Total Synthesis Hot Paper

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Total Synthesis of Limonin**

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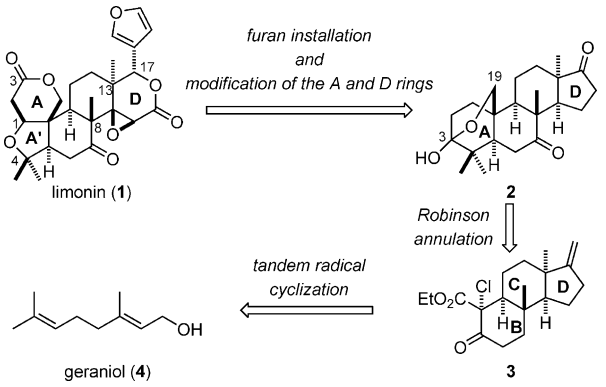
Abstract: *Limonoids are highly oxygenated C13α-triterpenes and common secondary metabolites. Several hundred congeners have been isolated to date. The first total synthesis of (±)-limonin, the flagship congener of the limonoids, is now reported and features 1) a tandem radical cyclization generating the BCD ring system with the C13α 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-13α-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 (±)-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 C13α 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 C13α configuration as the major product along with the C13β 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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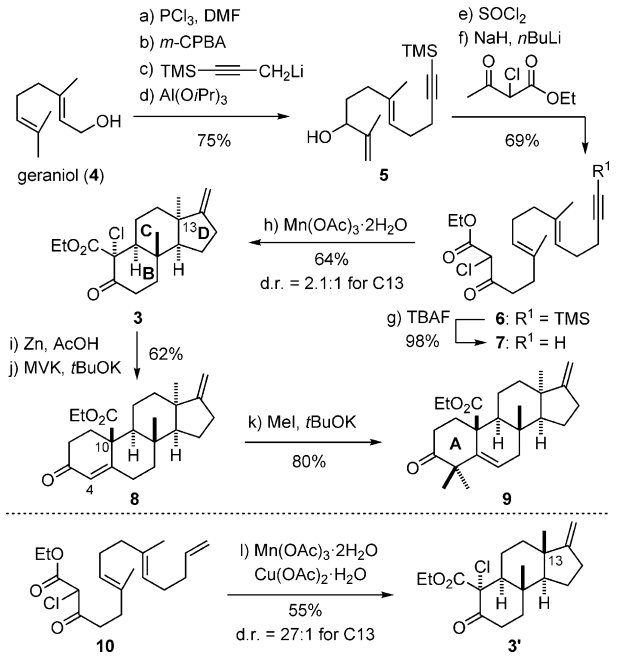
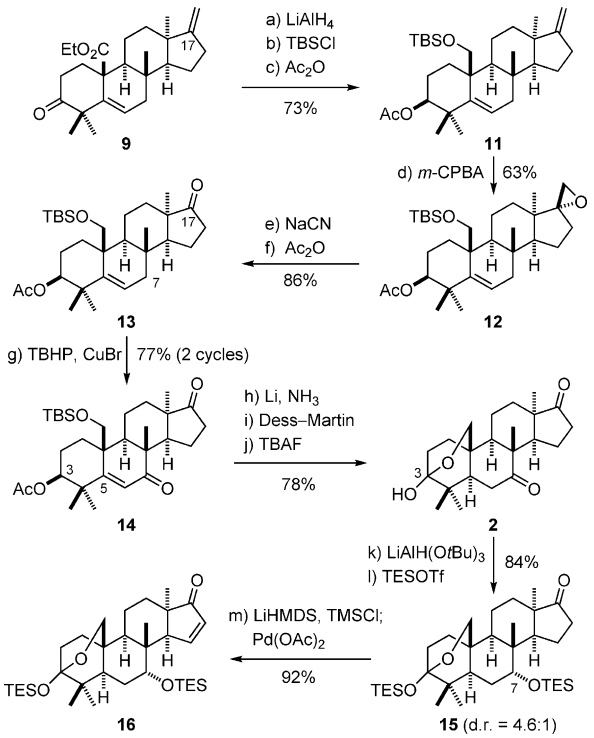


