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Total Synthesis of (−)-Laulimalide

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Laulimalide (**1**), also known as figianolide B, a 20-membered macrolide isolated from the Indonesian sponge *Hyattella* sp., has shown remarkable antitumor activities.[1] Recently, Laulimalide was also isolated from an Okinawan sponge *Fasciospongia rimosa*.[2] It displayed potent cytotoxicity against the KB cell line with an IC_{50} value of 15 ng/mL.[1] Furthermore, it has shown cytotoxicity against P388, A549, HT29, and MEL28 cell lines in the range of 10–50 ng/mL (IC_{50} values).[2b] The structure of **1** was initially established by NMR studies. Subsequently, its absolute configuration was established by X-ray analysis by Higa and coworkers.[2] The significant clinical potential of laulimalide has stimulated considerable interest in its synthesis and structure-function studies.[3] Herein, we report the first synthesis of (−)-laulimalide **1**.

As outlined in Figure 1, our synthetic strategy of laulimalide is convergent and involves the assembly of C_3−C_{16} segment **2** and C_{17}−C_{28} segment **3** by Julia olefination, followed by an intramolecular Horner-Emmons reaction between the C_{19} phosphonoacetate and C_3 aldehyde. The sensitive epoxide at C_{16}−C_{17} was selectively introduced at the final stage of the synthesis by Sharpless epoxidation.[4] The construction of both dihydropyran rings of laulimalide was achieved by ring-closing olefin metathesis utilizing Grubbs' catalyst as the key step.[5]

The synthesis of C_3−C_{16} segment is accomplished by modifications of the previously published sequence.[3a] As outlined in Scheme 1, diastereomerically pure *δ*-lactone **5** was prepared efficiently by exposure of acryloyl ester **4** to Grubbs' catalyst (10 mol %) in CH_2Cl_2.[3a] DIBAL reduction of **5** at −78 °C in CH_2Cl_2 followed by reaction with ethanol and CSA afforded the ethyl glycoside.[6] Reaction of this ethyl acetal with *tert*-butyldimethylsilyl vinyl ether and Montmorillonite K-10 as the Lewis acid in CH_2Cl_2 at 23 °C followed by $NaBH_4$ reduction of the resulting aldehyde afforded the corresponding dihydropyran as a single isomer (by ^1H and ^{13}C NMR). Protection of the alcohol with TBSCl and imidazole furnished the TBS ether **6**. Removal of the benzyl group by lithium in liquid ammonia provided the alcohol which was subsequently converted to iodide **7**. To install the C_{13} methylene unit and the C_{15} hydroxyl group, alkylation of lactone **8** was carried out by treatment with NaH in DMF at 0 °C for 15 min followed by reaction with iodide **7** at 23 °C for 15 min and then 60 °C for 12 h, which furnished lactone **9** as a mixture

Supporting Information Available:

Experimental procedures and spectral data for compounds **1**–**3**, **6**–**11**, **15**–**20**; ^1H NMR spectra for compounds **1**, **3**, **11**, **15**–**17**, **19**, **20**; and ^{13}C NMR for compounds **1**, **3**, **11**, **17**, and **19** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

(4.2:1 by ^{1}H NMR) of isomers. Reduction of the mixture of lactone **9** by Red-Al provided the diol **10**. Benzoylation of **10** afforded the corresponding dibenzoate which was exposed to Na−Hg in MeOH at −20 °C to provide the olefin **11**.[7] Protection of the C_{15} hydroxyl group as a MOM ether, removal of the PMB group and Swern oxidation of the resulting alcohol furnished the C_3−C_{16} segment, aldehyde **2**.

The synthesis of the C_{17}−C_{28} segment **3** has been achieved by modification of reaction sequences published previously.[3b] Optically active dihydropyran derivative **12** was prepared in multigram quantity by utilizing ring-closing olefin methathesis[5] and Corey-Fuchs' homologation[8] reactions as the key steps. The alkynyl anion of **12** was readily obtained by treatment with *n*-BuLi at −78 °C for 1 h followed by warming to 23 °C for 1 h (Scheme 2). Reaction of the resulting alkynyl anion with optically active aldehyde **13** at −78 °C furnished a diastereomeric mixture (1.8: 1) of alcohols **14** and **15**, which upon oxidation with Dess-Martin periodinane[9] gave the corresponding alkynyl ketone. L-Selectride reduction of this ketone at −78 °C furnished the desired *syn*alkynyl alcohol **15** as a single diastereomer (by ^{1}H NMR and ^{13}C NMR). Red-Al reduction of **15** set the C_{21}−C_{22} *trans*-olefin geometry. Removal of the C_{19} PMB group by exposure to TFA[10] and subsequent reaction of the resulting diol with *p*-methoxybenzylidene acetal and CSA provided acetal **16**. DIBAL reduction of **16** at −78 °C in CH_2Cl_2 afforded the C_{17}−C_{28} segment **3** as a single regio isomer (by ^{1}H and ^{13}C NMR).

