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DOI: 10.1002/anie.200((will be filled in by the editorial staff))

Total Synthesis of Three Classes of Ring C-*seco* Limonoids

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Abstract: The nimbin-type, salannin-type and nimbolinin-type are three structurally related classes of ring C-*seco* limonoids possessing a complicated hexacyclic framework with a broad range of biological activities. Herein, a convergent and divergent route to access these classes was disclosed by the efficient and protecting-group-free syntheses of 52 ring C-*seco* limonoids. Key transformations include: 1) a catalytic asymmetric intermolecular Diels-Alder reaction to forge the A-ring bearing desired stereochemistry at C4 and C5; 2) a diastereoselective Pd-catalyzed reductive Heck reaction for the formation of the C8-C9 bond; 3) a sulfonyl hydrazone-mediated etherification and a regioselective 5-*exo*-trig radical cyclization for construction of the central tetrahydrofuran ring of the natural products; 4) $BF_3{\cdot}Et_2O$-promoted biomimetic skeletal rearrangement reaction of the salannin-type to generate the nimbolinin-type.

Introduction

Limonoids, mainly originate from the Rutaceae and Meliaceae plants, are natural tetranortriterpenoids with immense structural diversity resulting from skeletal oxidations and rearrangements.[1] These natural products have displayed a variety of biological activities, including analgesic,[2] antioxidant,[3] anti-inflammatory,[4] antimalaria,[5] antiviral,[6] and anticancer properties,[7] which have therefore attracted massive attention from synthetic chemists and become important targets for chemical synthesis for decades (Figure 1a).[1] In 1987, Corey reported a groundbreaking total synthesis of azadiradione by using a polyene cyclization to construct the skeleton of azadiradione in a biomimetic manner.[8] This polycyclization strategy was further extended for the total synthesis of protolimonoid by Corey and developed for the landmark synthesis of limonin by Yamashita.[9, 10] In 2007, Ley succeeded in achieving the historical relay synthesis of azadirachtin through a 22-year synthetic campaign.[11] Continuing exploration in limonoids also led to the impressive syntheses of khayasin, proceranoide and mexicanolide by Williams through employment of an one-pot cascade ketal-Claisen rearrangement and an intramolecular 1,6-conjugate addition as key transformations.[12] In 2016, the Hao/Yang/Shen group isolated a new limonoid perforanoid A and achieved an elegant synthesis by using Rh-catalyzed Pauson–Khand reaction to form the skeleton.[13] From 2017, the Newhouse group accomplished remarkable syntheses of five targets, namely, andirolide N, xylogranatopyridine B, granatumine A, xylogranatin F and xylogranatin G through efficient strategies and methodologies.[14] Additionally, the Yang/Chen group reported a concise synthesis of haperforin G by taking advantage of photoredox catalysis for cross-coupling of structurally complex fragments.[15] In 2022, the Renata group completed the chemoenzymatic synthesis of gedunin through utilization of enzymatic oxidation that has become a powerful tool to simplify synthetic route.[16] Recently, the Qin/Yu group reported a modular synthesis of nimbolide, related five limonoid natural products and a variety of synthetic derivatives with preliminary studies of their cellular cytotoxicity and PARP1 trapping activity.[17] Nevertheless, due to the lack of complete biosynthetic pathways and production routes for the diverse natural product classs, less than 30 members of more than 3000 members have been synthesized so far, which limits the further utility and biological investigation of the limonoids.[18]

Rring C-*seco* limonoids are described as being derived from the havanensin or vilasinin precursors of the Meliaceae family through the bond fission between C-12 and C-13, most of which possess the ether bridge unit.[19] Rring C-*seco* limonoids are divided into six classes by Luo, according to the position of the ether bridge unit, namely, nimbin-type (C-7/15), nimbolidin-type (C-6/28), salannin-type (C-7/15, C-6/28), nimbolinin-type (C-6/28, C-12/15), azadirachtin-type (C-6/28, C-15/21) and azadirachtinin-type (C-6/28, C-7/13, C-15/21) (Figure 1b). Many of these family members are known to demonstrate significant biological activities and pharmacological effects. Among them, 6-acetylnimbandiol is a potent tyrosinase inhibitor that inhibits MITF expression and melanin production.[20] Nimbolide targets a substrate recognition domain in E3 ligase RNF114, implying that this compound may serve as as a covalent recruiter for the E3 ligase to apply in proteolysis targeting chimera (PROTAC), and a molecular glue to recruit and degrade neo-substrates.[21] Additionally, azadirachtin has been widely used as an insecticide because of its antifeedant activity, and it could also induce cell apoptosis through the mitochondrial pathway.[22] Structurally diverse and bioactive ring C-*seco* limonoids spur a wave of biomedicinal efforts to discover more novel mechanism of action and therapeutic targets, therefore a intensive SAR (structure-activity relationship) studies on these compounds is highly desirable. To conduct comprehensive SAR studies, a divergent and concise route to these natural products is required. Herein, we report a concise and divergent approach for the total syntheses of 52 ring C-*seco* limonoids from the three subfamilies with minimal functional group and protecting-group-free manipulations.

