaction conditions, and yields are not shown in the scheme caption). From these results, it was suggested that the conversion of **6** into **5a** and **5b** proceeded via a two-step sequence of reactions (i.e., **6** → **16** → **5a** and **5b**). In support of this suggestion, it was found that treatment of **6** with HCO_2H in refluxing cyclohexane for 2 h provided only **16** in 83% yield. It was also found that **16** reacted slowly under the same conditions to give, after four weeks, a mixture of **5a** and **5b** (1:1) in 40% yield. To shorten the reaction time, **6** was treated with the stronger acid $ClSO_3H$ at –78 °C in 2-nitropropane; the cyclization was complete within 30 min under these conditions, furnishing a mixture of **5a** and **5b** in 43% yield. In this cyclization step, unfortunately, the products **5a** and **5b** were formed as an inseparable mixture of C8 epimers with the undesired β-methyl isomer being favored (**5a**/**5b**, 1:2.5); this result appears to be a considerable disadvantage of this approach. To take the synthesis forward, installation of the formyl group was carried out by bromine/lithium exchange of a mixture of **5a** and **5b** (1:2.5) followed by the addition of *N*,*N*-dimethylformamide (DMF). This gave *O*,*O*'-dimethylliphagal (**17**) in 22% yield after separation by high-performance liquid chromatography (HPLC). Finally, the demethylation of **17** using BI_3 afforded (±)-liphagal [(±)-**1**] in 64% yield. This total synthesis was achieved with an overall yield of 2.1% and a longest linear sequence of 12 steps from starting material **11**.

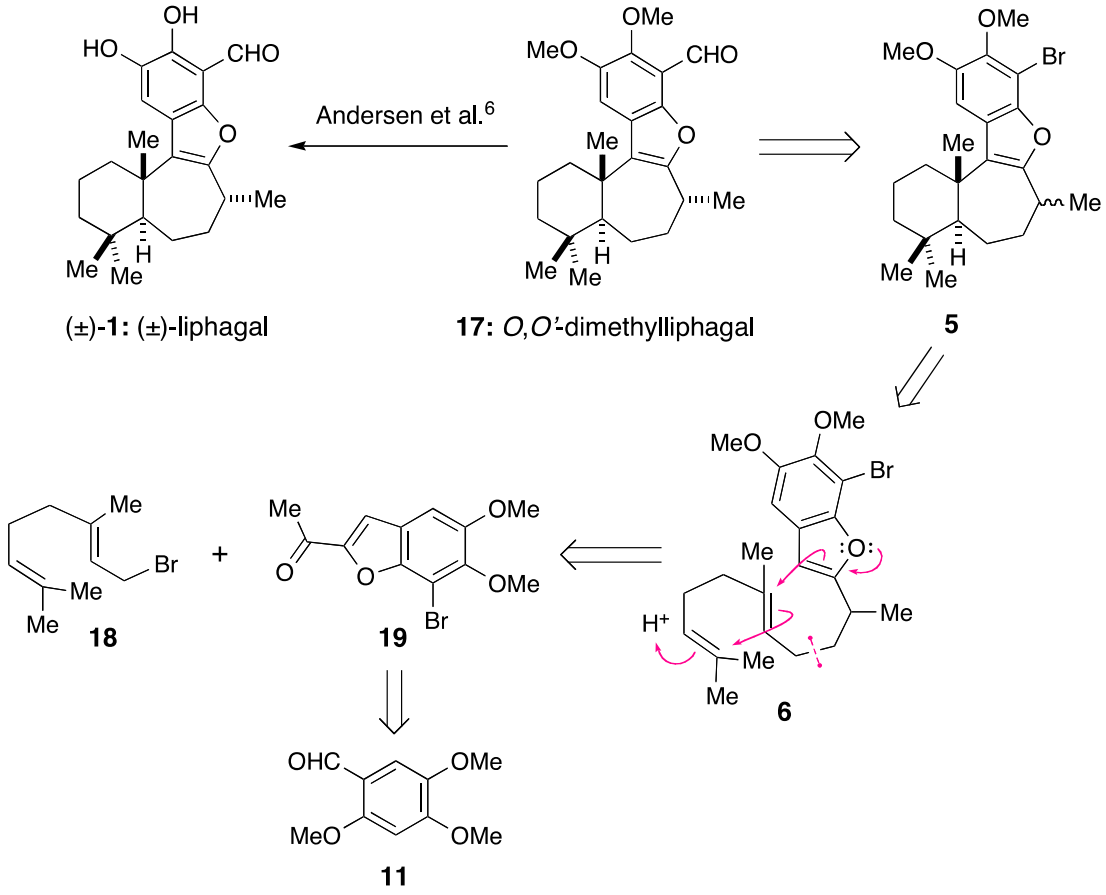


Scheme 7. Synthesis of (±)-liphagal [(±)-**1**]. (a) HCO_2H, cyclohexane, reflux, 2 h, 83%; (b) HCO_2H, cyclohexane, reflux, 4 weeks, 40% (**5a**/**5b**, 1:1); (c) $ClSO_3H$, 2-nitropropane, –78 °C, 30 min, 43% (**5a**/**5b**, 1:2.5); (d) *n*-BuLi, THF, –78 °C; add DMF, –78 °C to rt, 76%; (e) separation by HPLC, 22%; (f) BI_3, CH_2Cl_2, –78 °C to rt, 64%. DMF = *N*,*N*-dimethylformamide, HPLC = high-performance liquid chromatography.

2-2. Mehta's Formal Total Synthesis (2009)

2-2-1. Synthetic Strategy

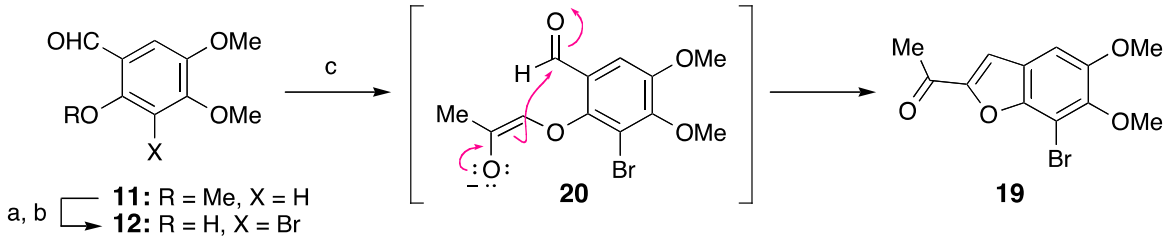
In 2009, Mehta et al. reported the formal total synthesis of (±)-**1**.[13] Their retrosynthetic plan is illustrated in Scheme 8, which is similar to that reported by Andersen et al.[6] (see Scheme 3 in section 2-1-1). Subtarget molecule *O*,*O*'-dimethylliphagal (**17**), which has already been converted to (±)-**1**, can be produced from brominated dienylbenzofuran **6** by biomimetic polyene cyclization followed by formylation on the aromatic ring (**6** → **5** → **17**). The key cyclization precursor **6** can be elaborated through the S_N2-type coupling reaction between acetylbenzofuran **19** and commercially available geranyl bromide (**18**). Intermediate **19** can be accessed from 2,4,5-trimethoxybenzaldehyde (**11**).



Scheme 8. Retrosynthetic plan for (±)-liphagal [(±)-**1**] according to Mehta et al.[13]

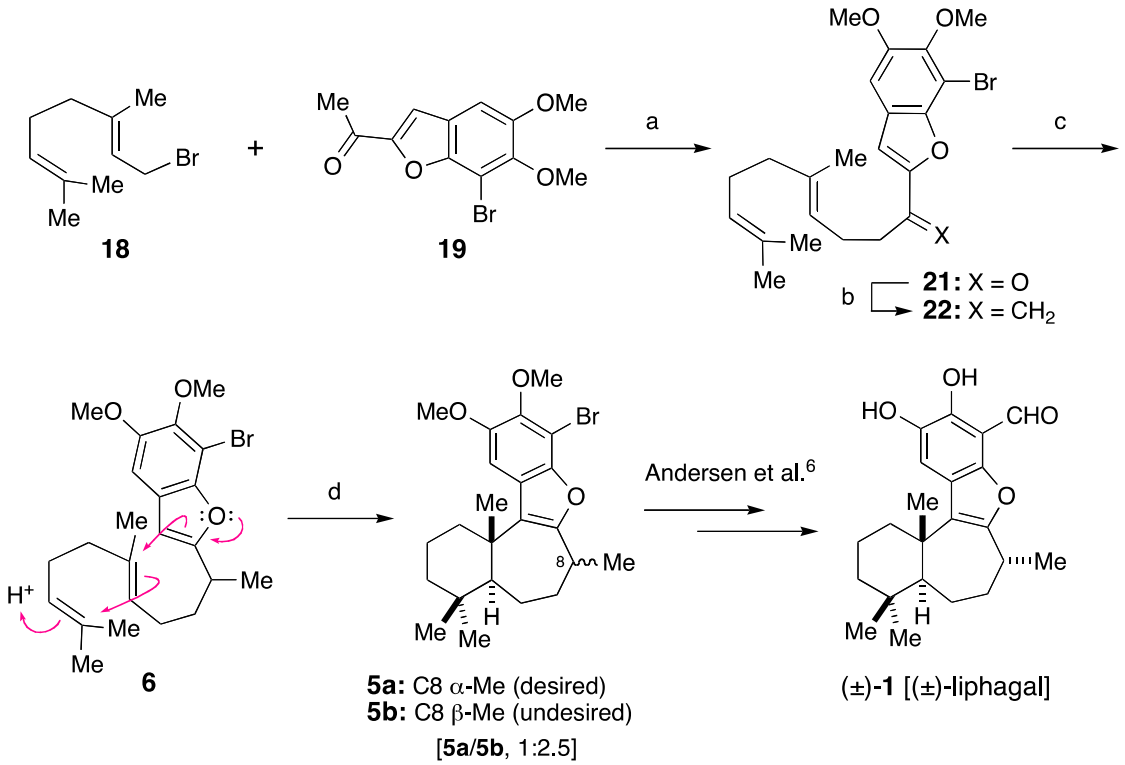
2-2-2. Formal Total Synthesis

The synthesis of intermediate **19** was carried out starting from **11**, as shown in Scheme 9. The site-selective demethylation of **11** followed by the site-selective bromination afforded bromophenol **12** in 67% yield in two steps. The subsequent one-pot furan annulation was performed by treating **12** with 2-chloroacetone in the presence of K_2CO_3 in refluxing 2-butanone to give benzofuran **19** in 76% yield via enolate ion intermediate **20**.



Scheme 9. Synthesis of intermediate **19**. (a) BBr_3, CH_2Cl_2, 0 °C to rt, 87%; (b) Br_2, $AlCl_3$, CH_2Cl_2, 0 °C to rt, 77%; (c) chloroacetone, K_2CO_3, 2-butanone, reflux, 76%.

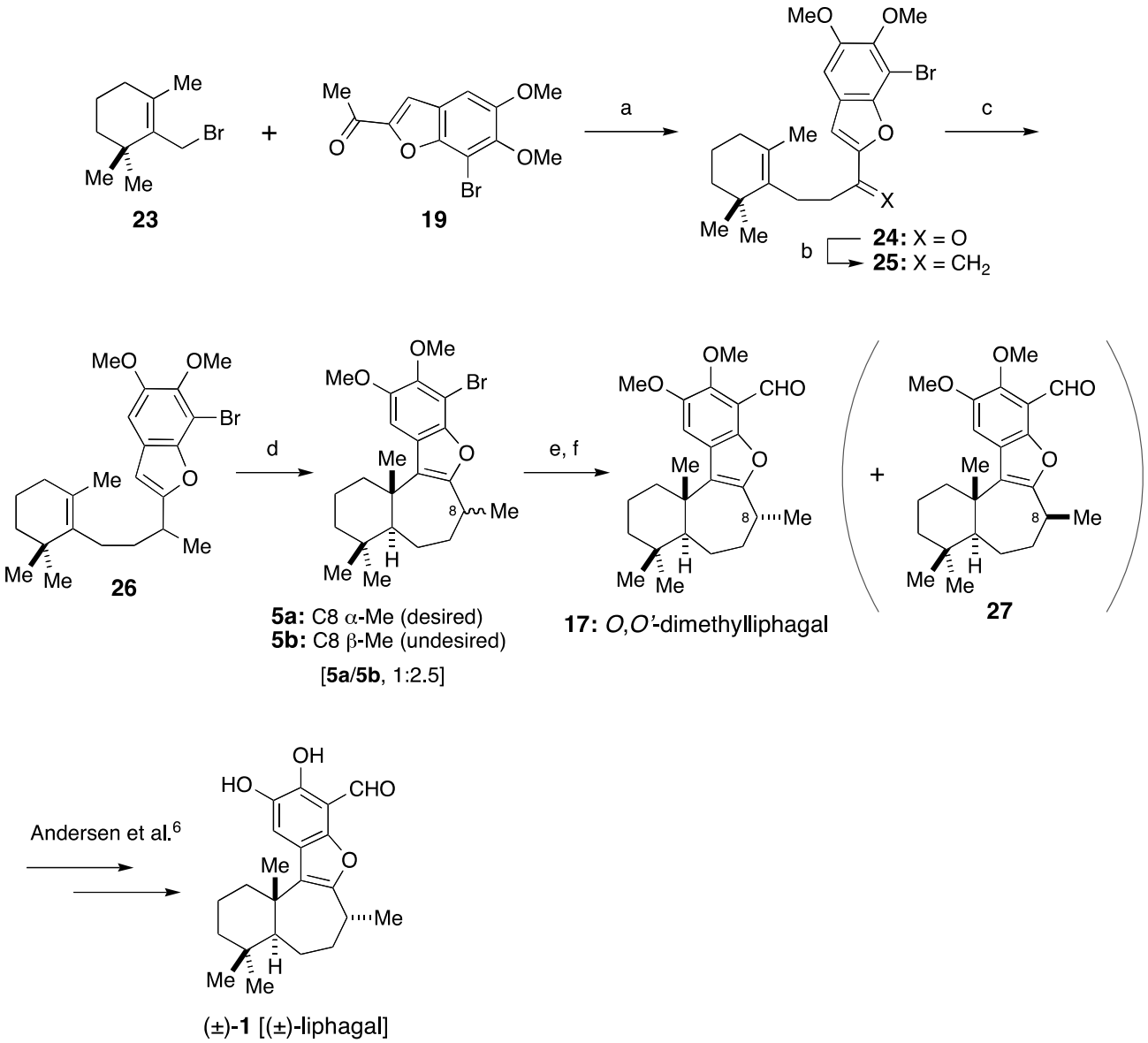
Next, the S_N2-type coupling reaction between **18** and **19** in an intermolecular manner was performed as shown in Scheme 10. Treating a mixture of **18** and **19** with *t*-BuOK at 0 °C furnished the expected coupling product **21** in 40% yield (based on recovery of the starting material). The subsequent Wittig methylenation of **21** afforded *exo*-methylene **22** in 78% yield, which was then subjected to site-selective hydrogenation of the *exo*-methylene moiety in triene **22** to form intermediate **6** in 88% yield. The pivotal biomimetic polyene cyclization was achieved by employing Andersen's protocol.[6] Exposure of **6** to $ClSO_3H$ in 2-nitropropane at –78 °C for 30 min afforded a mixture of tetracyclic products **5a** and **5b** (1:2.5) in 40% yield. This mixture has previously been converted into (±)-**1** by Andersen et al.[6] via a three-step operation (19% overall yield) including formylation, separation of the two C8 epimers, and demethylation (see **5a** + **5b** (1:2.5) → **17** → (±)-**1** in Scheme 7).