Our subsequent synthetic strategy calls for the assembly of fragments **2** and **3** by Julia olefination (Scheme 3). Thus, lithiation of sulfone derivative **3** with 2.1 equiv of *n*-BuLi in THF at −78 °C for 15 min followed by reaction of the resulting dianion with the aldehyde **2** at −78 °C to −40 °C for 2 h furnished the expected R-hydroxy sulfone derivatives. The hydroxy sulfone was transformed into the corresponding C_{16}−C_{17} olefin in a two step sequence involving (1) acylation of the hydroxy sulfone derivatives with Ac_2O, Et_3N and DMAP (cat.) and (2) exposure of the resulting acetates to Na(Hg) in methanol at −20 °C for 2 h followed by warming the reaction to 23 °C for 30 min. The C_{16}−C_{17} *trans* olefin **17** was obtained in 34% yield along with 10% *cis*-olefin, which was readily separated by silica gel chromatography.

Subsequent elaboration to the macrolactone possessing C_2−C_3 *cis*-olefin geometry proved to be a formidable task. We finally relied upon an intramolecular Horner-Emmons reaction of C_{19} phosphonoacetate and C_3 aldehyde using Still's protocol.[11] Thus, acylation of C_{19} hydroxyl group with bis-(2,2,2-trifluoroethyl)-phosphonoacetic acid followed by removal of the TBS group by exposure to aqueous acetic acid in THF at 23 °C furnished the acetate derivative **18** in near quantitative yield.[12] Oxidation of **18** with Dess−Martin periodinane provided the C_3 aldehyde which upon treatment with K_2CO_3 in the presence of 18-C-6 at −20 °C for 30 min and then at 0 °C for 2.5 h furnished a mixture (2:1) of macrolactones **19** and **20** in 84% yield (Scheme 3). Both *cis*and *trans*-lactones were separated by silica gel chromatography. Horner-Emmons reaction of the corresponding (diphenylphosphono)acetate derivative provided slight improvement of the *cis*-selectivity (*cis:trans* =1:1.7, 69% isolated yield).[13] Further attempts to improve the ratio for **20** by changing reaction conditions or C_{20} protecting group have been unsuccessful. The overall

yield of the desired *cis*-macrolactone **20** was however improved to 47% after photoisomerization of the *trans*-macro-lactone **19**.[14] Thus, irradiation of **19** in ether under UV in a Rayonet photochemical reactor for 50 min afforded a mixture of *trans*-lactone **19** (33%) and the *cis*-lactone **20** (33%) which were separated by chromatography. The identity of the *cis*-olefin geometry of **20** was established by its observed coupling constant (J = 11.6 Hz). Macrolactone **20** was converted to synthetic (−)-laulimalide **1** as follows: removal of the MOM group by refluxing with PPTS in *t*-BuOH,[15] exposure of the resulting alcohol to Sharpless epoxidation[4] with (+)-DET and removal of the C_{20} PMB ether by exposure to DDQ. Spectral data (^{1}H and ^{13}C NMR) of synthetic **1** ($[\alpha]^{23}_D$ −196 *c* 0.23, $CHCl_3$) are identical to that from a sample of natural laulimalide (lit.[2a] $[\alpha]^{29}_D$ −200 *c* 1.03, $CHCl_3$) kindly provided by Professor Higa.

Thus, a stereocontrolled synthesis of (−)-laulimalide has been achieved. Considering its clinical potential as an antitumor agent, the present synthesis will enable important structure −function studies as well as synthesis of structural variants of laulimalide. Further improvement in synthesis and biological studies are currently in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment.