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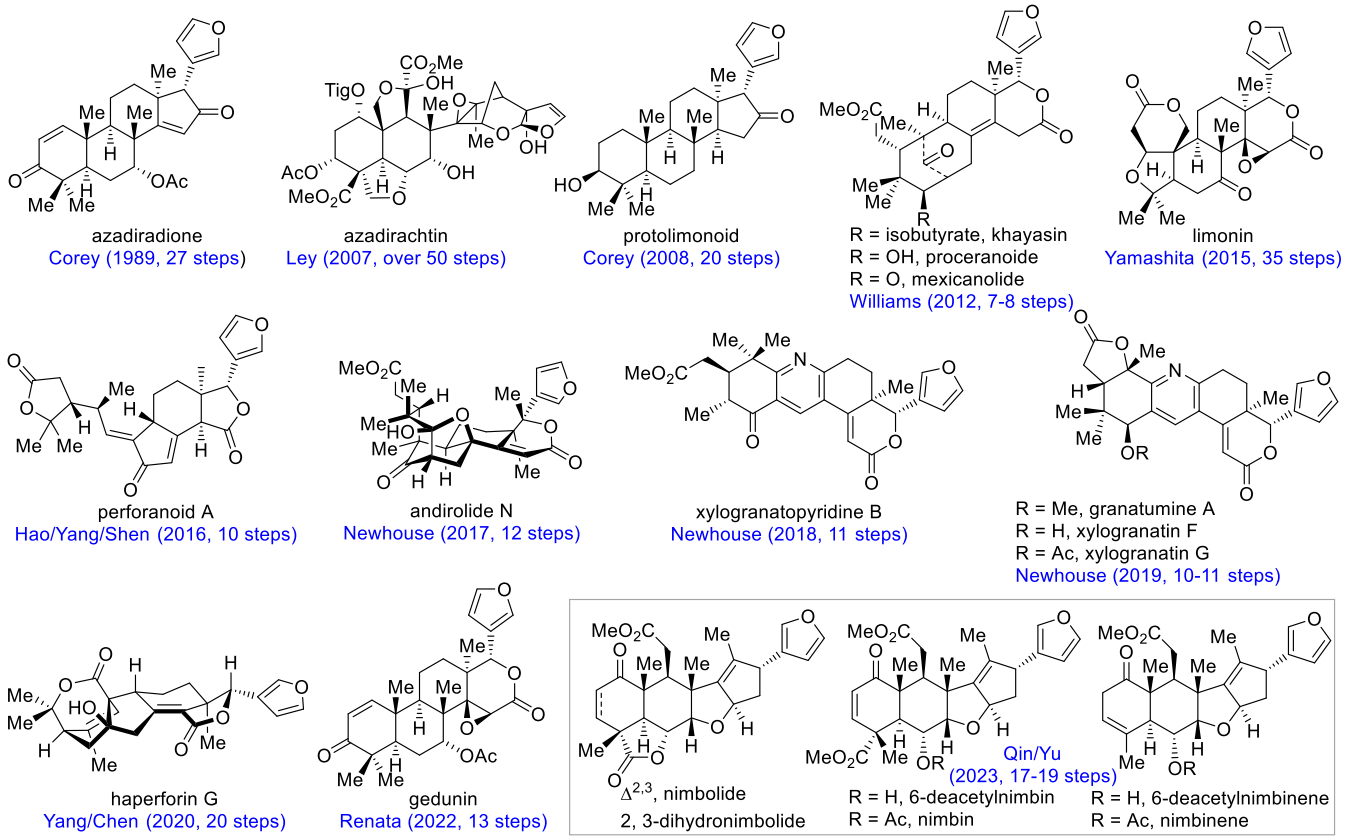
(a) Total syntheses of limonoids