Scheme 10. Synthesis of intermediates **5a** and **5b**: Formal synthesis of (±)-liphagal [(±)-**1**]. (a) *t*-BuOK, toluene, 0 °C, 40% (based on recovered starting material); (b) $Ph_3P^+CH_3Br^-$, *n*-BuLi, THF, 0 °C, 78%; (c) H_2 (1 atm), 5% $Pd/CaCO_3$ poisoned with Pb, MeOH, rt, 88%; (d) $ClSO_3H$, 2-nitropropane, –78 °C, 30 min, 40% (**5a**/**5b**, 1:2.5).

In a complementary route to (±)-**1**, as shown in Scheme 11, subtarget **17** (*O*,*O*'-dimethylliphagal) was synthesized using cyclogeranyl bromide (**23**) instead of geranyl bromide (**16**) in a manner similar to that described in Scheme 10. A coupling reaction between **23** and **19** under the same conditions described earlier (see **18** + **19** → **21** in Scheme 10) furnished the desired product **24** in slightly better yield (i.e., 50% yield based on recovery of the starting material) than that with **18** (40% yield based on recovery of

the starting material). The Wittig methylenation of **24** followed by the site-selective hydrogenation of the resulting *exo*-methylene **25** afforded the key cyclization precursor **26** in 72% yield in two steps. The $ClSO_3H$-mediated cyclization of **26** provided the expected tetracyclic products **5a** and **5b** in 40% yield as an inseparable mixture (1:2.5). The subsequent formylation of a mixture of **5a** and **5b** (1:2.5) provided a mixture of **17** and its C8-epimer **27** (75% combined yield). At this stage, the isolation of **17** from this mixture was performed by HPLC to give a pure sample of **17** in 29% yield. Since the conversion of **17** to (±)-**1** was already achieved by Andersen et al.,[6] this synthesis represents the formal total synthesis of (±)-**1**.

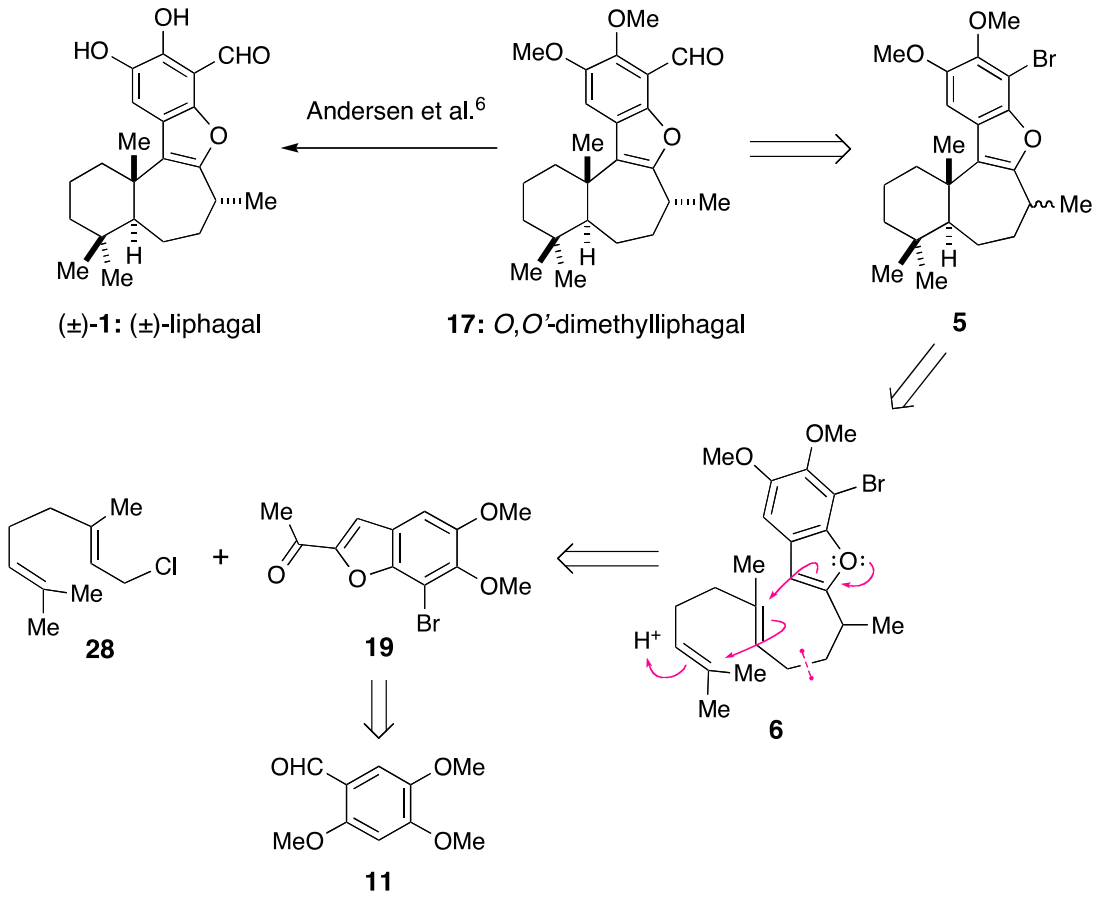


Scheme 11. Synthesis of intermediates **17**: Formal synthesis of (±)-liphagal [(±)-**1**]. (a) *t*-BuOK, toluene, 0 °C, 50% (based on recovered starting material); (b) $Ph_3P^+CH_3Br^-$, *n*-BuLi, THF, 0 °C, 80%; (c) H_2 (1 atm), 10% Pd/C, EtOAc, rt, 90%; (d) $ClSO_3H$, 2-nitropropane, –78 °C, 30 min, 40% (**5a**/**5b**, 1:2.5); (e) *n*-BuLi, THF, –78 °C; add DMF, –78 °C to rt, 75%; (f) separation by HPLC, 29%.

2-3. Kumar's Formal Total Synthesis (2011)

2-3-1. Synthetic Strategy

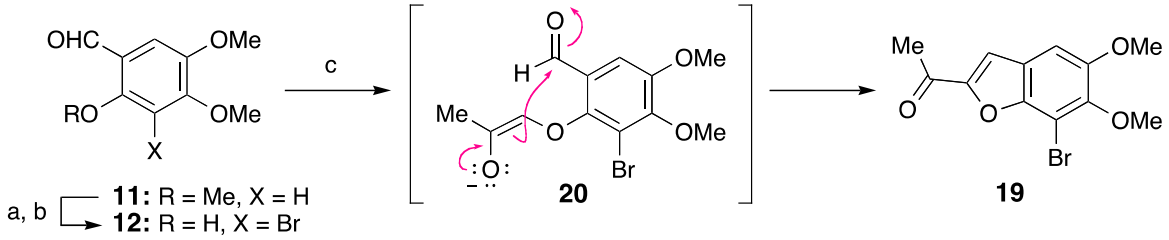
In 2011, Kumar et al. reported the formal total synthesis of (±)-**1**.[14] Their retrosynthetic plan is outlined in Scheme 12, which, for some reason, is almost the same as that described by Mehta et al.[13] (see Scheme 8 in section 2-2-1). Subtarget *O*,*O*'-dimethylliphagal (**17**) can be synthesized from brominated dienylbenzofuran **6** by sequential cyclization and formylation (**6** → **5** → **17**). The cyclization precursor **6** can be produced by the S_N2-type coupling of acetylbenzofuran **19** and commercially available geranyl chloride (**28**). Intermediate **19** is accessible from 2,4,5-trimethoxybenzaldehyde (**11**).



Scheme 12. Retrosynthetic plan for (±)-liphagal [(±)-**1**] according to Kumar et al.[14]

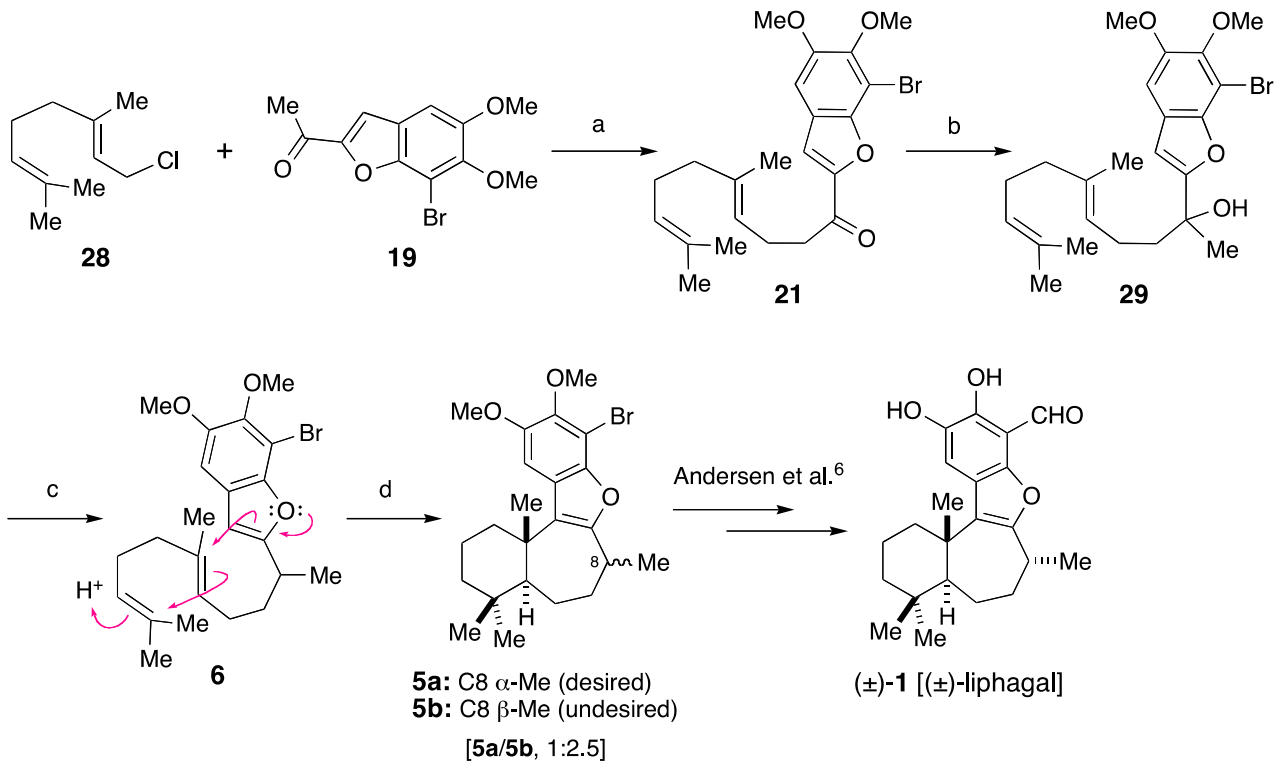
2-3-2. Formal Total Synthesis

As shown in Scheme 13, intermediate **19** was prepared from **11** in a manner similar to that depicted in Scheme 9. The reagents and reaction conditions were slightly different from those described in Scheme 9.



Scheme 13. Synthesis of intermediate **19**. (a) BBr_3, CH_2Cl_2, rt, 88%; (b) Br_2, AcONa, AcOH, rt, 54%; (c) chloroacetone, K_2CO_3, DMF, 100 °C, 60%.

A coupling reaction between **19** and **28** provided the expected product **21** in 30% yield (Scheme 14). The subsequent methylation of the carbonyl group in **21** afforded tertiary alcohol **29** in 82% yield. The hydroxy group in **29** was reductively removed by reaction with ZnI and $NaBH_3CN$ in refluxing CH_2Cl_2 to give the cyclization precursor **6** in 85% yield. The polyene cyclization event was performed by using Andersen's method[6] ($ClSO_3H$, 2-nitropropane, –78 °C, 30 min), which provided a mixture of tetracyclic products **5a** and **5b** (1:2.5) in 40% yield. Compound **5a** is Andersen's intermediate for the synthesis of (±)-**1** (see Scheme 7 in section 2-1-2); therefore, this study represents the formal total synthesis of (±)-**1**.

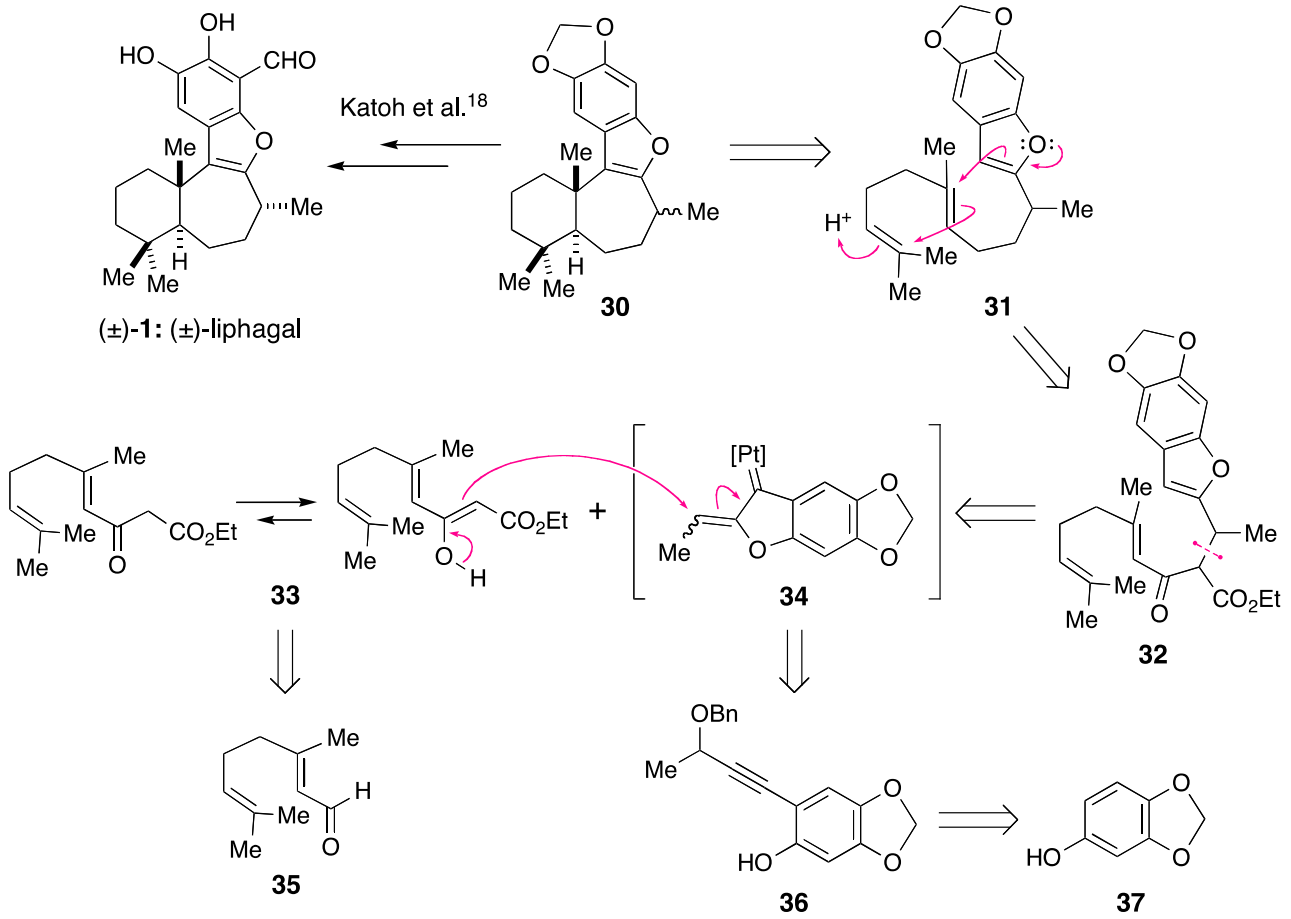


Scheme 14. Synthesis of intermediates **5a**: Formal synthesis of (±)-liphagal [(±)-**1**]. (a) NaH, DMF, 60 °C, 30%; (b) MeMgBr, THF, 0 °C, 82%; (c) ZnI, $NaBH_3CN$, CH_2Cl_2, reflux, 85%; (d) $ClSO_3H$, 2-nitropropane, –78 °C, 30 min, 40%.