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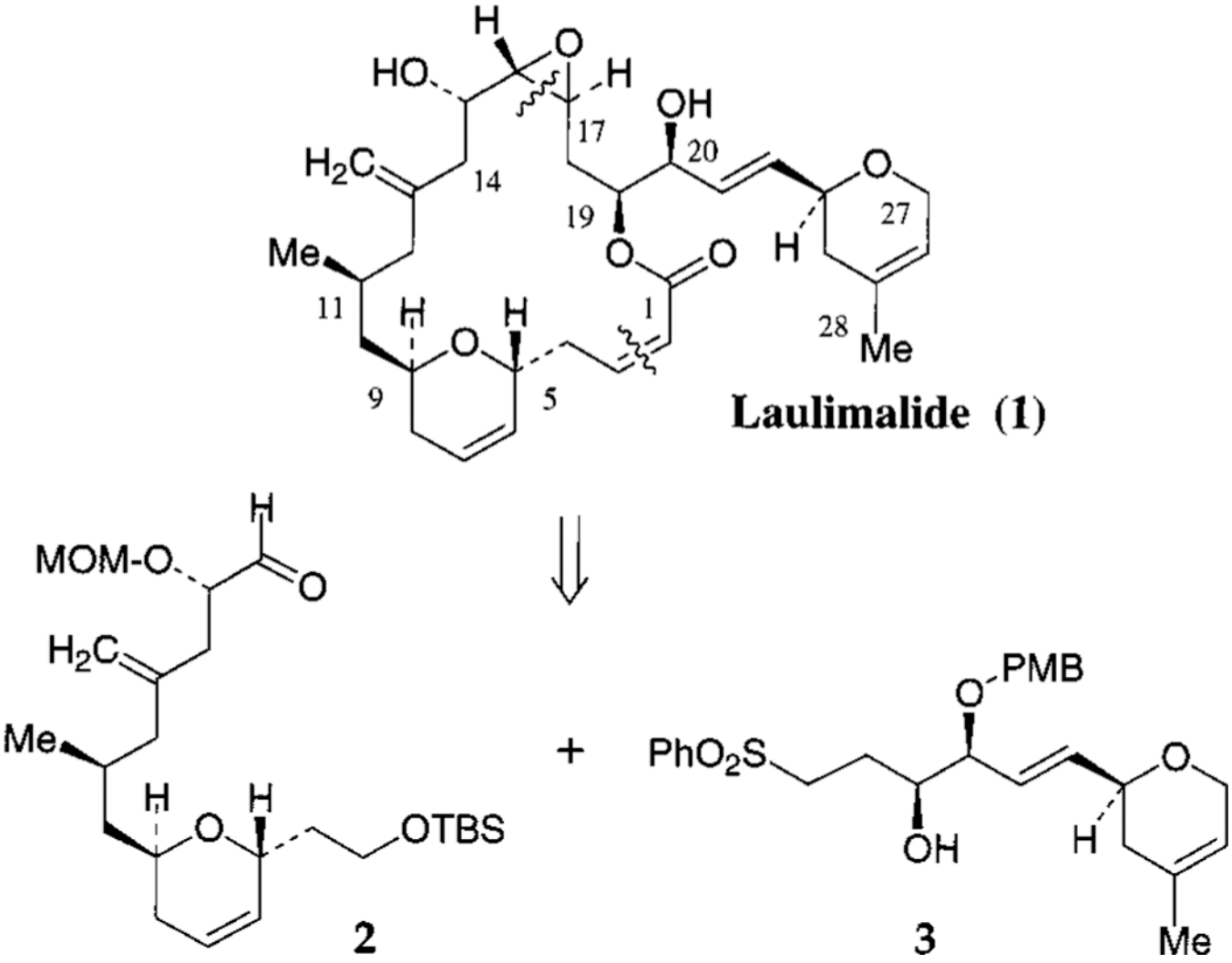