(b) Classification of ring C-*seco* limonoids and representative members

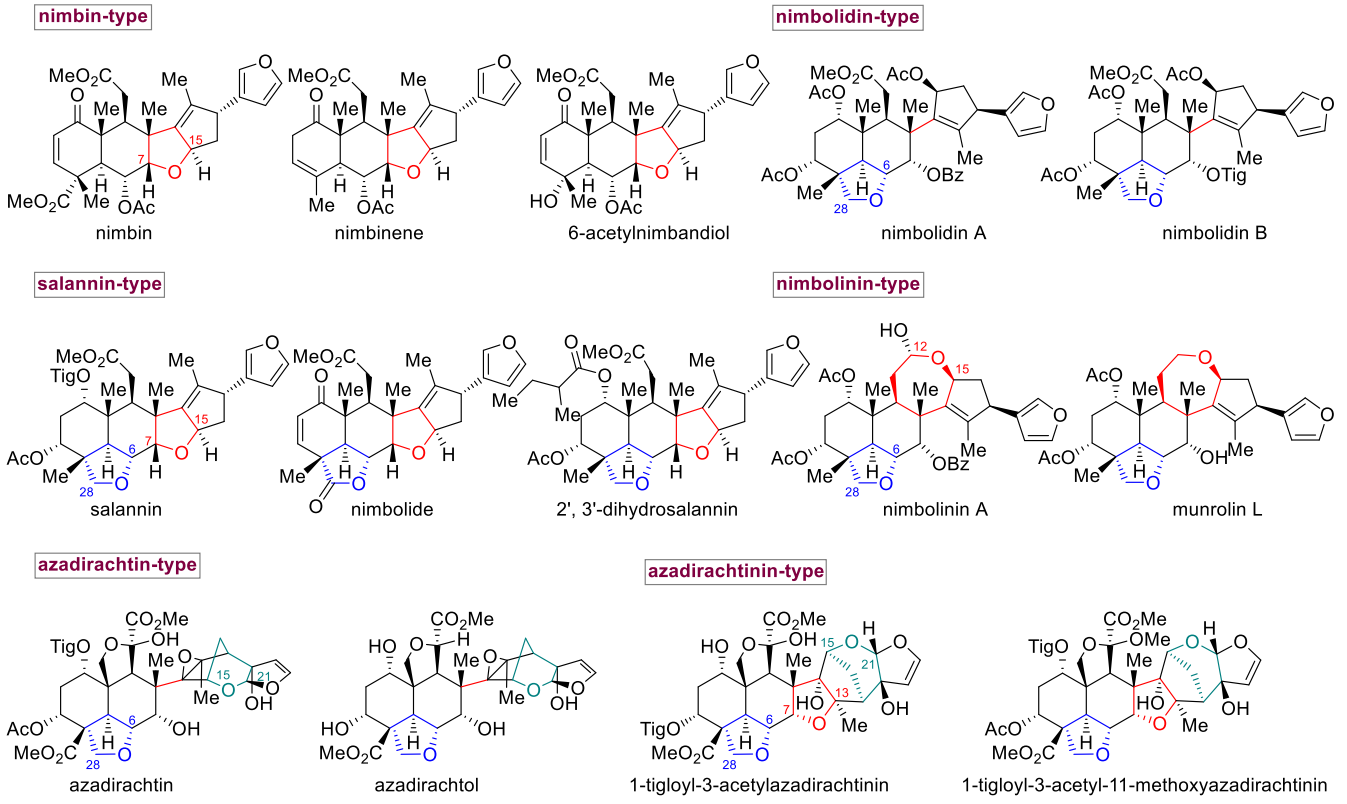


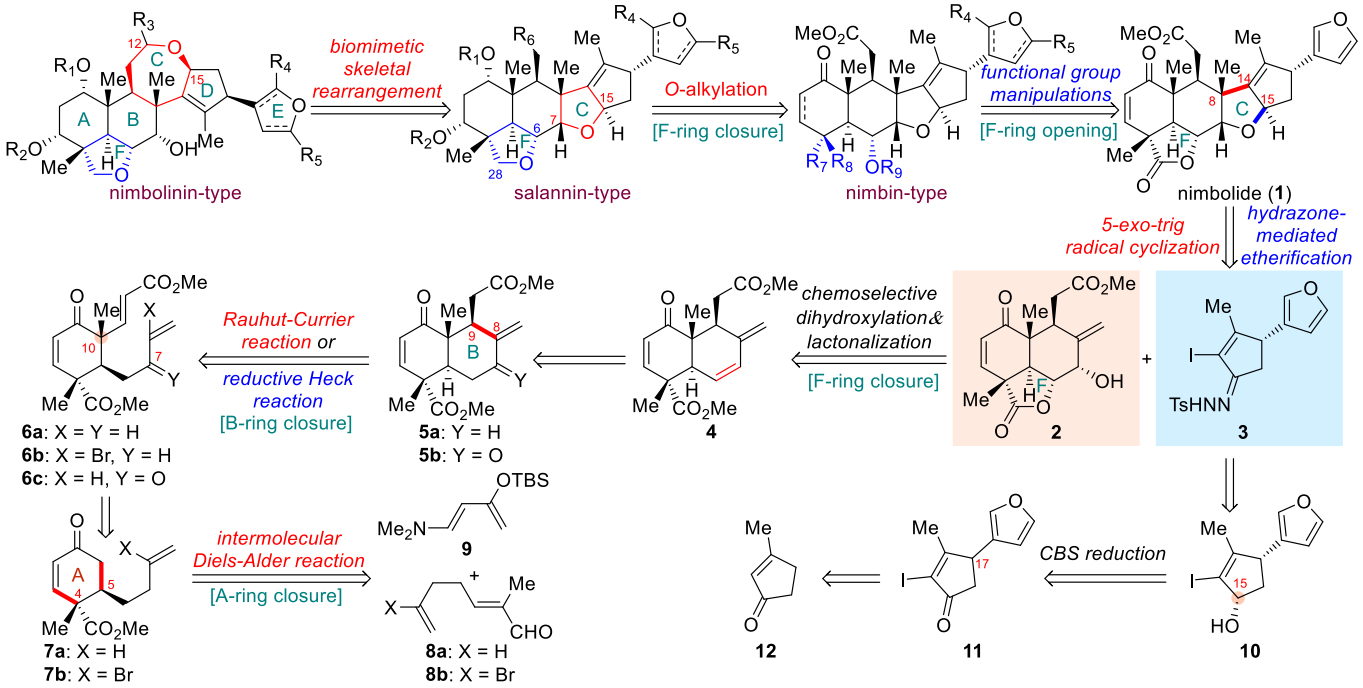
Figure 1. Total syntheses of limonoids and classification of ring C-*seco* limonoids