2-4. Ferreira's Formal Total Synthesis (2017)

2-4-1. Synthetic Strategy

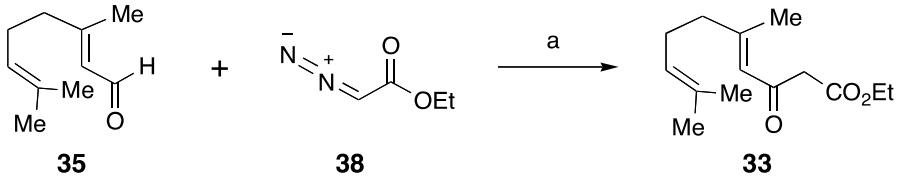
In 2017, Ferreira et al. reported the formal total synthesis of (±)-**1**.[19] The retrosynthetic plan is outlined in Scheme 15. In this plan, the stage for construction of the tetracyclic ring system (i.e., **31** → **30**) relies on Andersen's biomimetic approach[6] (see **6** → **5a** + **5b** in Scheme 7). The optically active version of **30** has already been converted into (+)-liphagal (**1**) in a two-step sequence (vide infra, see **73** → **88** → **1** in Scheme 33). The most intriguing step in this scheme is the nucleophilic attack of β-ketoester **33** on α,β-unsaturated platinum carbene species **34** to assemble the requisite carbon framework such as structure **32** (**33** + **34** → **32**). Intermediate **32** can be converted into **31** by sequential functional group manipulation. Carbene species **34** can be generated in situ from acetylenic phenol **36**, which is accessible from commercially available sesamol (**37**). Intermediate **33** can in turn be prepared from geranial (**35**).



Scheme 15. Retrosynthetic plan for (±)-liphagal [(±)-**1**] according to Ferreira et al.[19] Bn = benzyl.

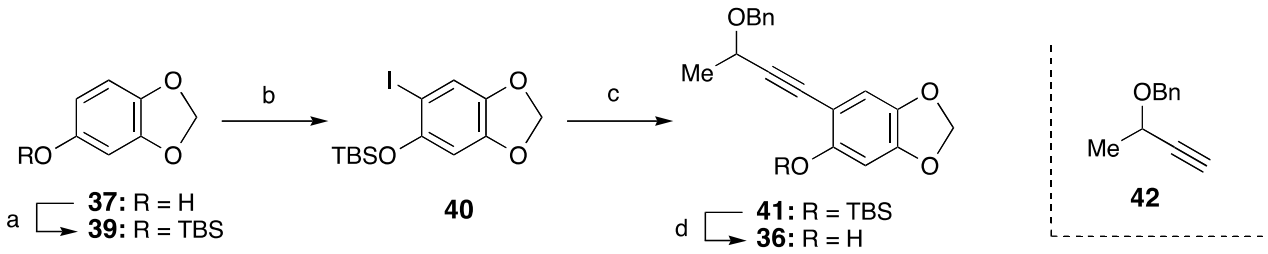
2-4-2. Formal Total Synthesis

At first, as shown in Scheme 16, intermediate **33**, the coupling partner of **34**, was prepared via the Roskamp reaction[22] between geranial (**35**) and ethyl diazoacetate (**38**) in 66% yield.



Scheme 16. Synthesis of intermediate **33**. (a) $SnCl_2$, CH_2Cl_2, rt, 66%.

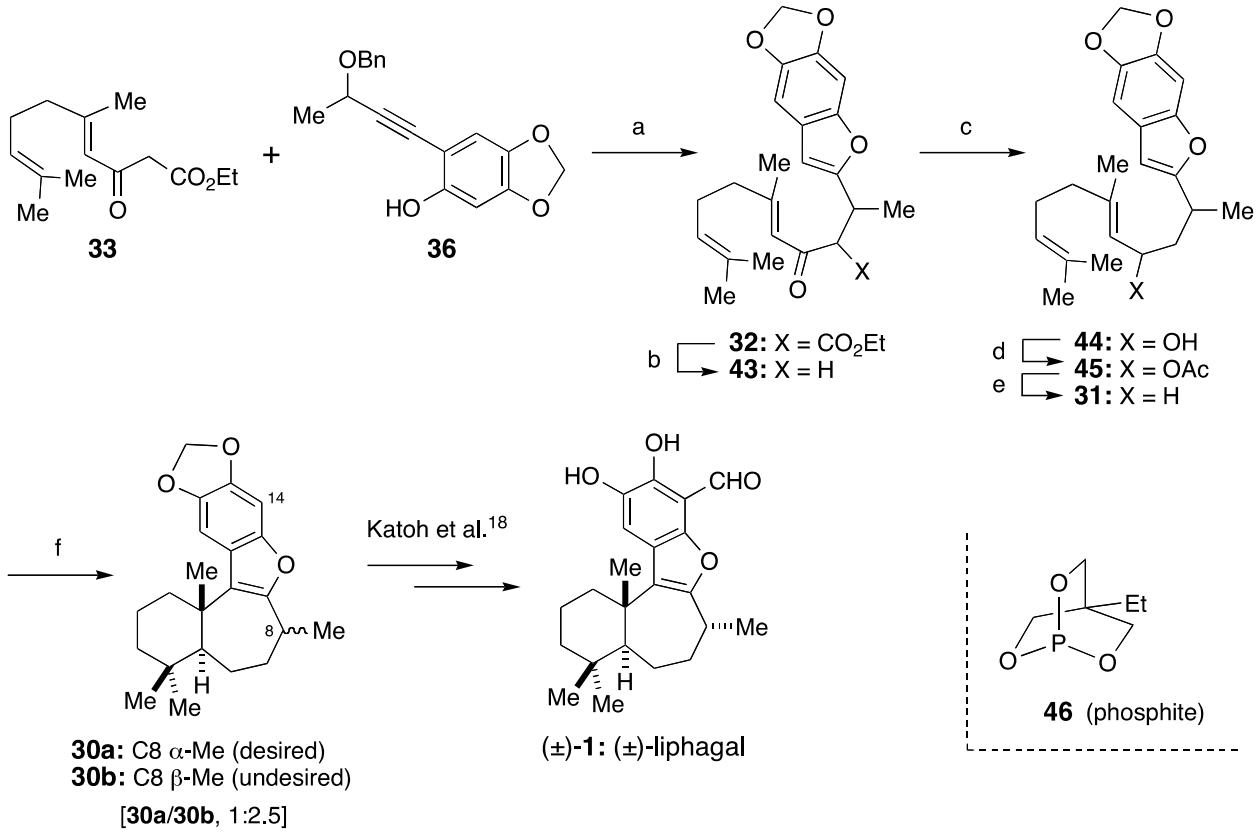
In Scheme 17, intermediate **36**, the precursor of the carbene species **34** (see Scheme 15), was synthesized starting from sesamol (**37**). Silyl protection of **37** (96% yield) followed by trifluoroacetic acid (TFA)-catalyzed iodination[23] of the resulting *O*-TBS-sesamol (**39**) afforded aryl iodide **40** (91% yield). Sonogashira coupling[24] of **40** with alkyne **42** (80% yield) and the subsequent deprotection of the *O*-TBS group of the product **41** furnished intermediate **36** (82% yield).



Scheme 17. Synthesis of intermediate **36**. (a) TBSCl, imidazole, DMAP, DMF, 0 °C to rt, 96%; (b) NCS, NaI, TFA, MeCN, 50 °C, 91%; (c) $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), Et_3N, rt, 10 min; add **42**, rt, 12 h, 80%; (d) 5 M NaOH, MeOH, rt, 82%. NCS = *N*-chlorosuccinimide, TFA = trifluoroacetic acid.

The crucial platinum-catalyzed α,β-unsaturated carbene formation from acetylenic phenol **36** followed by nucleophilic attack with β-ketoester **33** (i.e., **33** + **34** → **32** in Scheme 15) was next examined, as shown in Scheme 18. A mixture of **33** and **36** in 1,4-dioxane was treated with $[(C_2H_4)PtCl_2]_2$ (5 mol%) in the presence of $MgCl_2$ (5 mol%) to generate the expected product **32** in 76% yield as a mixture of two diastereomers (3:2). The deethoxycarbonylation of **32** afforded intermediate **43** in 81% yield. Intermediate **43** was then converted into the cyclization precursor **31** with an overall yield of 60% via a three-step procedure involving Luche reduction of the enone carbonyl group, acetylation of the resultant allyl alcohol **44**, and reductive deacetoxylation of the resulting allyl acetate **45** under mild conditions.[25] Finally, the polyene cyclization of **31** was carried out under Andersen's conditions[6] [$ClSO_3H$, 2-niropropane, –78 °C, 1 h], providing the requisite tetracyclic products **30a** and **30b** in 29% yield as a mixture of C8 epimers (**30a**/**30b**, 1:2.5). The optically active version of **30a** was previously converted into naturally occurring (+)-liphagal (**1**) by our group via a two-step sequence of reactions[18] (vide infra,

see **73** → **88** → **1** in Scheme 33); therefore, the synthesis of **30a** represents the formal total synthesis of (±)-**1**.



Scheme 18. Synthesis of intermediate **30a**: Formal synthesis of (±)-liphagal [(±)-**1**]. (a) $[(C_2H_4)PtCl_2]_2$ (5 mol%), $MgCl_2$ (5 mol%), 1,4-dioxane, 40 °C, 76% (3:2 mixture of diastereomers); (b) 2 M Cs_2CO_3, MeOH, 85 °C, 81%; (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, rt, 92% (1:1 mixture of diastereomers); (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 94% (1:1 mixture of diastereomers); (e) **46** (40 mol%), $[(C_3H_5)PdCl]_2$ (10 mol%), L-Selectride, THF, –78 to 0 °C, 69%; (f) $ClSO_3H$, 2-nitropropane, –78 °C, 1 h, 29% (**30a**/**30b**, 1:2.5).

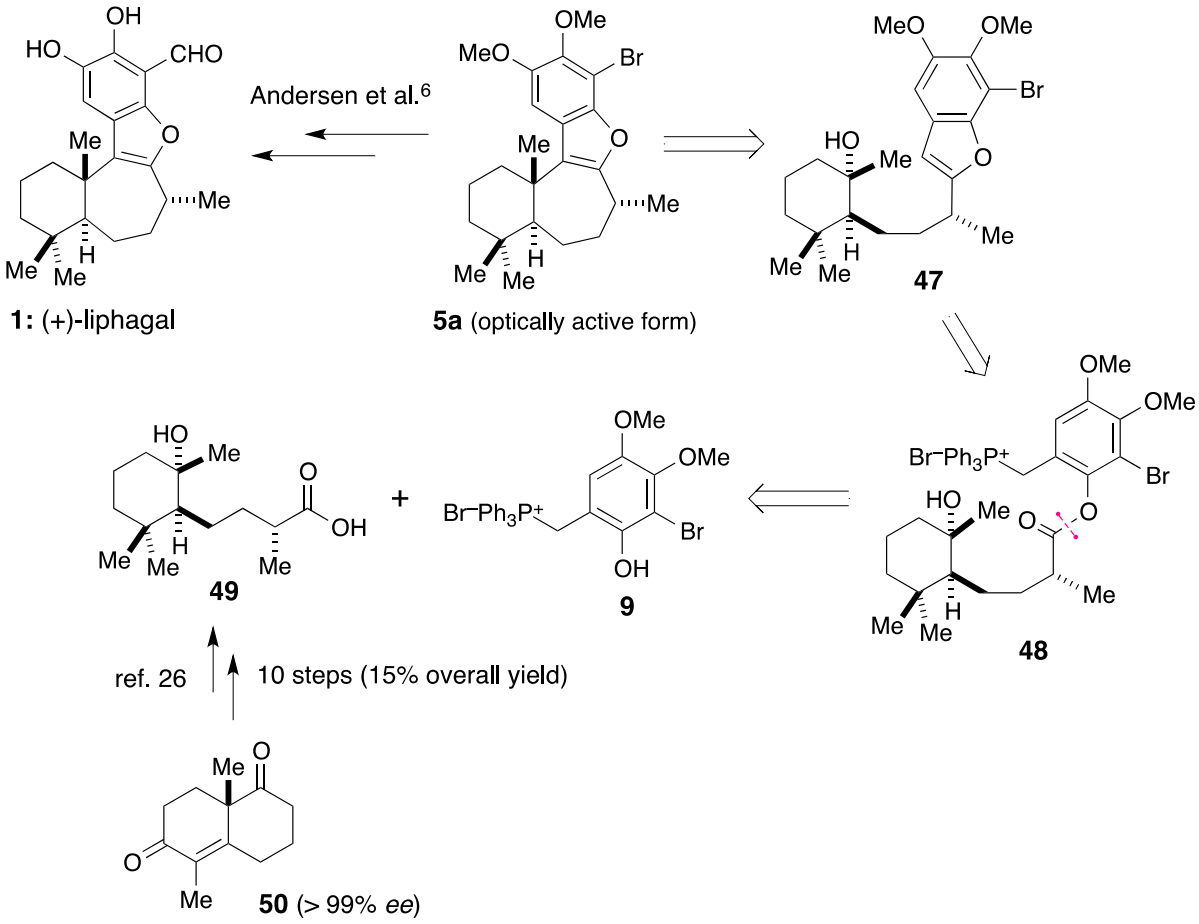
3. TOTAL SYNTHESIS OF (+)-LIPHAGAL

3-1. Andersen's Total Synthesis (2010)

3-1-1. Synthetic Strategy

In 2010, Andersen et al. reported the enantioselective total synthesis of naturally occurring (+)-liphagal (**1**),[15] which established the absolute configuration of natural **1**. Their retrosynthetic plan, which is based on their racemic synthesis (see Scheme 3 in section 2.1.1), is illustrated in Scheme 19. The acid-induced dehydroxylation/cyclization of brominated benzofuran **47** can deliver the requisite tetracyclic intermediate **5a** (**47** → **5a**). The racemic version of **5a** was previously converted into (±)-**1** [see **5a** → **17** → (±)-**1** in Scheme 7]. The cyclization precursor **47** can be formed by the intramolecular Wittig reaction of phosphonium salt **48**. Intermediate **48** can be prepared via the esterification of carboxylic acid **49** with

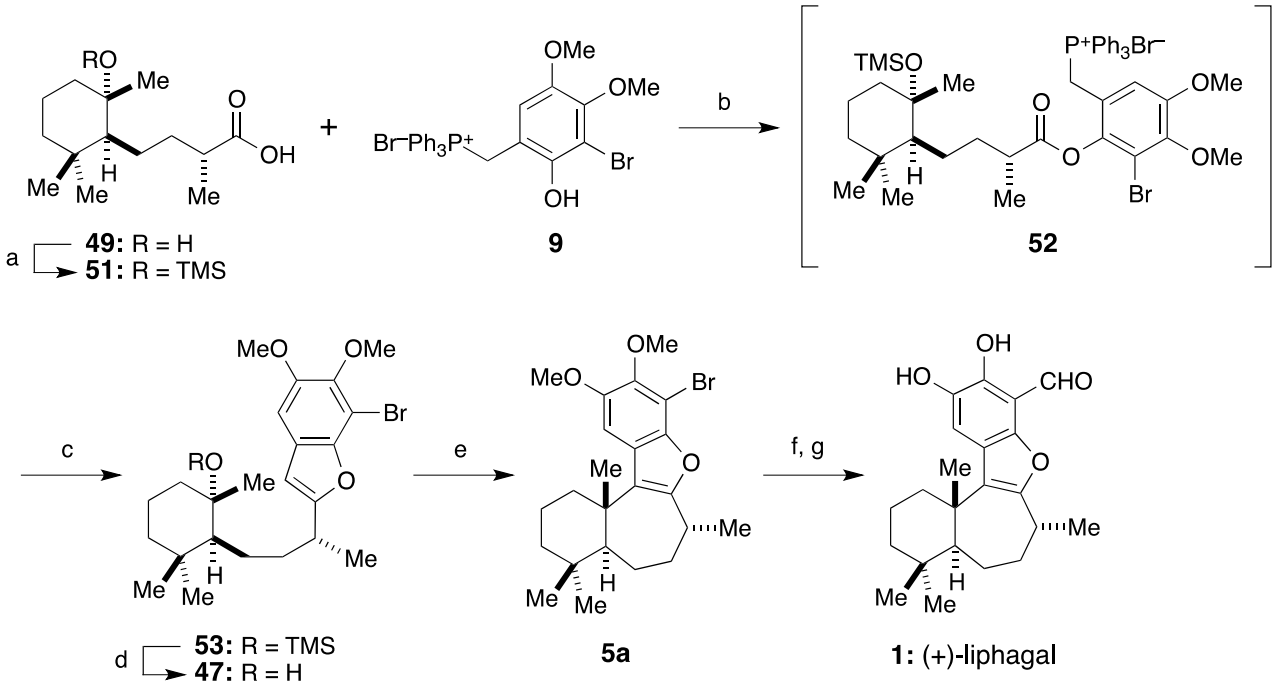
phenol **9**. As a starting material, known compound **49** is accessible from enantiomerically pure (+)-5-methyl-Wieland–Miescher ketone (**50**) via a ten-step sequence (15% overall yield) according to literature procedures.[26]



