

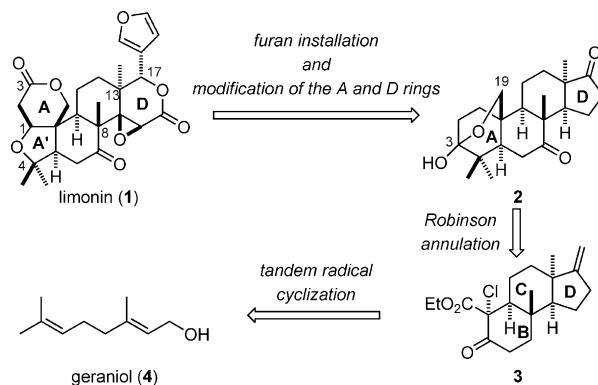


Total Synthesis of Limonin**

Shuji Yamashita,* Akito Naruko, Yuki Nakazawa, Le Zhao, Yujiro Hayashi, and Masahiro Hirama

Abstract: Limonoids are highly oxygenated C13 α -triterpenes and common secondary metabolites. Several hundred congeners have been isolated to date. The first total synthesis of ($\pm$)-limonin, the flagship congener of the limonoids, is now reported and features 1) a tandem radical cyclization generating the BCD ring system with the C13 α configuration that is essential to the limonoids and a Robinson annulation to construct the limonoid androstane framework, 2) a singlet-oxygen cycloaddition and a Baeyer–Villiger oxidation to synthesize the highly oxidized D ring, and 3) a Suárez reaction to construct the unique AA' ring system.

Limonin (**1**), the flagship congener of the limonoids (tetranortriterpenoids), was first isolated in 1841 during studies on the bitter components of the citrus fruit.^[1] However, the structure of **1** remained unknown until 1960, when a historic collaboration between the Arigoni, Barton, Corey, Jeger, and Robertson groups led to the determination of the exact structure of **1** by chemical derivatization and X-ray diffraction methods (Scheme 1).^[2] Since then, several hundred limonoids have been isolated.^[3] The intact limonoid framework is characterized by a 4,4,8-trimethyl-17-furyl-13 α -androstane, but this family encompasses a diverse array of structural architectures as a result of oxidations and skeletal rearrangements. Not surprisingly, the unique architectures and the wide spectrum of biological properties of limonoids have attracted keen interest from the synthesis community,^[4] and for example, azadiradione,^[5] cipadonoid,^[6a] mexicanolides,^[6b] and azadirachtin have been synthesized.^[7] Herein, we describe the first total synthesis of ($\pm$)-limonin (**1**).



Scheme 1. Structure and brief retrosynthetic analysis of limonin (**1**).

Our retrosynthetic analysis of **1** is shown in Scheme 1. We envisaged that installation of a furan moiety onto the limonoid skeleton **2** followed by modification of the A and D rings would give **1**. Tetracyclic compound **2** could be constructed by a Robinson annulation from the BCD ring system **3**, which would be synthesized by a tandem radical cyclization from the derivative of geraniol (**4**) that is based on processes developed by the Snider group. Control of the stereochemistry at the C13 α position is crucial in this synthetic scheme.

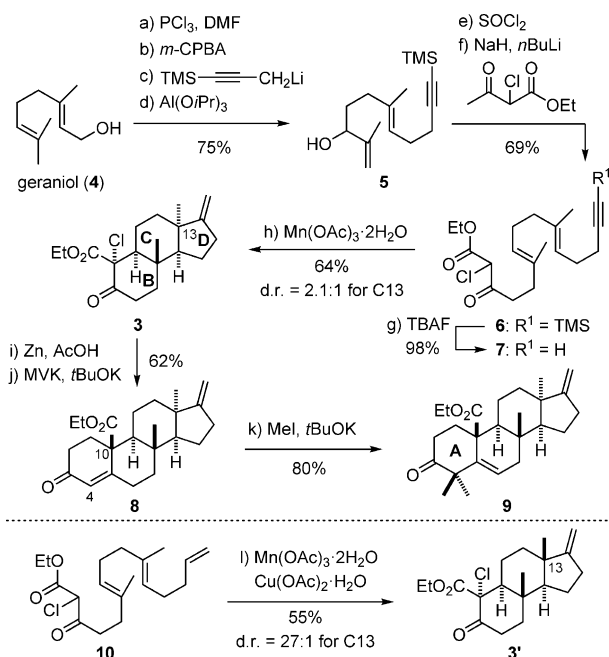
Our synthesis commenced with the preparation of tricyclic compound **3** (Scheme 2). Chlorination of **4** followed by regioselective epoxidation afforded epoxygeranyl chloride, which was successively treated with lithiated 1-(trimethylsilyl)propyne^[8] and aluminum isopropoxide,^[9] giving rise to allylic alcohol **5** in 75% overall yield. Subsequent treatment of **5** with thionyl chloride, the dianion of ethyl 2-chloroacetoacetate,^[10] and then TBAF afforded the requisite alkynyl β -ketoester **7**. Manganese-mediated tandem radical cyclization of **7** according to a method developed by the Snider group^[11,12] furnished the tricyclic BCD ring system **3** with C13 α configuration as the major product along with the C13 β epimer **3'** (d.r. = 2.2:1). The structure of **3** was confirmed by X-ray crystallographic analysis (see the Supporting Information). A similar radical cyclization of the corresponding terminal vinyl analogue **10** afforded **3'** almost exclusively. After reductive removal of chloride from **3**, treatment of the resultant β -ketoester with methyl vinyl ketone (MVK) in the presence of a catalytic amount of potassium *tert*-butoxide furnished the tetracyclic system with excellent diastereoselectivity at the C10 position. Lastly, installation of a dimethyl group at the C4 position of **8** was realized by treating the compound with iodomethane and *t*BuOK to furnish **9** in 80% yield.^[13]