Results and Discussion

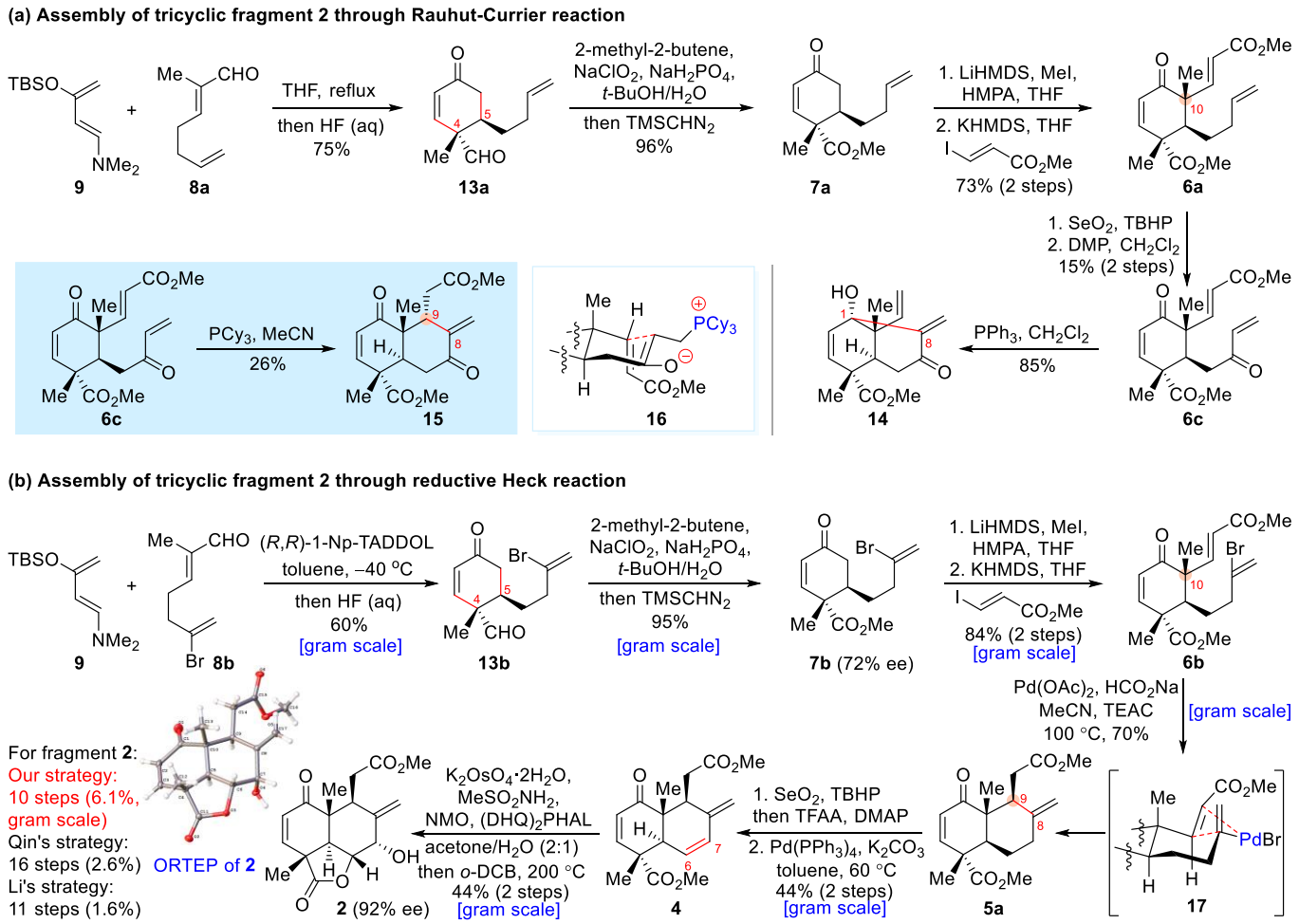
After careful consideration, the nimbin-, salannin- and nimbolinin-type limonoids were selected as targets for synthesis. Structural analysis of these natural products highlights the synthetic challenges, which include the following: (1) a complex pentacyclic or hexacyclic skeleton bearing a fused A/B/C/D-ring and a furan E-ring (scheme 1); (2) seven contiguous stereocenters (six stereocenters in a six-membered B-ring), including three all-carbon quaternary centers at the C-4, C-8 and C-10, and four tertiary carbon centers at C-5, C-6, C-7 and C-9 positions; (3) diverse functional groups in a densely packed skeleton, including enone, ester, tetrasubstituted double bond and various ether groups.

On the basis of structural analysis, we proposed our retrosynthetic analysis as depicted in Scheme 1. We envisioned that nimbolinin-type limonoids could be derived from salannin-type limonoids through the biomimetic skeletal rearrangement of the C-ring.[23] Salannin-type limonoids with the F-ether ring closure were expected to be generated by *O*-alkylation of nimbin-type limonoids, which could be further obtained from nimbolide (**1**) by F-lactone ring opening and some simple functional group manipulations. In order to achieve the convergent synthesis of nimbolide (**1**), we decided to install the tetrahydrofuran ring at late stage via a diastereoselective C-O bond formation between allyl alcohol **2** and sulfonyl hydrazone **3** followed by a regioselective 5-*exo*-trig radical cyclization according to Qin's strategy.[17, 24] The desired tricycle **2** could be obtained via a sequence of chemo- and diastereo-selective dihydroxylation and lactonalization from diene **4**, which would be available from olefin **5** using an allylic desaturation strategy. For assembly of the highly congested *trans*-fused A/B-ring system of **5** with the desired stereochemistry at C9, a Rauhut-Currier reaction[25] of enone **6c** or a reductive Heck reaction[26] of vinyl bromide **6b** was designed. Furthermore, the C10 quaternary stereocenter of **6** could be stereospecifically installed through substrate-controlled alkylation of **7**, which could in turn be assembled through an enantioselective intermolecular Diels-Alder reaction between enal **8** and Rawal's diene **9**.[27] For preparation of fragment **3**, the enantioenriched allyl ahcohol **10** was considered as the ideal intermediate, which could be elaborated via CBS reduction of racemic enone **11**.[28] Finally, enone **11** could be readily traced back to a commercially available starting material **12**.