Scheme 19. Retrosynthetic plan for (+)-liphagal (**1**) according to Andersen et al.[15]

3-1-2. Total Synthesis

The enantioselective total synthesis of natural **1** was achieved as shown in Scheme 20. Silyl protection of the hydroxy group in **49** provided *O*-trimethylsilyl (TMS) carboxylic acid **51**. Esterification of **51** with phenol **9** afforded the corresponding ester **52**, which, without isolation, was then subjected to an intramolecular Wittig reaction to give benzofuran **53**. The subsequent removal of the *O*-TMS group from **53** furnished alcohol **47** (61% overall yield from **49**). Carbocation-initiated cyclization using $SnCl_4$ converted **47** to the requisite tetracyclic intermediate **5a** in 26% yield. Finally, formylation of **5a** followed by demethylation afforded (+)-liphagal (**1**). The optical rotation of the synthetic sample **1** was essentially identical to that of natural **1**, thereby establishing the absolute configuration of the natural product. This total synthesis was achieved with an overall yield of 1.2% in 16 steps from starting material **50**.

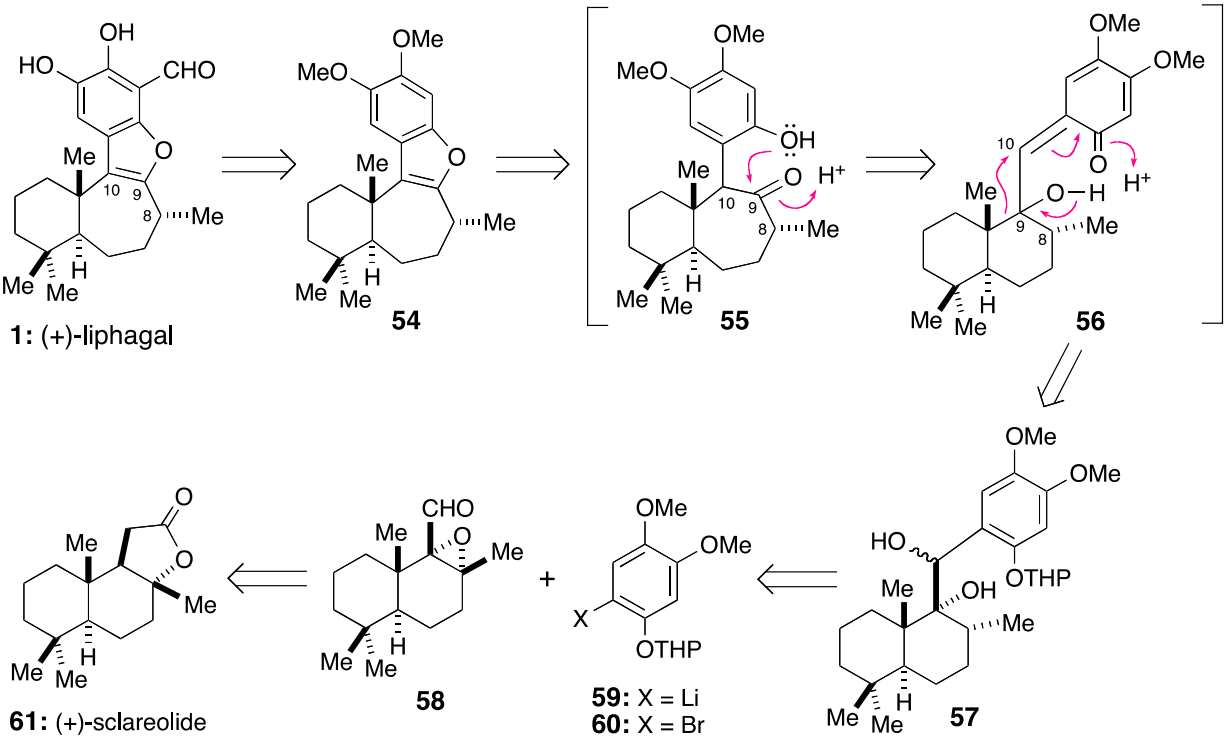


Scheme 20. Synthesis of (+)-liphagal (**1**). (a) TMSCl, Et_3N, CH_2Cl_2, rt; (b) DCC, DMAP, CH_2Cl_2, rt; (c) Et_3N, THF, reflux; (d) TBAF, CH_2Cl_2, rt, 61% (4 steps); (e) $SnCl_4$, 2-nitropropane, –78 °C, 20 min, 26%; (f) *n*-BuLi, THF, –78 °C; add DMF, –78 °C to rt, 76%; (g) BI_3, CH_2Cl_2, –78 °C to rt, 64%. TMS = trimethylsilyl, TBAF = tetrabutylammonium fluoride.

3.2. George's Total Synthesis (2010)

3.2.1. Synthetic Strategy

In 2010, George et al. reported the enantioselective total synthesis of natural **1** slightly earlier than when Andersen's paper was published.[12] Through the total synthesis, George et al. independently determined the absolute configuration of **1**.[12] Their retrosynthetic plan is illustrated in Scheme 21, which relies on the biosynthetic pathway proposed by Andersen et al.[6] (see pathway A in Scheme 1). The key feature of this plan is the acid-induced pinacol rearrangement of vicinal diol **57** to construct the requisite fused 6,7-ring system (i.e., structure **55**) via the ring expansion of *o*-quinone methide intermediate **56** (**57** → **56** → **55**). Tetracyclic intermediate **54** can be produced by the acid-induced benzofuran formation of **55**. Formylation of **54** followed by demethylation could deliver the target liphagal (**1**). The key ring expansion substrate **57** can be obtained via a coupling reaction between epoxy decalin aldehyde **58** and aryllithium **59** (accessible from aryl bromide **60**). Intermediate **58** can, in turn, be derived from commercially available (+)-sclareolide (**61**, > 99% *ee*), an inexpensive chiral pool starting material. Notably, this strategy, which provides the fused 6,7-ring system from a readily available 6,6-ring system, can avoid the poor yield and low stereoselectivity of the direct polyene cyclization reported by Andersen et al. (sections 2-1 and 3-1),[6,15] Mehta et al. (section 2-2),[13] Kumar et al. (section 2-3),[14] and Ferreira et al. (section 2-4).[19]

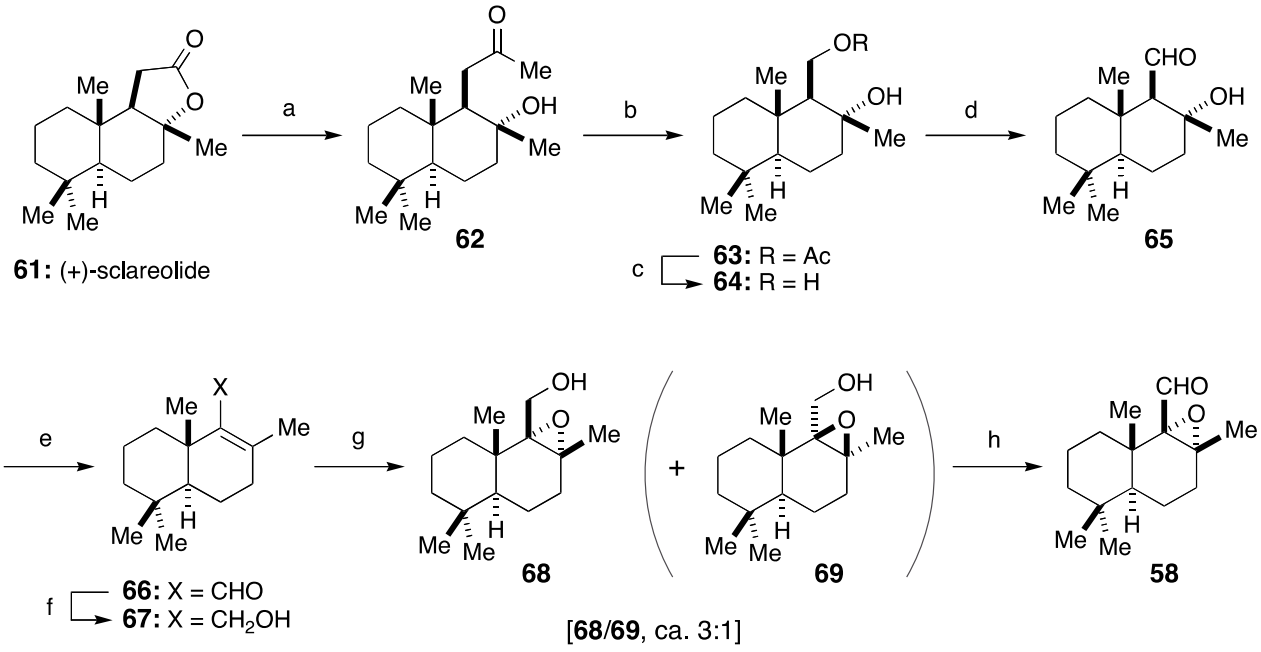


Scheme 21. Retrosynthetic plan for (+)-liphagal (**1**) according to George et al.[12] THP = tetrahydropyranyl.

3-2-2. Total Synthesis

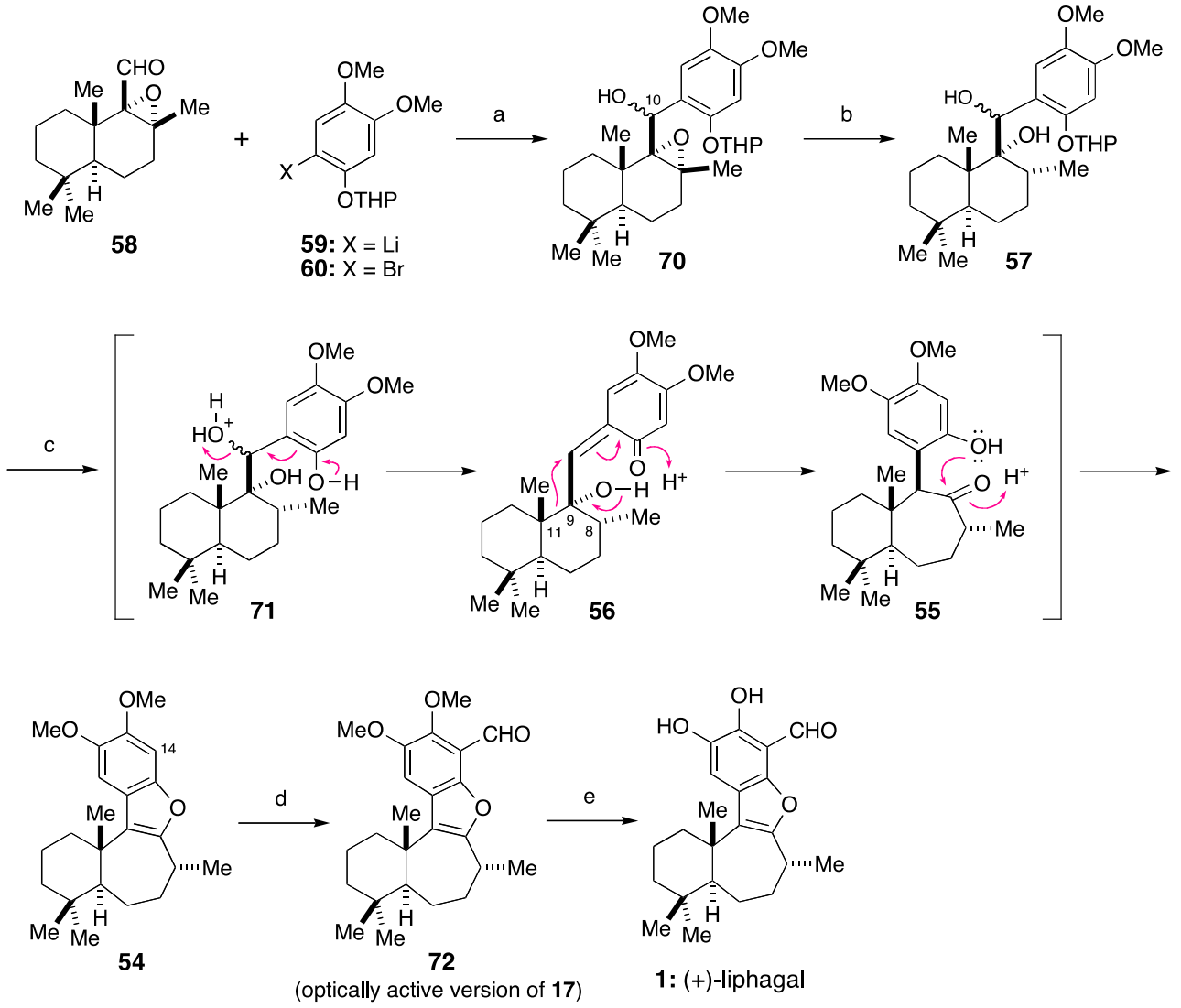
First, the synthesis of intermediate **58**, a coupling partner of aryllithium **59**, was performed starting from **61**, as shown in Scheme 22. The conversion of **61** into known drimanediol **64** was carried out via a three-step sequence (**61** → **62** → **63** → **64**, 80% overall yield) according to the procedure of Kuchkova et al.;[27] the sequence of reactions involves γ-lactone ring opening, Baeyer–Villiger oxidation, and alkaline hydrolysis. Swern oxidation of **64** gave β-hydroxyaldehyde **65** in 85% yield, which was then subjected to dehydration by $BF_3 \cdot Et_2O$ in CH_2Cl_2 to furnish α,β-unsaturated aldehyde **66** in 74% yield. After $NaBH_4$ reduction of **66** (82% yield), the resulting allyl alcohol **67** was epoxidized with *m*-chloroperoxybenzoic acid (*m*CPBA) to give a mixture of α-epoxide **68** (69% yield) and β-epoxide **69** (22% yield), which were separated by silica-gel column chromatography. Oxidation of **68** with Dess–Martin periodinane then provided the requisite epoxy decalin aldehyde **58** in 83% yield.