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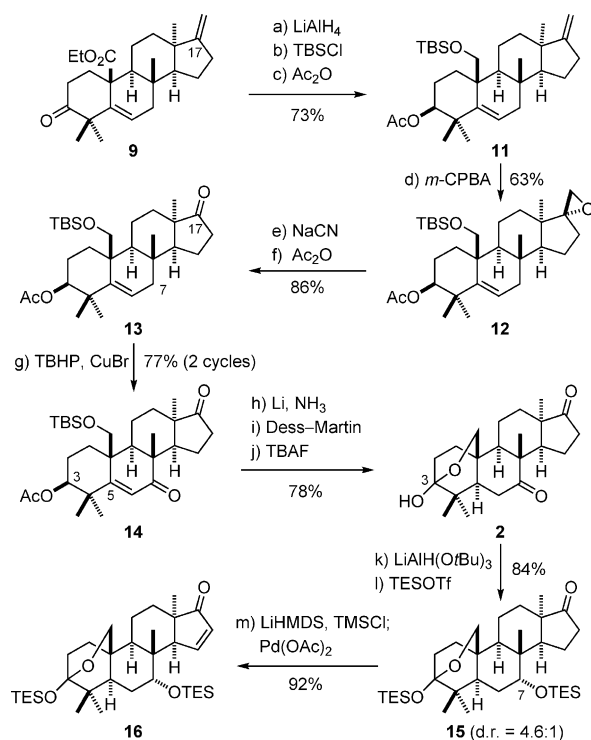
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.201503794>.



Scheme 2. Construction of the limonoid framework. Reagents and conditions: a) PCl_3 , DMF, THF, RT; b) $m\text{-CPBA}$, K_2CO_3 , CH_2Cl_2 , -60 to 0°C ; c) 1-(trimethylsilyl)propyne, $n\text{BuLi}$, THF, -40 to 0°C , 85% (3 steps); d) $\text{Al}(\text{O}i\text{Pr})_3$, toluene, reflux, 88%; e) SOCl_2 , Et_2O , pentane, 0°C ; f) ethyl 2-chloroacetoacetate, NaH , $n\text{BuLi}$, DMPU, THF, 0°C , 69% (2 steps); g) TBAF, THF, RT, 98%; h) $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$, EtOH , RT, 64% (d.r. = 2.1:1); i) Zn , AcOH , RT; j) MVK, $t\text{BuOK}$, $t\text{BuOH}$, 35°C , 62% (2 steps); k) $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$, $\text{Cu}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$, EtOH , RT, 55% (d.r. = 27:1). DMPU = 1,3-dimethylhexahydro-2-pyrimidinone, $m\text{-CPBA}$ = *meta*-chloroperbenzoic acid, MVK = methyl vinyl ketone, TBAF = tetrabutylammonium fluoride.

Having successfully constructed the limonoid C13 α -androstande framework, we turned our attention to cleavage of the *exo* methylene group in **9**. Owing to severe steric hindrance around this moiety, conventional direct oxidative cleavage procedures were unsuccessful.^[14] Therefore, an alternative stepwise method was developed (Scheme 3). Reduction of **9** with LiAlH_4 afforded the corresponding diol, and the two hydroxy groups were protected as a TBS ether and an acetate, respectively, to give compound **11**. Chemo- and stereoselective epoxidation of the *exo* methylene group of **11** was achieved with $m\text{-CPBA}$ to provide epoxide **12**. We observed an interesting C–C bond-cleavage reaction when **12** was heated to 120°C in the presence of NaCN in DMSO, which is possibly due to nitrile addition to the epoxide followed by elimination of acetonitrile.^[15] This process directly provided the desired ketone **13** along with the corresponding deacetylated compound, which was re-acetylated to give **13**.