On the basis of the above analysis, we commenced our synthesis as depicted in Scheme 2a by probing the Rauhut-Currier reaction envisioned to access a *trans*-decaline of enone **5b** as a racemate. As indicated, a thermal Diels-Alder reaction between enal **8a** and Rawal's diene **9,** followed by treatment with aqueous HF smoothly delivered the desired enone **13a**. After conversion of aldehyde **13a** to ester **7a** via Pinnick oxidation and subsequent esterification, sequential methylation (LiHMDS/MeI) and Michael addition/elimination with (*E*)-methyl 3-iodoacrylate were conducted to create a quaternary carbon center stereoselectively.[29] Notably, the stereogenic center at C-5 in **7a** exhibited sufficient steric blocking to enforce addition from the desired α-face in a highly distereoselective manner to afford **6a**. With **6a** in hand, we initially converted it to enone **6c** through allylic oxidation, and then applied the intramolecular Rauhut-Currier reaction to install the fused six-membered ring. Unfortunately, the common amine nucleophiles (DABCO, DBU, quinine) used in the Rauhut-Currier reaction showed no conversion and the typical triphenylphosphine-mediated conditions gave the intramolecular Morita-Baylis-Hillman reaction product **14** exclusively. After some attempts, we found that the desired cyclization occurred by using a more nucleophilic phosphane (PCy_3) as the mediator and MeCN as the solvent.[30] However, the adduct **15** possessed an undesired stereochemistry at C9, and further attempts with various chiral phosphane nucleophiles to reverse the stereochemistry of the Rauhut-Currier reaction proved to be futile. To rationalize this undesired stereoselectivity outcome, we proposed that the thermodynamic enolate was formed as the major configuration because of the steric and electrostatic factors. With the formation of the Z-enolate, the cyclization went through the chair-like transition state, in which two conformations were possible in terms of the location of the conugated ester group, equatorial and axial.



Scheme 1. Retrosynthetic analysis of nimbin-, salannin- and nimbolinin-type limonoids

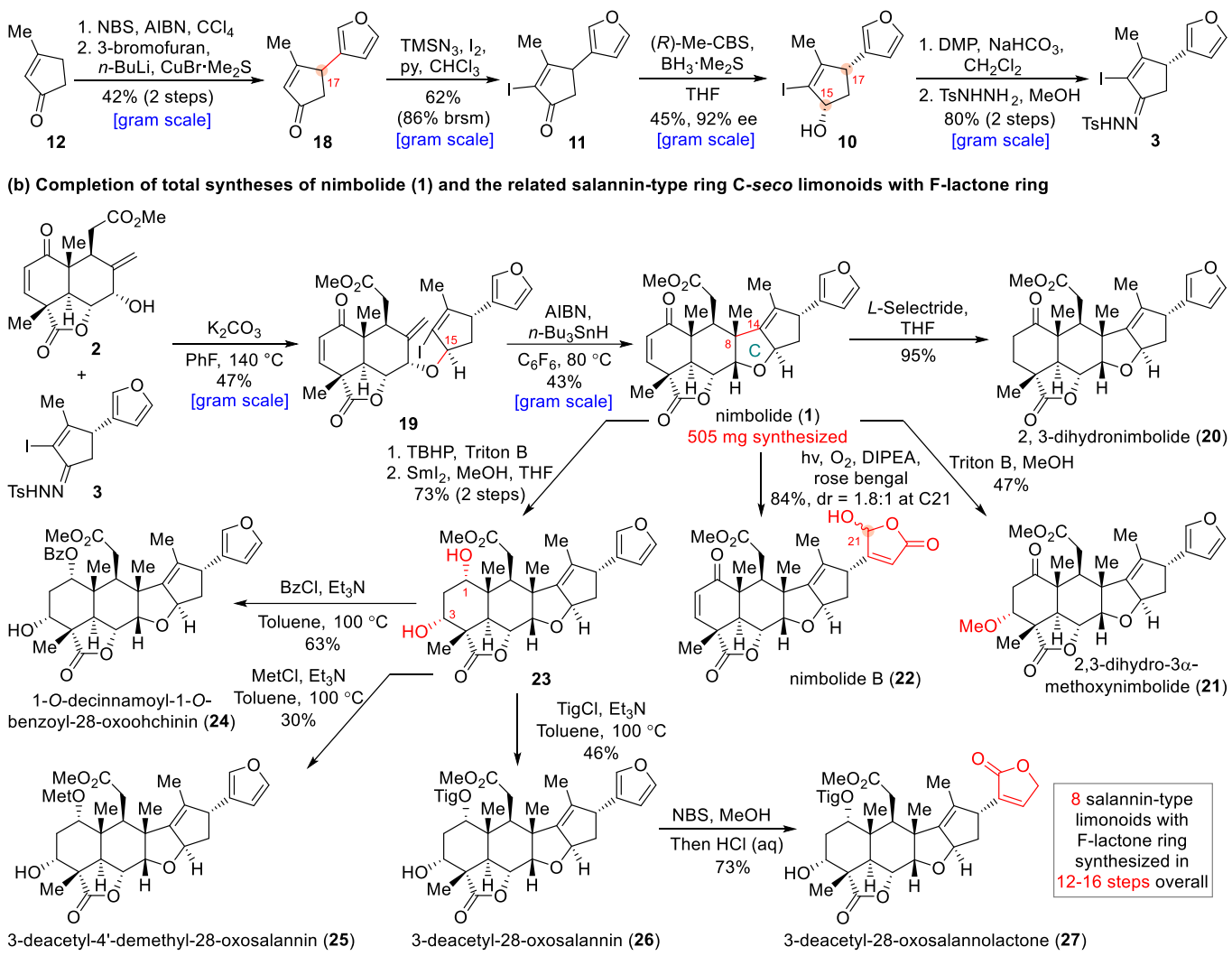


Scheme 2. Assembly of tricyclic fragment **2**. TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, LiHMDS = lithium bis(trimethylsilyl) amide, HMPA = hexamethylphosphoric triamide, KHMDS = potassium bis(trimethylsilyl) amide, DMP = Dess-Martin periodinane, PCy_3 = tricyclohexyl phosphine, TEAC = tetraethylammonium chloride, TBHP = *tert*-butyl hydroperoxide, TFAA = trifluoroacetic anhydride, DMAP = 4-dimethylaminopyridine, NMO = 4-methylmorpholine *N*-oxide, $(DHQ)_2PHAL$ = hydroquinine 1,4-phthalazinediyl diether, *o*-DCB = 1, 2-dichlorobenzene.