Completion of the total synthesis of (+)-liphagal (**1**) is outlined in Scheme 23. The crucial coupling reaction was efficiently achieved by treating **58** with aryllithium **59**, generated in situ from **60** via bromine/lithium exchange, at –78 °C to room temperature for 30 min. The expected coupling product **70** was obtained in excellent yield (94%) as a mixture of four diastereomers [due to the C10 hydroxy group and the *O*-tetrahydropyranyl (THP) protecting group]. Reductive epoxide ring opening of **70** with $LiAlH_4$ afforded the requisite vicinal diol **57**. After obtaining **57**, the key pinacol rearrangement (the ring expansion) was investigated. Treatment of **57** with TFA in CH_2Cl_2 at –78 °C followed by gradually



Scheme 22. Synthesis of intermediate **58**. (a) MeLi, THF, –78 °C; (b) Ac_2O, 30% H_2O_2, maleic anhydride, CH_2Cl_2, rt; (c) KOH, MeOH, rt, 80% (3 step); (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 to 0 °C, 85%; (e) $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 74%; (f) $NaBH_4$, EtOH, 0 °C, 82%; (g) *m*CPBA, CH_2Cl_2, 0 °C, 69% for **68**, 22% for **69**; (h) Dess–Martin periodinane, CH_2Cl_2, rt, 83%. DMSO = dimethyl sulfoxide, *m*CPBA = *m*-chloroperoxybenzoic acid.

warming to room temperature produced the expected ring-expanded tetracyclic product **54** in 74% yield from **70**. This cascade reaction presumably proceeds via the initial removal of the THP protecting group to give phenol **71**, which could undergo a facile dehydration to form the reactive *o*-quinone methide species **56**. Rearrangement of **56** via the selective migration of the more electron-rich C9–C11 bond in preference to the C8–C9 bond would then give cycloheptanone **55**, which could undergo benzofuran formation accompanied by dehydration to afford the tetracyclic product **54**. The synthesis was continued by site-selective *ortho*-lithiation of the aromatic moiety in **54** followed by quenching with DMF to install the formyl group at C14 on the aromatic ring, furnishing *O*,*O'*-dimethylliphagal (**72**) in 87% yield. A racemic version of **72** was previously converted into (±)-liphagal [(±)-**1**] by Andersen et al. (see **17** → (±)-**1** in Scheme 7); therefore, **72** was converted to (+) **1** according to Andersen's procedure[6] (BI_3, CH_2Cl_2, –78 °C, 64% yield). This total synthesis was accomplished with an overall yield of 9.2% in 13 steps from starting material **61**.



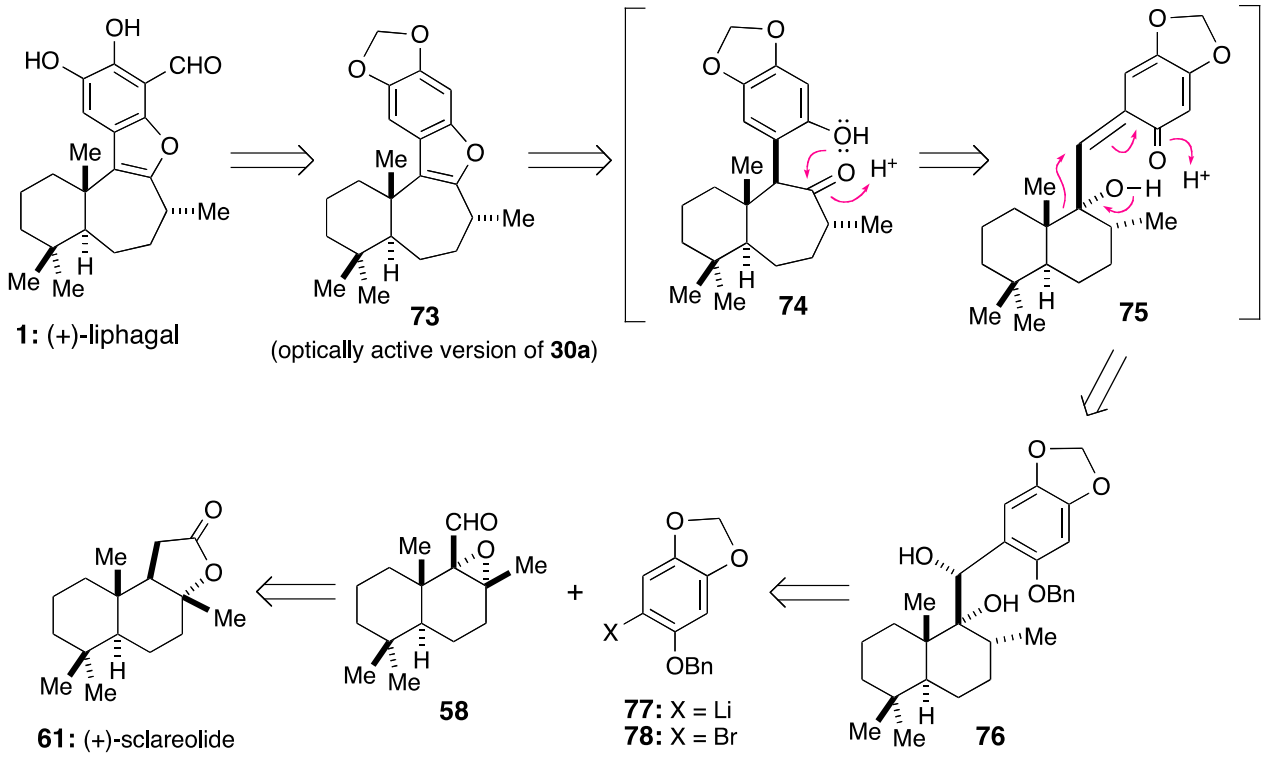
Scheme 23. Synthesis of (+)-liphagal (**1**). (a) **60**, *t*-BuLi, THF, –78 °C, 30 min; add **58**, –78 °C to rt, 94%; (b) $LiAlH_4$, THF, 60 °C; (c) TFA, CH_2Cl_2, –78 °C to rt, 74% (2 steps); (d) *n*-BuLi, TMEDA, THF, 0 °C; add DMF, 0 °C to rt, 87%; (e) BI_3, CH_2Cl_2, –78 to 0 °C, 64%. TMEDA = tetramethylethylenediamine.

3-3. Alvarez-Manzaneda's Total Synthesis (2010)

3-3-1. Synthetic Strategy

In 2010, Alvarez-Manzaneda et al. reported the enantioselective total synthesis of natural (+)-liphagal (**1**) at almost the same time as George et al.[16] (vide supra, see section 3-2). Through their synthetic study, they also independently established the absolute configuration of **1**. The retrosynthetic plan illustrated in Scheme 24 is essentially the same as that presented by George et al. (see Scheme 21 in section 3-2-1), but the protecting groups for the trihydroxy functionalities on the aromatic portion are different (i.e., the *O*-Bn and methylenedioxy groups vs. the *O*-THP and two *O*-Me groups). It is envisaged that the advanced key intermediate **73**, which corresponds to the optically active version of **30a** (see Scheme 18 in section 2-4-2), can be produced by pinacol rearrangement of vicinal diol **76** followed by benzofuran

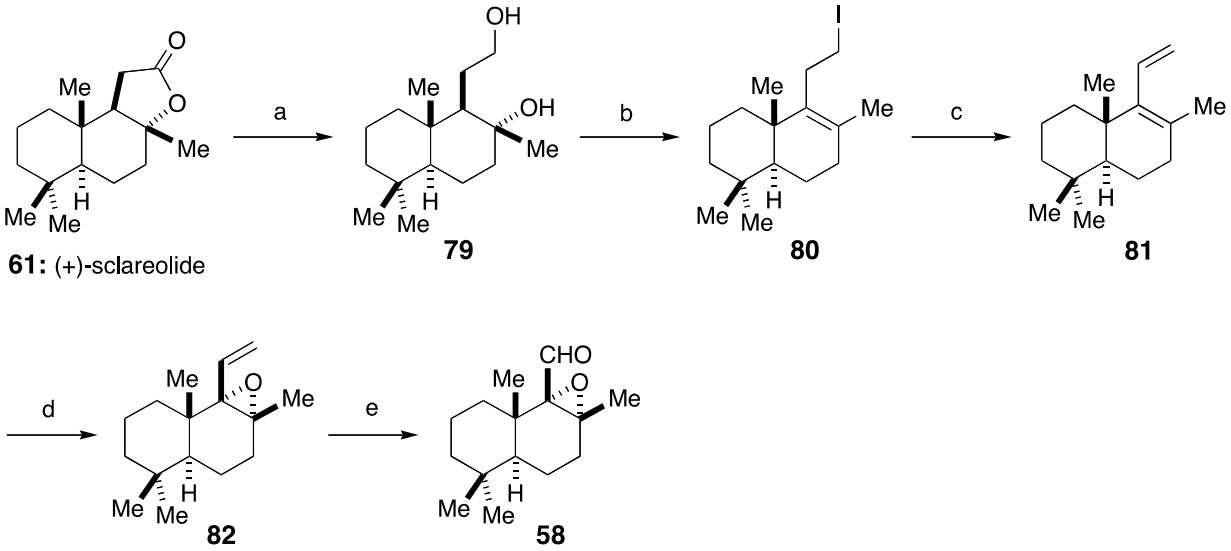
formation of the resultant cycloheptanone **74** in a one-pot operation (**76** → [**75** → **74**] → **73**). The tetracyclic intermediate **73** can be converted to the target liphagal (**1**) via formylation and deprotection. The key rearrangement precursor **76** can be assembled by a coupling reaction between epoxy decalin aldehyde **58** (accessible from **61**) and aryllithium **77** (accessible from aryl bromide **78**).



Scheme 24. Retrosynthetic plan for (+)-liphagal (**1**) according to Alvarez-Manzaneda et al.[16]

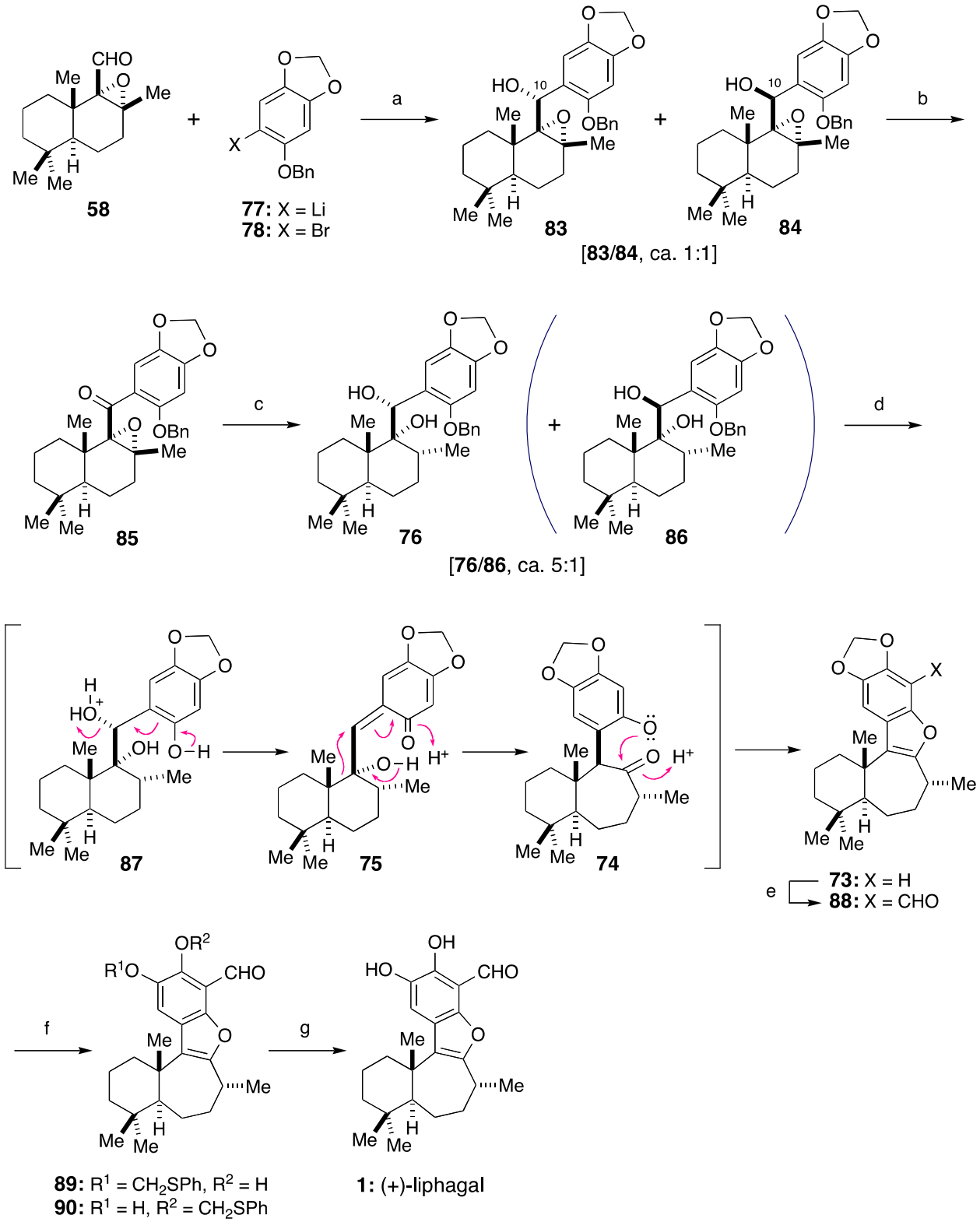
3-3-2. Total Synthesis

First, intermediate **58** was prepared starting from **61**, as shown in Scheme 25. KBH_4 reduction of **61** provided diol **79** (96% yield), which was then converted into diene **81** via a two-step sequence of reactions including iodination (**79** → **80**, 83% yield) and dehydroiodination (**80** → **81**, 81% yield). Chemo- and stereoselective epoxidation of **81** was achieved with *m*CPBA at low temperature (–40 °C) to give epoxy alkene **82** in 82% yield as a single product. Ozonolysis of **82** afforded epoxy aldehyde **58** in 91% yield.



Scheme 25. Synthesis of intermediate **58**. (a) KBH_4, EtOH, reflux, 96%; (b) I_2, PPh_3, CH_2Cl_2, rt, 83%; (c) *t*-BuOK, DMSO/Et_2O, rt, 81%; (d) *m*CPBA, CH_2Cl_2, –40 °C, 82%; (e) O_3, CH_2Cl_2, –78 °C; add PPh_3, rt, 91%.

With intermediate **58** in hand, the total synthesis of **1** was investigated, as shown in Scheme 26. A coupling reaction between epoxy decalin aldehyde **58** and aryllithium **77** (derived from aryl bromide **78**) provided coupling products **83** and **84** in 81% yield as a mixture of C10 epimers (ca. 1:1). Oxidation of this mixture (i.e., **83** and **84**) with pyridinium dichromate (PDC) gave ketone **85** in 91% yield. Subsequent $LiAlH_4$ reduction of **85** afforded a mixture of vicinal diols **76** and **86** (ca. 5:1) in 85% yield. The crucial pinacol rearrangement/benzofuran formation process was efficiently achieved by treatment of **76** with 10% palladium on carbon and Amberlyst® A-15 (acidic ion exchange resin) under a hydrogen atmosphere, resulting in the formation of the requisite tetracyclic product **73** in excellent yield (90%). This cascade event can proceed via three possible intermediates **87**, **75**, and **74** in a manner analogous to that described earlier (see [**71** → **56** → **55**] → **54** in Scheme 23). Finally, the advanced key intermediate **73** was converted into the target liphagal (**1**) via a three-step sequence including formylation of **73** (83% yield), cleavage of the methylenedioxy ring in the resulting aldehyde **88** (93% yield), and removal of the *O*-phenylthiomethyl groups from the resulting sulfides **89** and **90** (91% yield). This total synthesis was achieved with an overall yield of 15.9% in 12 steps from starting material **61**.