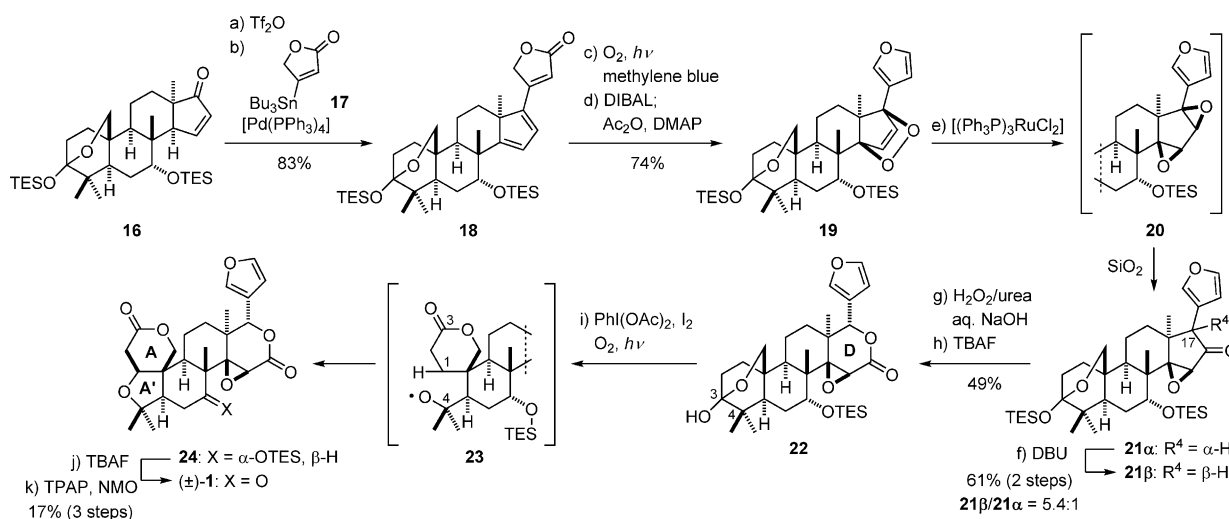
Allylic oxidation of **13** by means of *tert*-butyl hydroperoxide (TBHP) in the presence of a catalytic amount of CuBr ^[16] furnished enone **14** in 77% yield after two cycles. Installation of the C5 stereocenter and removal of the acetyl group were achieved by Birch reduction of **14**. Dess–Martin oxidation^[17] and TBAF treatment afforded hemiacetal **2** in 78% overall yield. Reduction of **2** using $\text{LiAlH}(\text{O}i\text{Bu})_3$



Scheme 3. Development of a method for the cleavage of the *exo* methylene group. Reagents and conditions: a) LiAlH_4 , THF, 0°C to reflux, 97%; b) TBSCl, NaH , THF, 0°C to RT, 75%; c) Ac_2O , pyridine, DMAP, CH_2Cl_2 , RT, quant.; d) $m\text{-CPBA}$, NaHCO_3 , CH_2Cl_2 , -20 to -5°C , 63%; e) NaCN , DMSO, 120°C ; f) Ac_2O , pyridine, DMAP, CH_2Cl_2 , RT, 86% (2 steps); g) TBHP, CuBr , CH_2Cl_2 , RT, 77% (after 2 cycles); h) Li , NH_3 , $t\text{BuOH}$, THF, -60 to -40°C ; i) Dess–Martin periodinane, NaHCO_3 , CH_2Cl_2 , RT, 86% (2 steps); j) TBAF, THF, 0°C to RT, 91%; k) $\text{LiAlH}(\text{O}i\text{Bu})_3$, THF, -60°C ; l) TESOTf, 2,6-lutidine, CH_2Cl_2 , -40 to -20°C , 69% (for **15** over 2 steps; 15% for the C7 epimer over 2 steps); m) LiHMDS , TMSCl, Et_3N , THF, -78 to -60°C ; $\text{Pd}(\text{OAc})_2$, MeCN, RT, 92%. DMAP = 4-dimethylaminopyridine, LiHMDS = lithium hexamethyldisilazide, TBHP = *tert*-butyl hydroperoxide, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

caused a chemoselective reduction of the C7 ketone; TES protection of the hydroxy groups then afforded compound **15** in 69% yield (along with the C7 epimer in 15% yield). Ito–Saegusa oxidation of ketone **15** proceeded smoothly to give enone **16**.^[18]