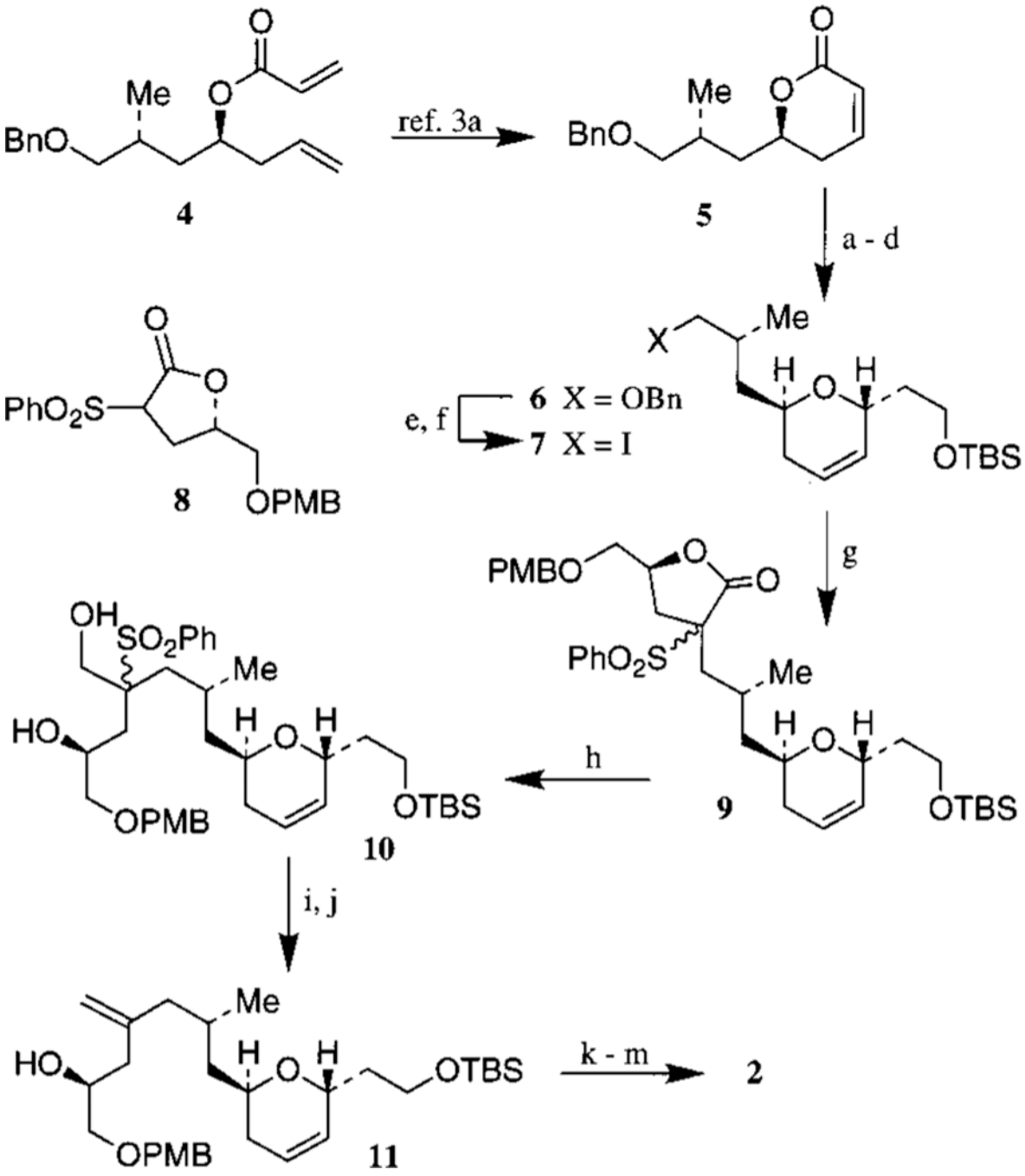
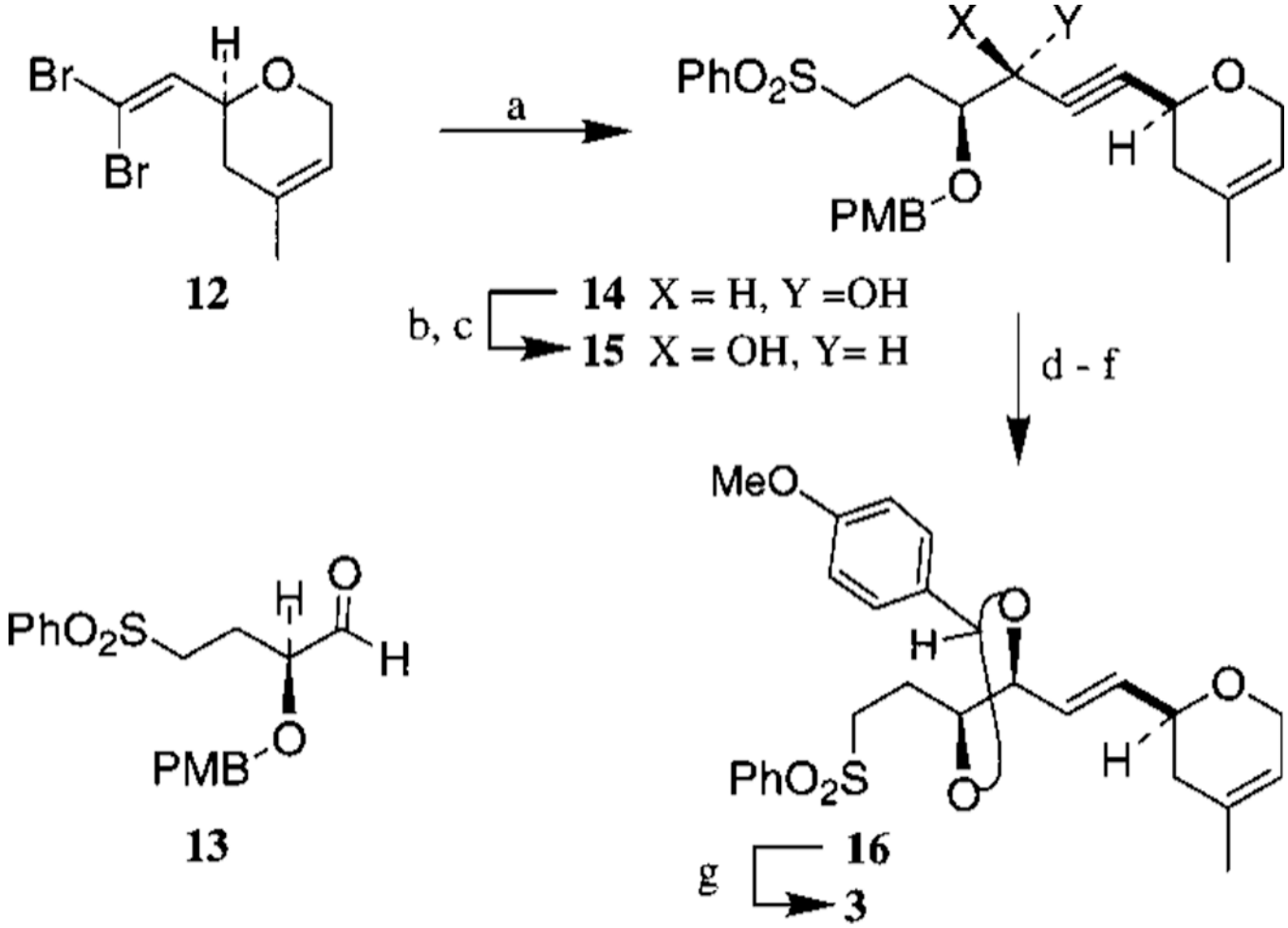