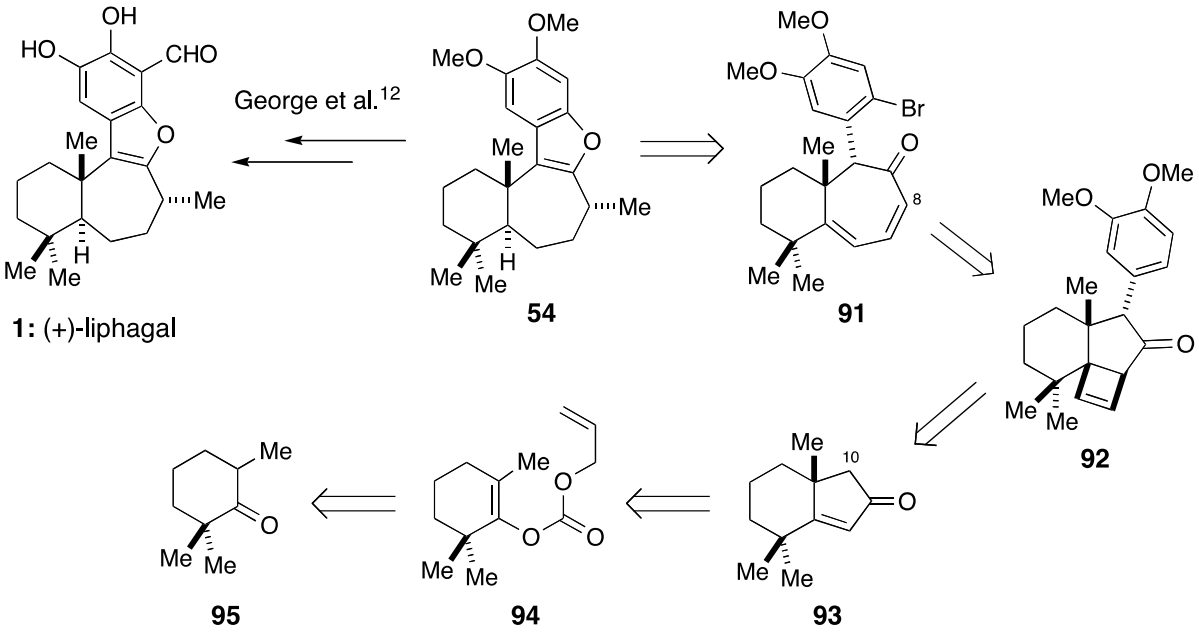


Scheme 26. Synthesis of (+)-liphagal (**1**). (a) **78**, *n*-BuLi, THF, –78 °C, 30 min; add **58**, –78 °C, 1 h, 81% (42% for **83**, 39% for **84**); (b) PDC, CH_2Cl_2, rt, 91%; (c) $LiAlH_4$, THF, rt to reflux, 71% for **76**, 14% for **86** (**76**/**86**, ca. 5:1, separation by recrystallization); (d) H_2 (1 atm), 10% Pd/C, Amberlyst® A-15, MeOH, rt, 90%; (e) *n*-BuLi, THF, –78 °C; add DMF, –78 °C, 83%; (f) PhSH, K_2CO_3, HMPA, 160 °C, 93%; (g) conc. HCl, MeOH, reflux, 91%. PDC = pyridinium dichromate, HMPA = hexamethylphosphoramide.

3-4. Stoltz's Total Synthesis (2011)

3-4-1. Synthetic Strategy

In 2011, Stoltz et al. reported the first catalytic enantioselective total synthesis of natural (+)-liphagal (**1**).[17] Their retrosynthetic plan is illustrated in Scheme 27, which was designed according to a nonbiomimetic approach. Subtarget **54** was previously converted to (+)-liphagal (**1**) by George et al.[12] via formylation and deprotection (see **54** → **72** → **1** in Scheme 23). George's intermediate **54** can be produced from α-bromoaryl dienone **91** by the C8 methylation, benzofuran formation, and olefin reduction. Intermediate **91** can be obtained from intermediate **92** by bromination at the aromatic ring followed by ring expansion of the strained cyclobutene moiety. Intermediate **92** can be formed by [2 + 2] cycloaddition of chiral cyclopentenone **93** followed by stereoselective arylation at the C10 position. Intermediate **93** can be derived from the known achiral enol carbonate **94** via a palladium-catalyzed enantioselective decarboxylative allylation (i.e., asymmetric Tsuji allylation). Intermediate **94** is accessible from commercially available 2,2,6-trimethylcyclohexanone (**95**).

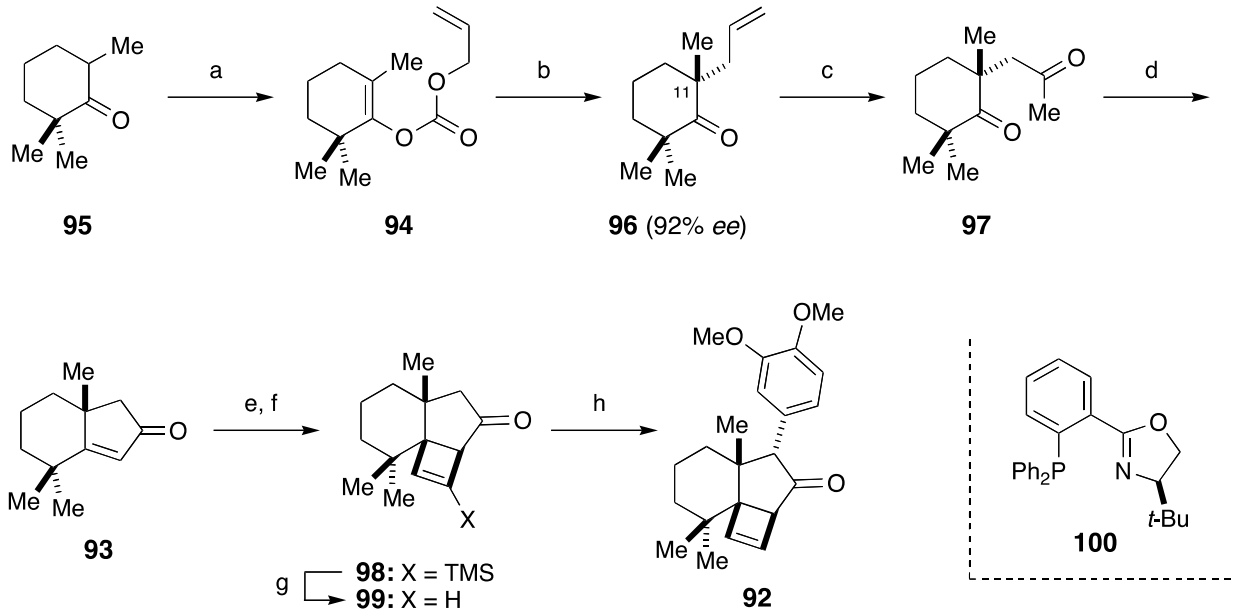


Scheme 27. Retrosynthetic plan for (+)-liphagal (**1**) according to Stoltz et al.[17]

3-4-2. Total Synthesis

The synthesis of intermediate **92** was carried out starting from **95** as shown in Scheme 28. The allyl enol carbonate formation of **95** provided intermediate **94** in 59% yield. The crucial palladium-catalyzed enantioselective decarboxylative allylation of **94** was efficiently achieved using chiral ligand (*R*)-*t*-Bu-PHOX (**100**) (6.1 mol%) and $Pd_2(dba)_3$ (2.5 mol%) in *t*-butyl methyl ether at room temperature for 15 h.[28] The requisite product **96** containing the C11 quaternary carbon center was obtained in 87%

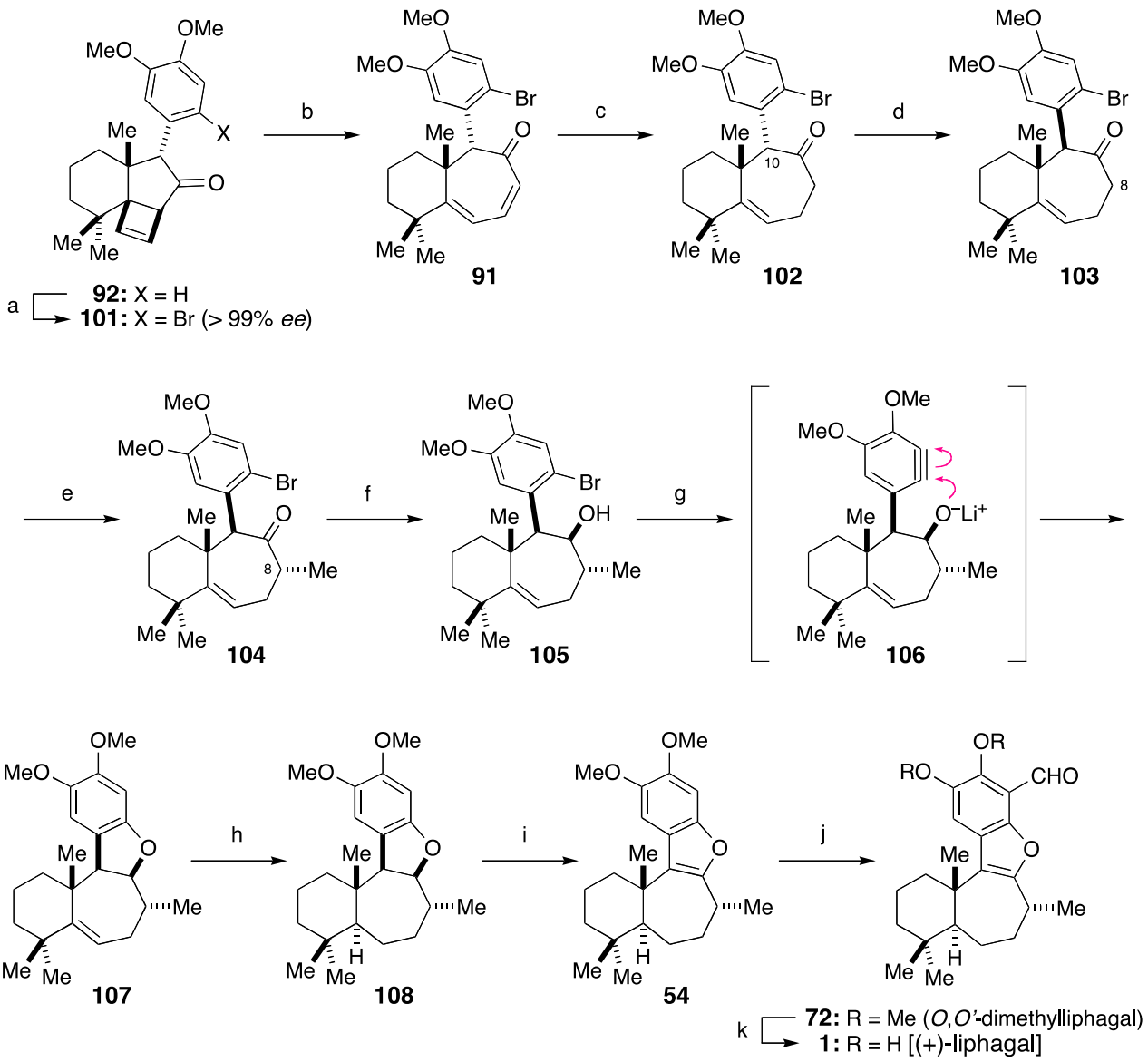
yield in 92% *ee*. Intermediate **96** was then converted to bicyclic intermediate **93** via Wacker oxidation[29] (63% yield) and intramolecular aldol condensation of the resulting diketone **97** (92% yield). Exposure of **93** to TMS-acetylene under ultraviolet (UV) irradiation promoted a [2 + 2] photocycloaddition reaction;[30] the crude reaction mixture was briefly treated with $BF_3 \cdot Et_2O$, resulting in the formation of tricyclic cyclobutene **98** in 73% yield in two steps. Subsequent removal of the TMS group with TBAF provided intermediate **99** in 94% yield. Microwave-assisted palladium-catalyzed α-arylation of **99** with 4-bromoveratrole installed the aromatic moiety in a stereocontrolled manner,[31,32] thereby producing the requisite intermediate **92** in 67% yield as a single diastereomer.



Scheme 28. Synthesis of intermediate **92**. (a) allyl chloroformate, $LiN(TMS)_2$, THF, 0 °C, 59%; (b) $Pd_2(dba)_3$ (2.5 mol%), (*R*)-*t*-Bu-PHOX (**100**) (6.1 mol%), *t*-butyl methyl ether, rt, 87% (92% *ee*); (c) $PdCl_2$ (10 mol%), $Cu(OAc)_2 \cdot H_2O$ (33 mol%), O_2 (1 atm), DMA/H_2O, rt, 63%; (d) KOH, xylene, 110 °C, 92%; (e) TMS-acetylene, UV-B lamp (~313 nm), MeCN, rt; (f) $BF_3 \cdot Et_2O$, CH_2Cl_2, rt, 73% (2 steps); (g) TBAF, THF, 40 °C, 94%; (h) 4-bromoveratrole, *t*-BuONa, $Pd[P(t\text{-}Bu)_3]_2$ (5 mol%), THF, microwave, 120 °C, 67%. dba = *trans*, *trans*-dibenzylideneacetone, DMA = *N*,*N*-dimethylacetamide.

Completion of the total synthesis of **1** is outlined in Scheme 29. Chemo- and site-selective aromatic bromination of **92** in the presence of the olefinic double bond provided bromoarene **101** in 65% yield. Recrystallization of the crude product **101** increased the enantiomeric excess to > 99%. The crucial ring expansion of the strained cyclobutene moiety in **101** was successfully achieved by using microwave heating at 250 °C in *o*-dichlorobenzene for 3 h.[33] The desired 6,7-bicyclic core structure **91** was produced in 68% yield. Intermediate **91** was further converted into intermediate **105**, a precursor poised for the key benzofuran formation, via a four-step sequence involving chemoselective reduction of dienone **91** with

Adams' catalyst (PtO_2) under hydrogen (1 atm) (69% yield), epimerization of the C10 aryl substituent in the resulting ketone **102** (78% yield after three cycles of equilibration), stereocontrolled methylation at the C8 position in the β-oriented α-aryl ketone **103** (68% yield), and reduction of the carbonyl group in the resulting cycloheptenone **104** (91% yield). The subsequent benzofuran formation was efficiently achieved by exposure of bromoarene **105** to lithium diisopropylamide in THF at –20 °C, with the reaction proceeding through aryne intermediate **106**;[34] the requisite tetracyclic product **107** was obtained in 83%