Scheme 2. Construction of the limonoid framework. Reagents and conditions: a) PCl_3, DMF, THF, RT; b) *m*-CPBA, K_2CO_3, CH_2Cl_2, −60 to 0 °C; c) 1-(trimethylsilyl)propyne, *n*BuLi, THF, −40 to 0 °C, 85% (3 steps); d) $Al(OiPr)_3$, toluene, reflux, 88%; e) $SOCl_2$, Et_2O, pentane, 0 °C; f) ethyl 2-chloroacetoacetate, NaH, *n*BuLi, DMPU, THF, 0 °C, 69% (2 steps); g) TBAF, THF, RT, 98%; h) $Mn(OAc)_3 \cdot 2H_2O$, EtOH, RT, 64% (d.r. = 2.1:1); i) Zn, AcOH, RT; j) MVK, *t*BuOK, *t*BuOH, 35 °C, 62% (2 steps); k) MeI, *t*BuOK, *t*BuOH, 40 °C, 80%; l) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2 \cdot H_2O$, EtOH, RT, 55% (d.r. = 27:1). DMPU = 1,3-dimethylhexahydro-2-pyrimidinone, *m*-CPBA = *meta*-chloroperbenzoic acid, MVK = methyl vinyl ketone, TBAF = tetrabutylammonium fluoride.

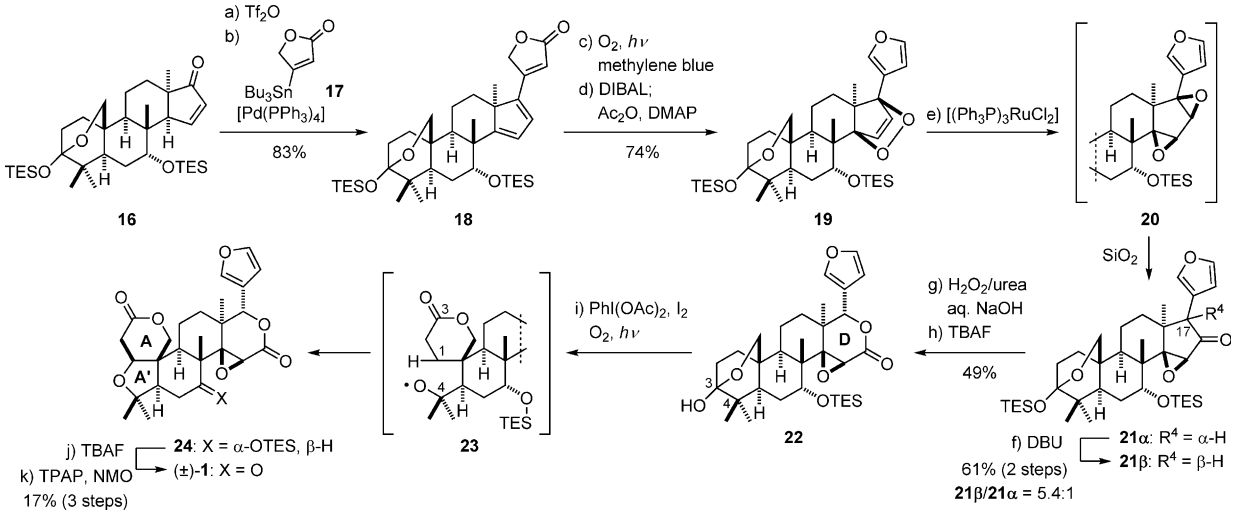


Scheme 3. Development of a method for the cleave of the *exo* methylene group. Reagents and conditions: a) $LiAlH_4$, THF, 0 °C to reflux, 97%; b) TBSCl, NaH, THF, 0 °C to RT, 75%; c) Ac_2O, pyridine, DMAP, CH_2Cl_2, RT, quant.; d) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, −20 to −5 °C, 63%; e) NaCN, DMSO, 120 °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*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) $LiAlH(OtBu)_3$, 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; $Pd(OAc)_2$, MeCN, RT, 92%. DMAP = 4-dimethylaminopyridine, LiHMDS = lithium hexamethyldisilazide, TBHP = *tert*-butyl hydroperoxide, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

Having successfully constructed the limonoid C13α-androstane 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*-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 $LiAlH(OtBu)_3$ 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) Tf_2O, DTBMP, CH_2Cl_2, 0 °C; b) **17**, $[Pd(PPh_3)_4]$, 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) $[(Ph_3P)_3RuCl_2]$, CH_2Cl_2, RT; SiO_2; f) DBU, toluene, 40 °C, 61% (2 steps, d.r. = 5.4:1); g) H_2O_2/urea, aq. NaOH (6 M), MeOH, DME, 45 °C; h) TBAF, THF, −60 to −20 °C, 49% (2 steps); i) $PhI(OAc)_2$, 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 **21α**. 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 **21β**/**21α** = 5.4:1 mixture in 61% overall yield. Baeyer–Villiger oxidation of ketone **21β** 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 (±)-**1** (17% over 3 steps). The ^1H and ^{13}C NMR spectra of synthetic (±)-**1** are identical to those of natural limonin.

In summary, we have achieved the first total synthesis of (±)-limonin (**1**) in 35 steps from geraniol (**4**). Our synthesis features 1) the efficient construction of the limonoid androstane framework with C13α 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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