Figure 1.



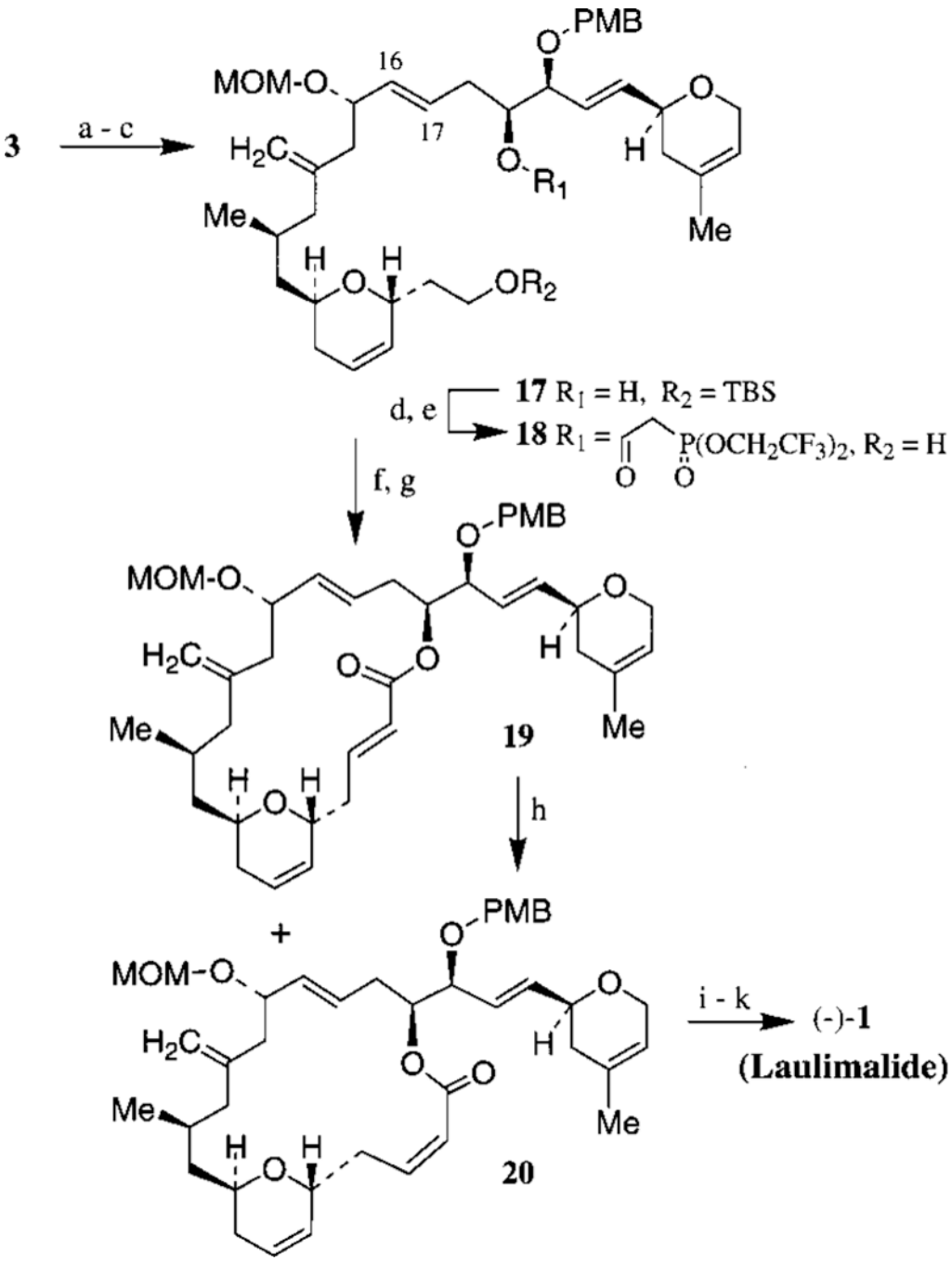
Scheme 1[a]