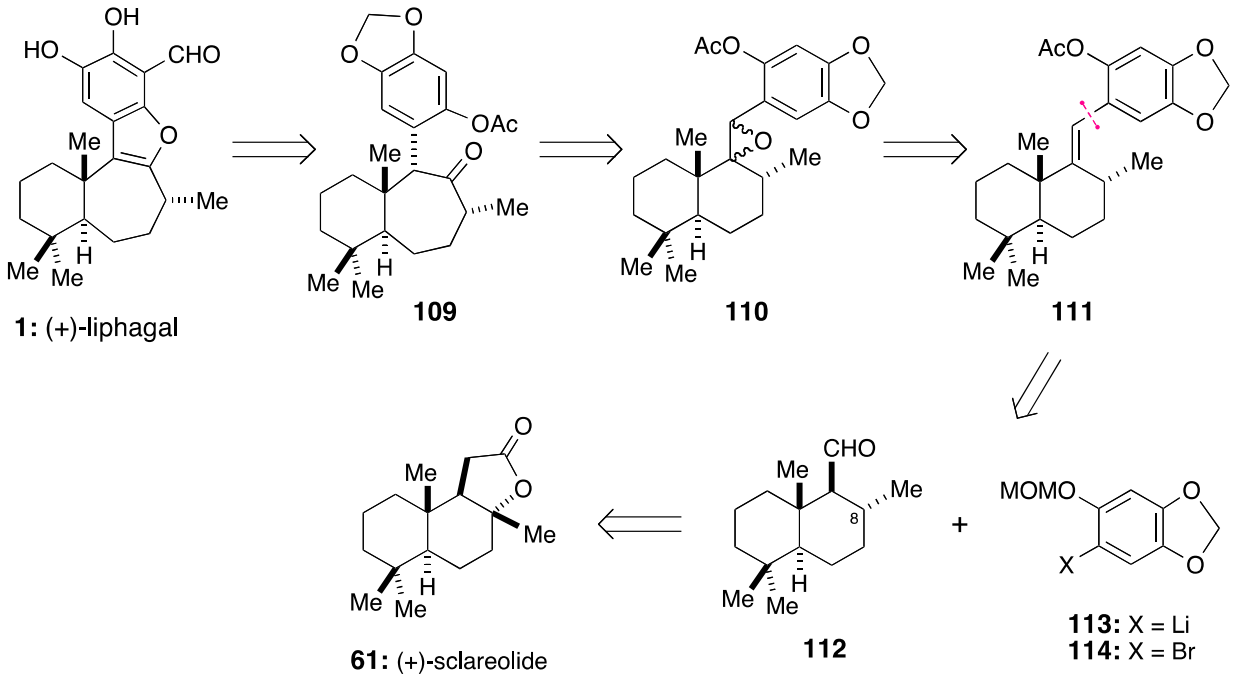
Scheme 29. Synthesis of (+)-liphagal (**1**). (a) Br_2, $CHCl_3$, rt, 65% (>99% *ee* after recrystallization); (b) microwave, *o*-dichlorobenzene, 250 °C, 68%; (c) H_2 (1 atm), PtO_2, EtOAc, rt, 69%; (d) MeONa, MeOH, 65 °C, 78% (after three cycles); (e) LiN*i*-Pr_2, THF, –78 to 0 °C; add MeI, –78 to 0 °C, 68%; (f) DIBAL, toluene, rt, 91%; (g) LiN*i*-Pr_2, THF, –20 °C, 83%; (h) H_2 (1 atm), 10% Pd/C, EtOH, rt, 97%; (i) $NO^+BF_4^-$, MeCN, 0 °C, 70%; (j) *n*-BuLi, TMEDA, THF, 0 °C; add DMF, 0 °C to rt, 70%; (k) BI_3, CH_2Cl_2, –55 to 0 °C, 45%. DIBAL = diisobutylaluminum hydride.

yield. Subsequent stereoselective hydrogenation of the trisubstituted olefinic double bond in **107** exclusively afforded the requisite *trans*-fused 6,7-ring system **108** in excellent yield (97%). Oxidative transformation from dihydrobenzofuran **108** to the corresponding benzofuran **54** was effectively carried out using $NO^+BF_4^-$ as an oxidizing agent in MeCN at 0 °C;[35] the requisite **54** was obtained in 70% yield. Intermediate **54** was previously converted to natural **1** by George et al.[12] (see Scheme 23 in section 3-2-2); therefore, the final two steps were conducted according to the George procedure. Site-selective lithiation of the aromatic ring in **54** followed by trapping with DMF installed the formyl group to deliver *O*,*O'*-dimethylliphagal (**72**) in 70% yield. Finally, demethylation of **72** using BI_3 furnished natural (+)-liphagal (**1**) in 45% yield. The present total synthesis was accomplished with an overall yield of 0.36% in 19 steps from starting material **95**.

3-5. Our Total Synthesis (2014)

3-5-1. Synthetic Strategy

In 2014, we reported the enantioselective total synthesis of natural **1**.[18] Our retrosynthetic plan is outlined in Scheme 30. The key element of this plan is the use of highly and appropriately functionalized intermediate **110**, which corresponds to biogenetic intermediate **IIb** (see pathway A in Scheme 1). This epoxide type of intermediate **IIb** represented by **110** has not been previously used in the total synthesis of **1**; thus, our approach is much closer to the proposed biosynthetic pathway. In addition, as mentioned in

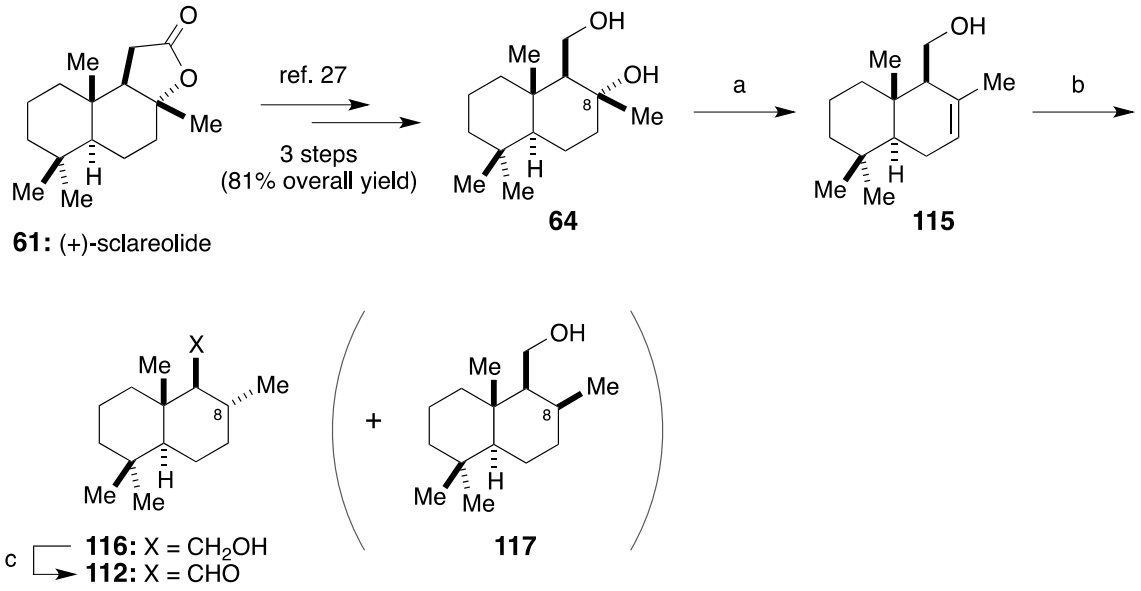


Scheme 30. Retrosynthetic plan for (+)-liphagal (**1**) according to Katoh et al.[18] MOM = methoxymethyl.

the Introduction section, intermediate **IIb** is also proposed as a possible biogenetic precursor of the structurally unique spirosesquiterpenoids, corallidictyals A (**3**) and B (**4**) (see Scheme 2); therefore, the use of **110** was of great interest from a biogenetic viewpoint. Biomimetic ring expansion of **110** can produce cycloheptanone **109**, which can then be converted into target molecule **1** by benzofuran formation followed by deprotection. The epoxidation precursor, corresponding to siphonodictyal B (**2b**) in the proposed biosynthesis (see Scheme 1), can be prepared by condensation of decalin aldehyde **112** with trioxyaryllithium **113**, which is accessible from known trioxyaryl bromide **114**. Intermediate **112** can be accessed from (+)-sclareolide (**61**).

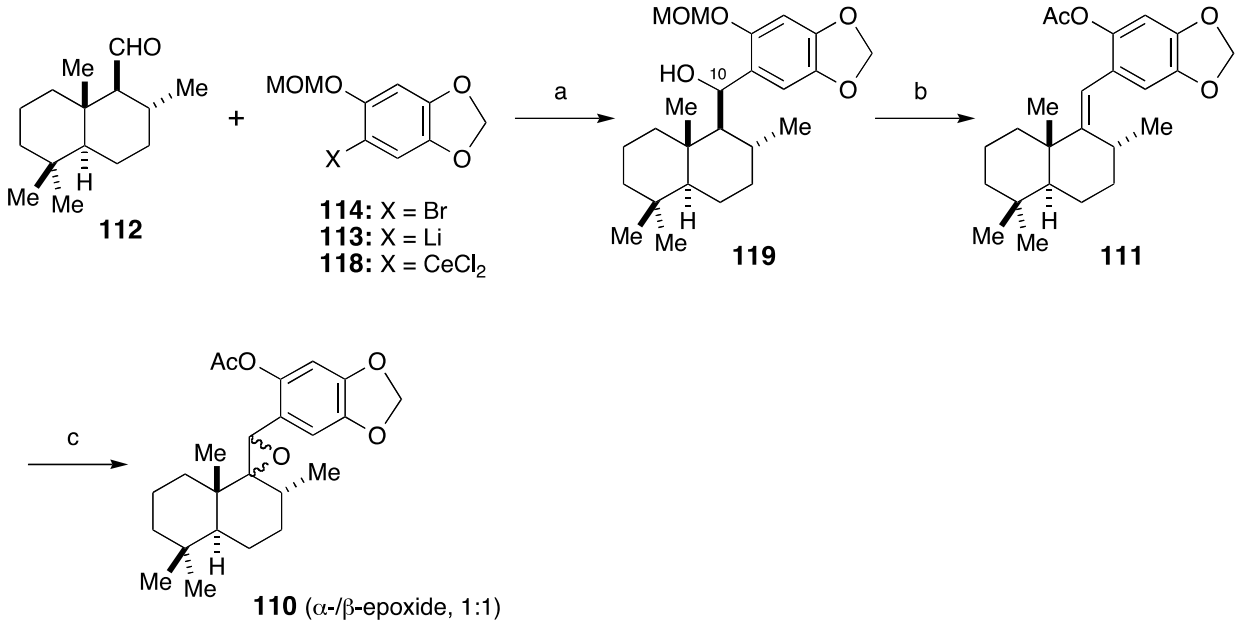
3-5-2. Total Synthesis

As shown in Scheme 31, the synthesis of intermediate **112** commenced with known drimanediol **64**, which was prepared from commercially available **61** in three steps in 81% overall yield according to a previously reported method.[27] Regioselective dehydration of the C8 tertiary hydroxy group in **64** furnished *endo*-olefin **115** as a single regioisomer in 79% yield. Intermediate **115** was then subjected to hydroxy-group-directed hydrogenation using Crabtree's catalyst {[Ir(COD)(PCy$_3$(py))$^+$[PF$_6$]$^-$]} (1.0 mol%),[36] which resulted in the stereoselective formation of desired **116** (89% yield) along with a small amount of C8 epimer **117** (9% yield). These stereoisomers could be separated by silica-gel column chromatography. Swern oxidation of **116** afforded decalin aldehyde **112** in 97% yield.



Scheme 31. Synthesis of intermediate **112**. (a) *p*-TsOH·H$_2$O, CH$_2$Cl$_2$, rt, 79%; (b) H$_2$ (1 atm), Crabtree's catalyst {[Ir(COD)(PCy$_3$(py))$^+$[PF$_6$]$^-$]} (1.0 mol%), CH$_2$Cl$_2$, 0 °C, 89% for **116**, 9% for **117**; (c) (COCl)$_2$, DMSO, *i*-Pr$_2$NEt, CH$_2$Cl$_2$, –78 to 0 °C, 97%. COD = 1,5-cyclooctadiene, Cy = cyclohexyl, py = pyridine.

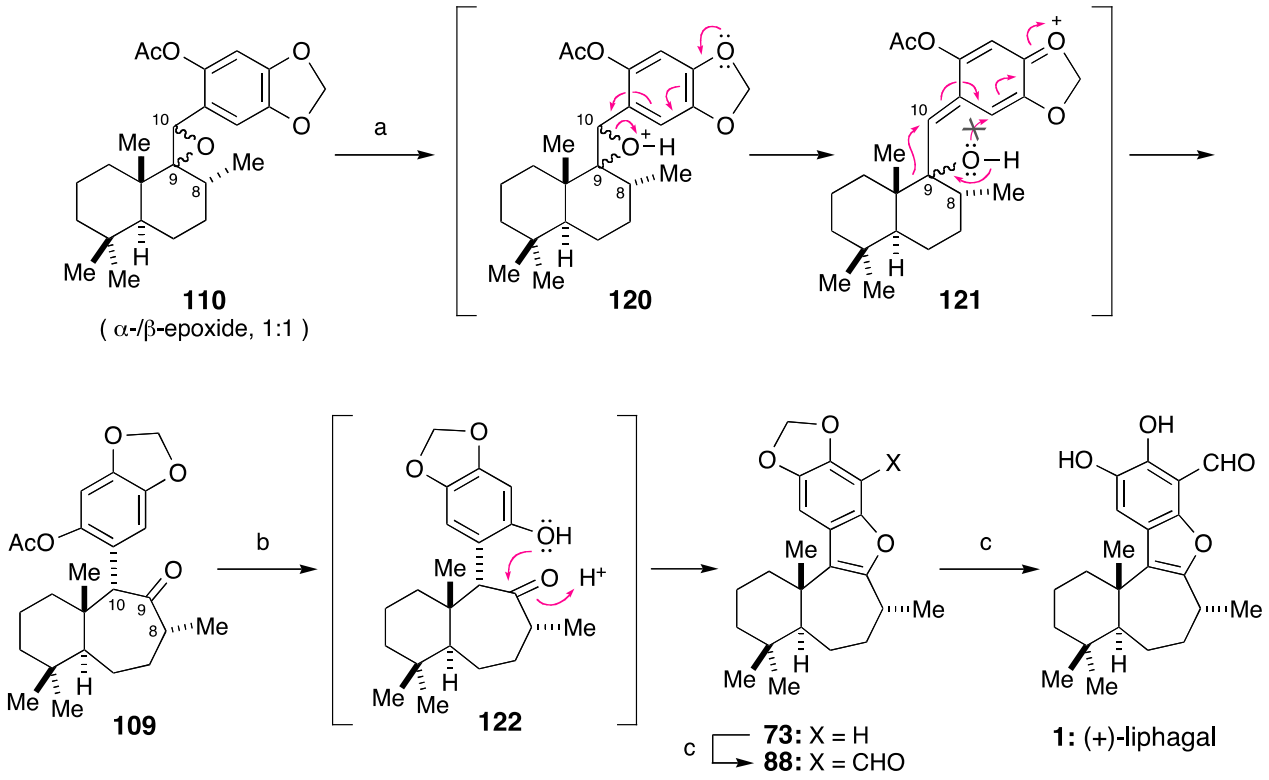
After obtaining intermediate **112**, the synthesis of intermediate **110** (the precursor for the biomimetic key step) was carried out as shown in Scheme 32. A coupling reaction between **112** and the aromatic portion of **114** to assemble the requisite carbon skeleton was efficiently achieved by the use of organocerium reagent **118**[37] (prepared from aryl bromide **114** via aryllithium **113**), resulting in the formation of the desired product **119** in 85% yield as a single stereoisomer with respect to the C10 position. In this coupling reaction, the use of organolithium reagent **113** resulted in a lower yield of **119** (35–40%). Subsequent conversion of **119** into olefin **111** was carried out in quantitative yield by $MgBr_2$-catalyzed acetylation[38] of the sterically hindered hydroxy group followed by elimination of the resulting acetate in a one-pot operation. In this process, the *O*-methoxymethyl (MOM) protecting group in **119** was replaced with an acetyl group. Epoxidation of **111** with *m*CPBA furnished **110** in 89% yield as an inseparable mixture of α- and β-epoxides (1:1 as assessed by ^{1}H NMR spectroscopic analysis).



Scheme 32. Synthesis of intermediate **110**. (a) **113**, *n*-BuLi, THF, –78 °C, 30 min; $CeCl_3$, –78 °C, 1 h; add **112**, –78 °C, 1 h, 85%; (b) $MgBr_2$, Ac_2O, CH_2Cl_2, rt to reflux, 99%; (c) *m*CPBA, CH_2Cl_2, 0 °C to rt, 89%.