We next focused on the installation of the furan moiety and the construction of the epoxylactone D ring (Scheme 4). Treatment of **16** with Tf_2O in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP)^[19] afforded the corresponding vinylogous enol triflate; butenolide **17**^[20] was then attached to this intermediate in a Stille coupling^[21] to give **18** in 83% overall yield. The [4+2] cycloaddition of singlet oxygen to diene **18** smoothly provided the endoperoxide in a stereoselective manner.^[22] Sequential treatment of the butenolide with diisobutylaluminum hydride (DIBAL) and acetic anhydride/DMAP led to the formation of furan **19** in 74% yield from **18**. Ruthenium-catalyzed isomerization of the endoperoxide in **19** according to Noyori's method^[23] furnished bis-(epoxide) **20**, which smoothly underwent a 1,2-hydride shift



Scheme 4. Total synthesis of limonin. Reagents and conditions: a) TiF_2O , DTBMP, CH_2Cl_2 , 0°C ; b) **17**, $[\text{Pd}(\text{PPh}_3)_4]$, CuCl , LiCl , DMSO , 40°C , 83% (2 steps); c) O_2 (1 atm), methylene blue, NaHCO_3 , CH_2Cl_2 , $h\nu$ (sunlamp), 0°C , 92%; d) DIBAL, CH_2Cl_2 , -90°C ; Ac_2O , DMAP, -90°C to RT, 80%; e) $[(\text{Ph}_3\text{P})_3\text{RuCl}_2]$, CH_2Cl_2 , RT; f) DBU, toluene, 40°C , 61% (2 steps, d.r. = 5.4:1); g) $\text{H}_2\text{O}_2/\text{urea}$, aq. NaOH (6 M), MeOH , DME, 45°C ; h) TBAF, THF, -60 to -20°C , 49% (2 steps); i) $\text{PhI}(\text{OAc})_2$, I_2 , O_2 (10 atm), cyclohexane, CCl_4 , $h\nu$ (sunlamp), 40°C ; j) TBAF, THF, RT; k) TPAP, NMO, molecular sieves (4 Å), CH_2Cl_2 , RT, 17% (3 steps). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIBAL = diisobutylaluminum hydride, DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, NMO = 4-methylmorpholine *N*-oxide, TPAP = tetrapropylammonium perruthenate.

on silica gel to give epoxyketone **21 α** . This compound was isomerized by heating at 40°C in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to provide a **21 β** /**21 α** = 5.4:1 mixture in 61% overall yield. Baeyer–Villiger oxidation of ketone **21 β** under basic conditions followed by selective deprotection of the TES acetal afforded epoxylactone **22**.

The remaining task was the construction of the AA' ring system of **24**, which was accomplished by a Suárez reaction in a single operation.^[24] Specifically, treatment of **22** with iodobenzene diacetate and iodine under an oxygen atmosphere with sunlamp irradiation likely caused homolytic cleavage of the C3–C4 bond and subsequent C4 oxidation to generate alkoxy radical **23**. This radical underwent C1 hydrogen abstraction and iodination followed by formation of a tetrahydrofuran ring to provide **24**. Removal of the TES group of **24** followed by a Ley oxidation^[25] gave ($\pm$)-**1** (17% over 3 steps). The ^1H and ^{13}C NMR spectra of synthetic ($\pm$)-**1** are identical to those of natural limonin.

In summary, we have achieved the first total synthesis of ($\pm$)-limonin (**1**) in 35 steps from geraniol (**4**). Our synthesis features 1) the efficient construction of the limonoid androstane framework with C13 α configuration by a tandem radical cyclization and subsequent Robinson annulation (**7**→**3**→**9**), 2) a ketone formation from the hindered *exo* methylene group, possibly through epoxidation and nitrile addition followed by MeCN elimination (**11**→**13**), 3) the installation of an epoxylactone moiety by singlet-oxygen cycloaddition, ruthenium-catalyzed bis(epoxide) formation, and Baeyer–Villiger oxidation (**18**→**22**), and 4) a Suárez reaction to construct the unique AA' ring system from the hemiacetal (**22**→**24**). We believe that the synthetic strategy developed here will allow for the synthesis of diverse limonoid architectures.

Keywords: cycloaddition · limonoids · oxidation · radical reactions · total synthesis

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