While the equatorial transition state generated two gauche interactions, the axial transition state induced one gauche. Additionally, there is less eclipsed interaction between the conjugated ester group and CH_2PCy_3 group with the axial transition state, when the enolate approached to the conjugated ester group.

Failed to obtain the desired intermediate via the Rauhut-Currier reaction, we turned our attention to employ a reductive Heck reaction of the vinyl bromide **6b**.[26] We envisioned that the reaction might proceed via a chair-like transition state **17** to form the B-ring with the desired stereochemistry at C9, in which the Pd group could approach more easily (lower activation energy with less twisted chair transition state) to the vinyl group of the conjugated ester at the pseudoequatorial than at the axial, as well as avoidance more 1,3-diaxial hindrances. At this stage, an enantioselective intermolecular Diels-Alder reaction between enal **8b** and Rawal's diene **9** was carried out (Scheme 2b). After examining a wide range of chiral catalysts, we were pleased to find that the adduct **13b** was obtained in 60% yield and 72% ee after subsequent acidic work-up by using (*R*,*R*)-1-Np-TADDOL as the catalyst. Similarly, the enone **6b** was prepared by means of a three-step procedure described above. The conversion of **6b** to **5a** proved to be a challenging task. Initially, we used a typical condition ($Pd(PPh_3)_4/HCO_2Na$) to conduct the reductive Heck reaction, but no desired cyclization product **5a** was determined, with the formation of the debrominated product **6a**. After extensive screening of the reaction parameters, we ultimately found that the desired bicyclic product **5a** could be produced stereoselectively and efficiently with the best combination of HCO_2Na as the reductive agent, TEAC as the additive, and CH_3CN as the solvent. It was noteworthy that radical-mediated cyclization ($AIBN/Bu_3SnH$, Et_3B/Bu_3SnH) and $[Ni(cod)_2]$-promoted cyclization of vinyl bromide **6 b** also led only to the formation of the debrominated compound **6a**.[31]

Having secured an efficient access to the expected cyclization product **5a**, we continued our synthesis to the tricycle **2** (Scheme 2b). A site-selective allylic oxidation of **5a** at C7 and subsequent esterification were performed in an one-pot protocol to afford the trifluoroacetate, which was converted to diene **4** through a Pd-mediated allylic elimination.[32] It was found that direct dehydration of the allylic alcohol in various approaches only led to the diene **4** in low yields. The subsequent chemo- and diastereo-selective dihydroxylation of **4** was another formidable challenge because of the presence of three possible reaction sites. Indeed, initial attempt with OsO_4/NMO led to the formation of the desired C6-C7 dihydroxylation product, but the yield was rather low owing to poor regioselectivity and overoxidation. To overcome the undesired transformations, we decided to regulate the dihydroxylation selectivity by employing suitable ligands. After



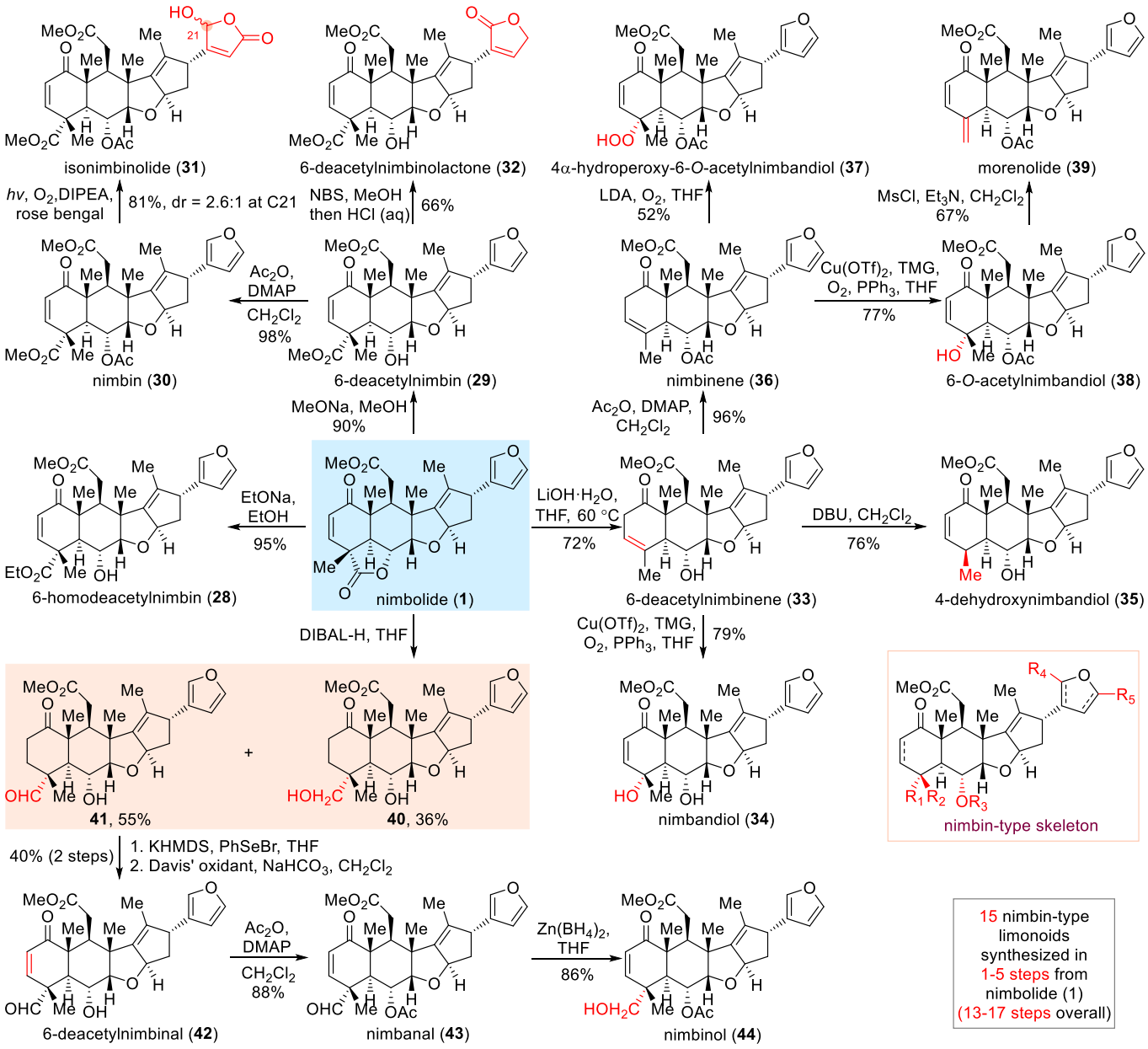
Scheme 3. Synthesis of sulfonyl hydrazone **3** and completion of total syntheses of nimbolide (**1**) and the related salannin-type ring C-*seco* limonoids with F-lactone ring. NBS = *N*-bromosuccinimide, CBS = Corey-Bakshi-Shibata, TMS = trimethylsilyl, DMP = Dess-Martin periodinane, Ts = tolylsulfonyl, AIBN = 2, 2'-azobis(isobutyronitrile), *L*-selectride = lithium tri-*sec*-butylborohydride, DIPEA = *N*, *N*-diisopropylethylamine, Tinton B = benzyl trimethylammonium hydroxide, TBHP = *tert*-butyl hydroperoxide, NBS = *N*-bromosuccinimide, Met = methacryloyl, Bz = benzoyl, Tig = (*E*)-2-methylbut-2-enoyl.