After synthesis of key intermediate **110**, our efforts were directed toward the synthesis of **1** via the crucial biomimetic transformation, as shown in Scheme 33. The expected ring expansion was efficiently achieved by exposure of **110** (α-/β-epoxide, 1:1) to TFA (5 equiv) in CH_2Cl_2 at 0 °C for 20 min; the desired cycloheptanone **109** was formed in excellent yield (97%) as a single stereoisomer. We believe that this ring expansion sequence proceeds through oxonium ion intermediates such as structures **120** and **121**. Note that, in this process, none of the spirocyclization products represented by structures **3** and **4** (see Scheme 2) were formed from *p*-quinone methide-type intermediate **121** (see the × mark in structure

121). This result suggested that the proposed biosynthesis of **3** and **4** (i.e., Scheme 2) is not likely to be realized. To advance the synthesis, the acetyl group in **109** was removed under standard conditions to form the requisite benzofuran **73** in 85% yield after acidic treatment. In this reaction, the liberated phenolic intermediate **122** should be involved. Formylation of the aromatic ring in **73** afforded the corresponding aldehyde **88** in quantitative yield. Finally, deprotection of the methylenedioxy moiety in **88** was effectively achieved by using Goodman's method[39] ($AlCl_3$, CH_2Cl_2, –40 to –10 °C, 30 min; conc HCl, MeOH, reflux, 1.5 h), providing target **1** in high yield (88%). Our total synthesis was accomplished with an overall yield of 29.7% in 13 steps from starting material **61**.

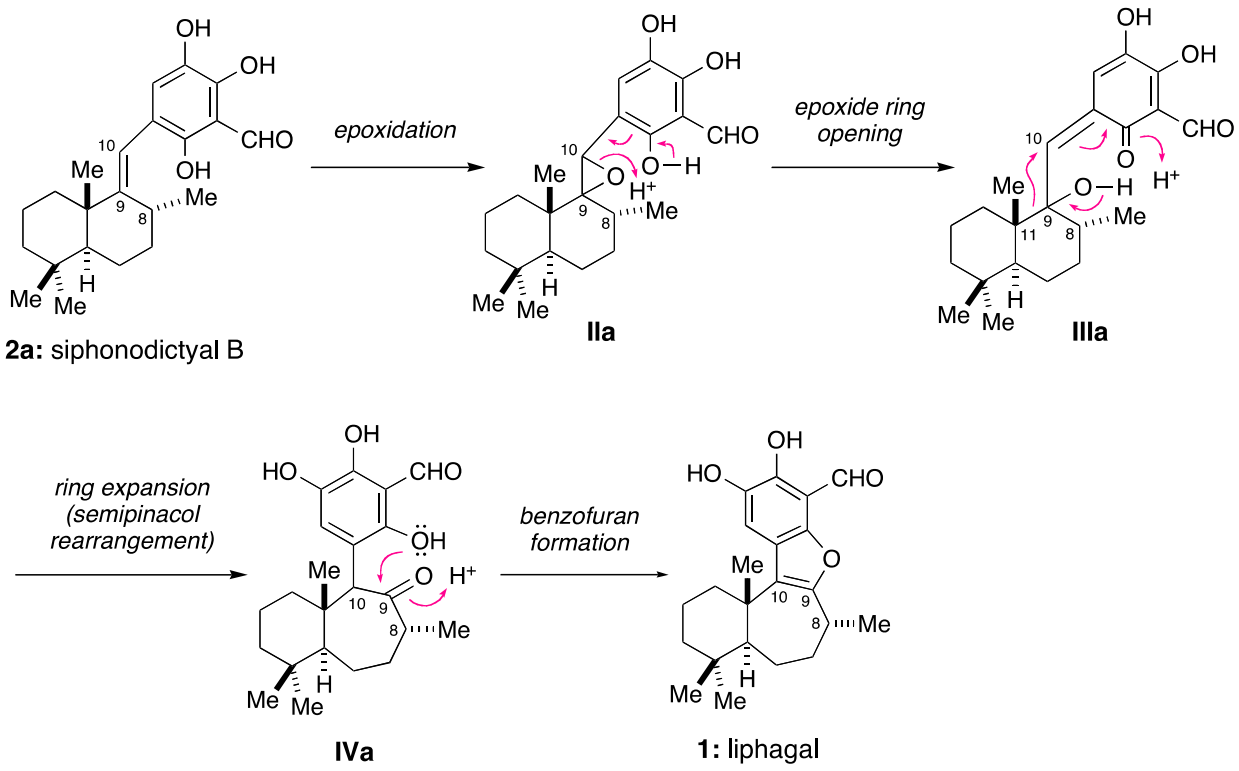


Scheme 33. Synthesis of (+)-liphagal (**1**). (a) TFA, CH_2Cl_2, 0 °C, 20 min, 97%; (b) K_2CO_3, MeOH, rt; 3 M HCl, 0 °C to rt, 85%; (c) *n*-BuLi, THF, –78 °C; add DMF, –78 to –40 °C, 99%; (d) $AlCl_3$, CH_2Cl_2, –40 to –10 °C; conc HCl, MeOH, reflux, 88%.

3-6. George's Total Synthesis (2015)

In 2015, George et al. reported a revision of the structure of siphonodictyal B, a possible biogenetic precursor of liphagal, through the total synthesis of both C8 epimers (i.e., **2a** and **2b** in Figure 1).[11] They concluded that the true structure of siphonodictyal B is **2a**, rather than the previously proposed **2b**. As a result, the plausible biosynthetic pathway to liphagal from siphonodictyal B was necessarily also revised, as shown in Scheme 34.[11] In detail, epoxidation of siphonodictyal B (**2a**) can produce intermediate **IIa**,

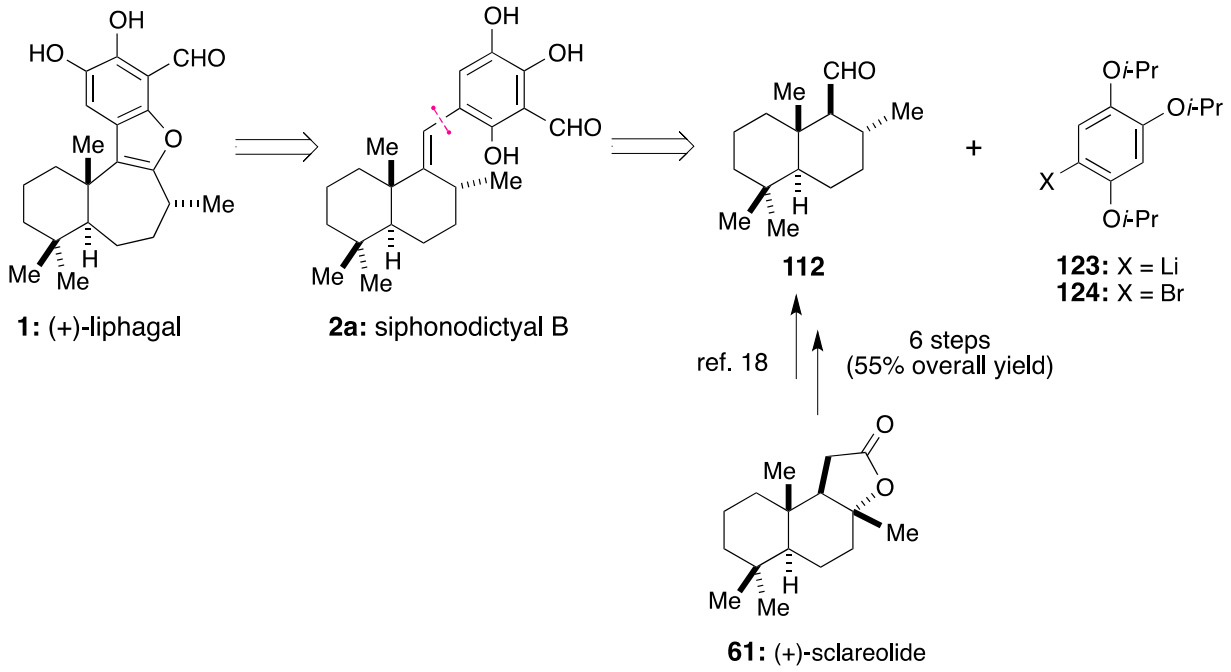
which can undergo epoxide ring opening to deliver *o*-quinone methide **IIIa**. This reactive intermediate can then undergo a ring expansion, with selective migration of the C9–C11 bond, to form 6,7-bicyclic intermediate **IVa**. Finally, benzofuran formation of **IVa** accomplished by dehydration can produce liphagal (**1**). For comparison, in the previously proposed biosynthesis of liphagal from siphonodictyal B (see pathway A in Scheme 1), the C8 epimerization event occurs during the later stage of cycloheptanone intermediate **IVb** leading to liphagal (**1**).



Scheme 34. Biosynthetic pathway to liphagal (**1**) from siphonodictyal B (**2a**) proposed by George et al.[11]

3-6-1. Synthetic Strategy

The retrosynthetic plan, which is based on the revised biosynthetic pathway (i.e., Scheme 34), is illustrated in Scheme 35.[11] The most crucial step is the direct conversion of siphonodictyal B (**2a**) into the target (+)-liphagal (**1**) in a one-pot operation (**2a** → **1**). Siphonodictyal B (**2a**) can be synthesized through the coupling of known decalin aldehyde **112** with aryllithium **123** accessible from aryl bromide **124**. As a starting material, compound **112** was prepared from (+)-sclareolide (**61**) in 6 steps with 55% overall yield by applying our method (see Scheme 31).[18]



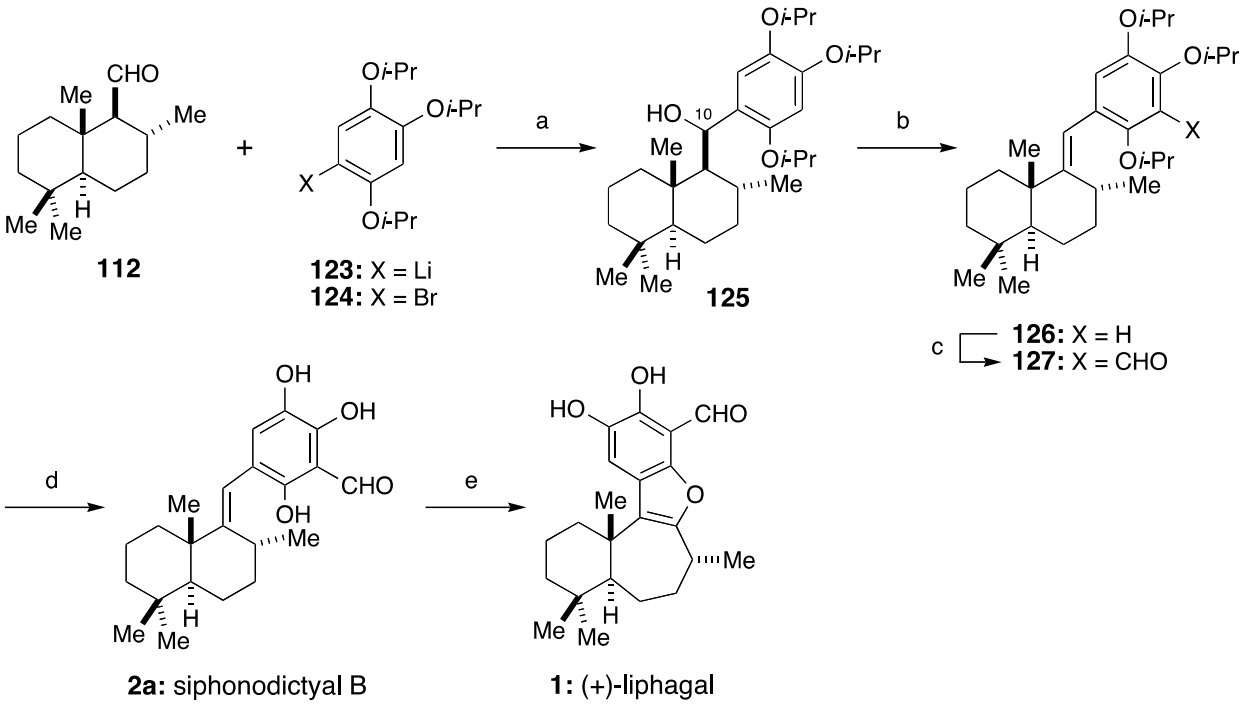
Scheme 35. Retrosynthetic plan for (+)-liphagal (**1**) according to George et al.[11]

3-6-2. Total Synthesis

The synthesis commenced with the coupling reaction between decalin aldehyde **112** and aryllithium **123** derived from aryl bromide **124**, as shown in Scheme 36. The expected coupling product **125** was obtained in 74% yield as a single stereoisomer with respect to the C10 position. The dehydration of **125** by treatment with $POCl_3$ and pyridine afforded *E*-alkene **126** in 54% yield. Intermediate **126** was then converted into siphonodictyal B (**2a**) via a two-step sequence including formylation at the aromatic moiety in **126** (65% yield) and simultaneous deprotection of the three *O*-isopropyl protecting groups in the resulting aldehyde **127** (77% yield). Finally, the key biomimetic conversion of **2a** into liphagal (**1**) was investigated. Exposure of **2a** to *m*CPBA in the presence of $NaHCO_3$ in CCl_4 at 0 °C for 1 h, followed by the treatment with TFA in CCl_4 at 0 °C to room temperature for 2 h resulted in the formation of the target (+)-liphagal (**1**) in 42% yield as the sole isolable product. This study strongly supports the mechanistic proposal for liphagal biosynthesis (see Scheme 34). The present total synthesis was accomplished with an overall yield of 4.6% in 11 steps starting from (+)-sclareolide (**61**).

5. CONCLUSION

In this article, the total syntheses of racemic (±)- and enantiomerically pure natural (+)-liphagal (**1**) have been summarized with a particular focus on the synthetic methodologies employed, which demonstrate the usefulness of biosynthetic speculation in the development of novel and efficient cascade reactions. The reported syntheses can be classified into three categories: i) biomimetic polyene cyclization approach



Scheme 36. Synthesis of (+)-liphagal (**1**). (a) **124**, *t*-BuLi, THF, –78 °C, 1 h; add **112**, –78 °C, 1 h, –78 °C to rt, 74%; (b) $POCl_3$, pyridine, toluene, 80 °C, 54%; (c) *n*-BuLi, TMEDA, THF, 0 °C, 1 h, add DMF, 65%; (d) BCl_3, CH_2Cl_2, 0 °C, 77%; (e) *m*CPBA, $NaHCO_3$, CCl_4, 0 °C, 1 h; add TFA, 0 °C to rt, 2 h, 42%.

(cf. **VII** → **1**, pathway B in Scheme 1) by the Andersen,[6,15] Mehta,[13] Kumar,[14] and Ferreira[19] groups; ii) biomimetic ring expansion (pinacol-type rearrangement) approach (cf. **IIIb** → **IVb**, pathway A in Scheme 1) by the George,[11,12] Alvarez-Manzaneda,[16] and our[18] groups; and iii) nonbiomimetic approach (cf. Scheme 27) by the Stoltz group.[17] Among them, the biomimetic ring expansion approach provides novel methodologies to construct the requisite tetracyclic core structures in a shorter number of steps with higher overall yields. Especially, the George's approach (2015),[11] which involves the direct conversion of siphonodictyal B into liphagal (cf. **2a** → **1** in Scheme 36), appears to be the most elegant methodology for the synthesis of the natural product. Relative to the enantioselective syntheses, the main advantage of our method is the higher overall yield [our synthesis (2014): 29.7% overall yield in 13 steps;[18] Andersen's synthesis (2010): 1.2% overall yield in 16 steps;[15] George's syntheses (2010, 2015): 9.2% overall yield in 13 steps,[12] 4.6% overall yield in 11 steps;[11] Alvarez-Manzaneda's synthesis (2010): 15.9% overall yield in 12 steps;[16] Stoltz's synthesis (2011): 0.36% overall yield in 19 steps[17]]. These syntheses are promising for the preparation of additional analogs of **1** in enantiomerically pure forms with the aim of exploring their structure–activity relationships, which will be useful for the design and development of novel therapeutic agents that target the inhibition of PI3Kα.

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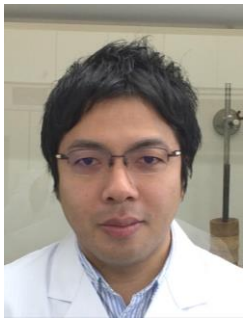

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