[a] (a) Dibal-H, −78 °C then CSA, EtOH, 23 °C; (b) K-10, CH_2 = CHOTBS, 23 °C; (c) $NaBH_4$, MeOH, 0 °C (54%); (d) TBSCl, imidazole, DMF, 23 °C (75%); (e) Li, NH_3 (95%); (f) I_2, PPh_3, Imidazole (96%); (g) **8**, NaH, DMF, 0°C then iodide **7**, 60 °C (89%); (h) Red-Al, THF, 0 °C; (i) PhCOCl, Et_3N, DMAP (cat.); (j) Na(Hg), Na_2HPO_4, MeOH, −20° to 23 °C (72%); (k) MOMCl, *i*-Pr_2NEt, 23 °C; (l) DDQ, pH 7 buffer, 23 °C (81%); (m) DMSO, $(COCl)_2$, *i*-Pr_2NEt, −60 °C (85%).



Scheme 2[a]

[a] (a) *n*-BuLi, −78 °C, 1 h and 23 °C, 1 h then **13**, −78 °C (64%); (b) Dess−Martin, CH_2Cl_2, 23 °C (81%); (c) L-Selectride, THF, −78 °C (87%); (d) Red-Al, THF, −20 °C (81%); (e) CF_3CO_2H, CH_2Cl_2, 23 °C; (f) *p*-MeO-Ph-$CH(OMe)_2$, CSA, CH_2Cl_2, 23 °C (71%); (g) Dibal-H, CH_2Cl_2, −78 °C (74%).



Scheme 3[a]

[a] (a) *n*-BuLi, −78°C, 15 min, Then **2**, −78 to −40 °C, 2 h; (b) Ac_2O, Et_3N, DMAP (cat.); (c) Na(Hg), Na_2HPO_4, MeOH, −20 to 23 °C (34%); (d) $(CF_3CH_2O)_2P(O)CH_2CO_2H$, $Cl_3C_6H_2COCl$, *i*-Pr_2NEt, DMAP; (e) AcOH-THF-H_2O (3:1:1), 23 °C (99%); (f) Dess −Martin, CH_2Cl_2, 23 °C (79%); (g) K_2CO_3, 18-C-6, −20 to 0 °C (84%); (h) *hv*, Et_2O, 50 min (66%); (i) PPTS, *t*-BuOH, 84 °C (45%) (j) $Ti(O^iPr)_4$, (+)-DET, *t*-BuOOH, −20 °C; (k) DDQ, pH 7, 23 °C (48%).