extensive optimization, we found that the yield of the desired dihydroxylation product could be improved to 52% by using $(DHQ)_2PHAL$ as the ligand, NMO as the oxidant and acetone/H_2O (2:1) as the solvent.[33] Importantly, this action further enriched the enantioselectivity of the dihydroxylation product to 92% ee, which was probably due to the introduction of $(DHQ)_2PHAL$ promoting the dihydroxylation of the exocyclic double bond of the minor enantiomer, as well as dihydroxylation of the C6-C7 double bond of the major enantiomer. Finally, heating the resultant diol at 200 °C in *o*-DCB promoted the anticipated lactonalization to deliver the tricycle **2**, whose structure was confirmed by X-ray crystallographic analysis. Compared with the oxidation-relay chemical synthesis (2.6% yield, 16 steps from dehydroabietic acid) by the Qin's group and the chemoenzymatic synthesis (1.2% yield, 11 steps from sclareolide) by the Li's group, [34] our synthesis of tricycle **2** (6.1% yield, gram scale, 10 steps from 4-bromo-4-pentenal) was more advantageous in both efficiency and selectivity.

In a parallel procedure, the synthesis of fragment **3** was conducted (Scheme 3a). The designed enone **18** containing the requisite furan ring at C17 was readily obtained from the enone **12** via Wohl–Ziegler bromination[35] and subsequent alkylation in 42% overall yield. Iodination of **18** with $TMSN_3$ and I_2 afforded the iodide **11**,[36] which underwent a chiral resolution via CBS reduction to provide the allylic alcohol **10** in 45% yield and 92% ee.[28] Further oxidation of **10** with DMP and subsequent condensation with tosyl hydrazide gave the desired sulfonyl hydrazone **3**.

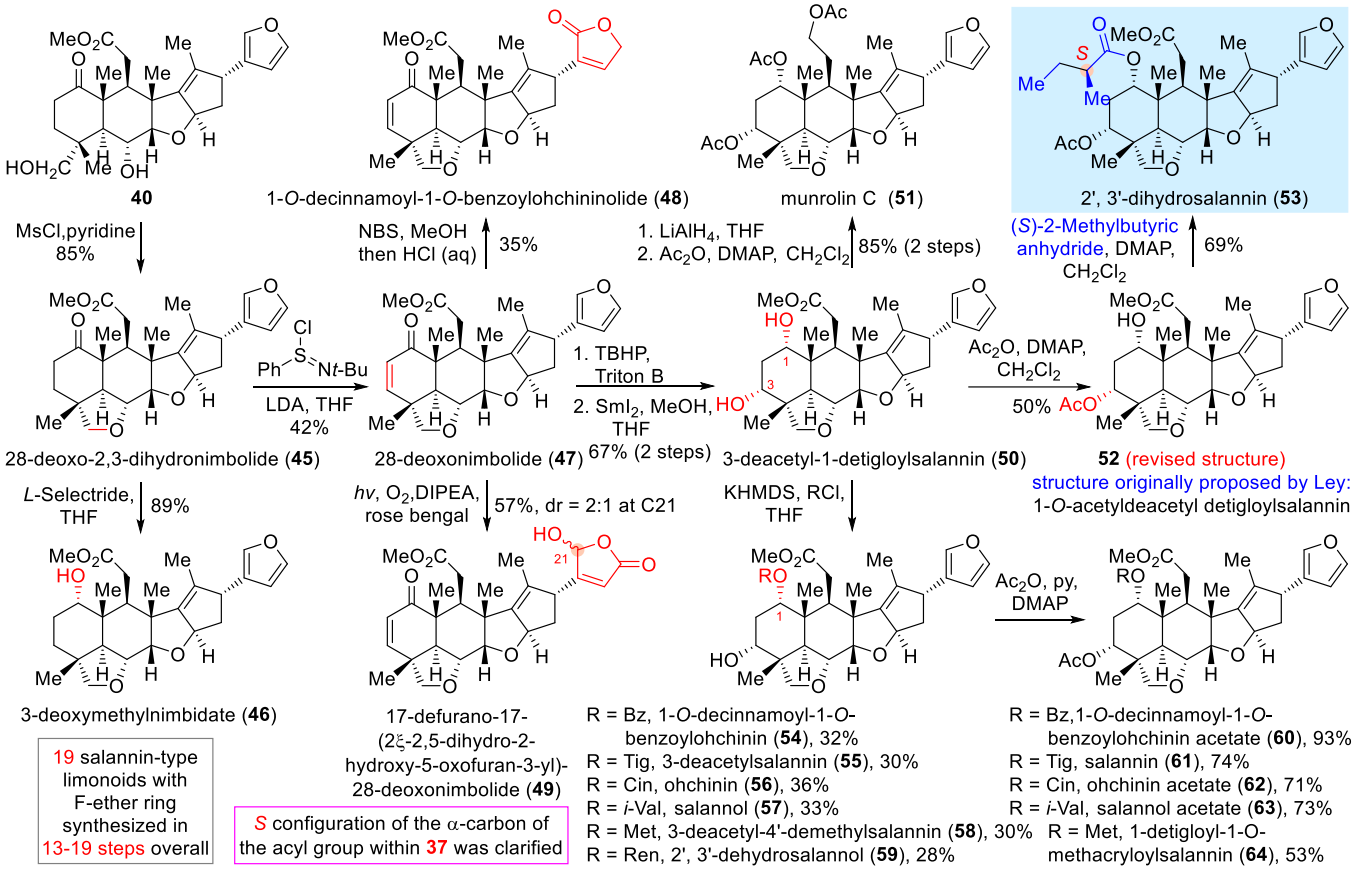
With a gram-scale route to **2** and **3**, the convergent coupling was investigated (Scheme 3b). Under the modified conditions,[17,24] etherification between allyl alcohol **2** and sulfonyl hydrazone **3** proceeded smoothly to afford **19** in 47% yield on a gram scale, which was further treated with AIBN/*n*-Bu_3SnH, leading to the regioselective formation of nimbolide (**1**). It was also worth noting that our initial attempts to produce the ether **19** via S_N2 reaction and transition-metal mediated coupling using related agents all failed to give any desired product. Notably, this scalable route to nimbolide (**1**) involved only 12 steps from 4-bromo-4-pentenal and provided more than 500 mg of nimbolide (**1**), an amount that was sufficient for the subsequent late-stage diversification studies to access various ring C-*seco* limonoids.

Having developed a concise synthetic route to nimbolide (**1**),



Scheme 4. Divergent total syntheses of nimbin-type ring C-*seco* limonoids. DMAP = 4-dimethylaminopyridine, DIPEA = *N*, *N*-diisopropylethylamine, NBS = *N*-bromosuccinimide, TMG = 1, 1, 3, 3-tetramethylguanidine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, LDA = lithium diisopropylamide, Ms = Methanesulfonyl, KHMDS = potassium bis(trimethylsilyl) amide, Davis' oxidant = 3-phenyl-2-(phenylsulfonyl)oxaziridine.

we turned our attention to the syntheses of the salannin-type ring C-*seco* limonoids bearing a F-lactone ring (Scheme 3b). Treatment of **1** with *L*-Selectride provided 2, 3-dihydronimbolide (**20**).[37] Diastereoselective oxa-Michael addition of **1** with MeOH and TBHP gave 2, 3-dihydro-3α-methoxynimbolide (**21**).[38] Regioselective photochemical oxidation[38] of **1** with $^1O_2$ generated from O_2/rose bengal furnished the nimbolide B (**22**).[40] Next, we explored the syntheses of 1-*O*-decinnamoyl-1-*O*-benzoyl-28-oxoohchinin (**24**),[41] 3-deacetyl-4'-demethyl-28-oxosalannin (**25**),[41] 3-deacetyl-28-oxosalannin (**26**)[42] and 3-deacetyl-28-oxosalannolactone (**27**)[43] from **1**, all of which contain a *cis*-1, 3-diol moiety. Although Ley reported a three-step sequence involving epoxidation of enone followed by reductive ring opening of the epoxide and stereoselective reduction of the resulting ketone for the synthesis of the functionalized decalin,[44] we found that subjecting **1** to the same conditions led to complex mixtures, with the major products resulting from the opening of the lactone ring. Eventually, we discovered that stereoselective epoxidation of **1** with TBHP and Triton B followed by global reduction of the resulting epoxide with SmI_2 furnished *cis*-1, 3-diol **23**,[45] providing a straightforward method for preparing the *cis*-1, 3-diol from the enone. It should be noted that only *trans*-1, 3-diol was obtained under different reduction conditions. At this stage, our next challenge was the selective acylation of the C1 hydroxy group of **23** with different acyl chlorides. Unfortunately, acylation of **23** occured at C3 rather than at C1 under the conventional condition (acyl chloride, DMAP, Et_3N), which indicated that the C3 hydroxy group of **23** was less sterically hindered. To obtain the desired natural products with the acylated C1 hydroxy group of **23**, we treated **23** with BzCl and Et_3N in toluene at 100 ºC, which furnished the desired 1-*O*-decinnamoyl-1-*O*-benzoyl-28-oxoohchinin (**24**) in 63% yield, together with the minor acylation product at C3. This interesting acylation selectivity could be due to a decrease in the sensitivity of the steric hindrance under the heating condition. Likewise, 3-deacetyl-4'-demethyl-28-oxosalannin (**25**) and 3-deacetyl-28-oxosalannin (**26**) could be

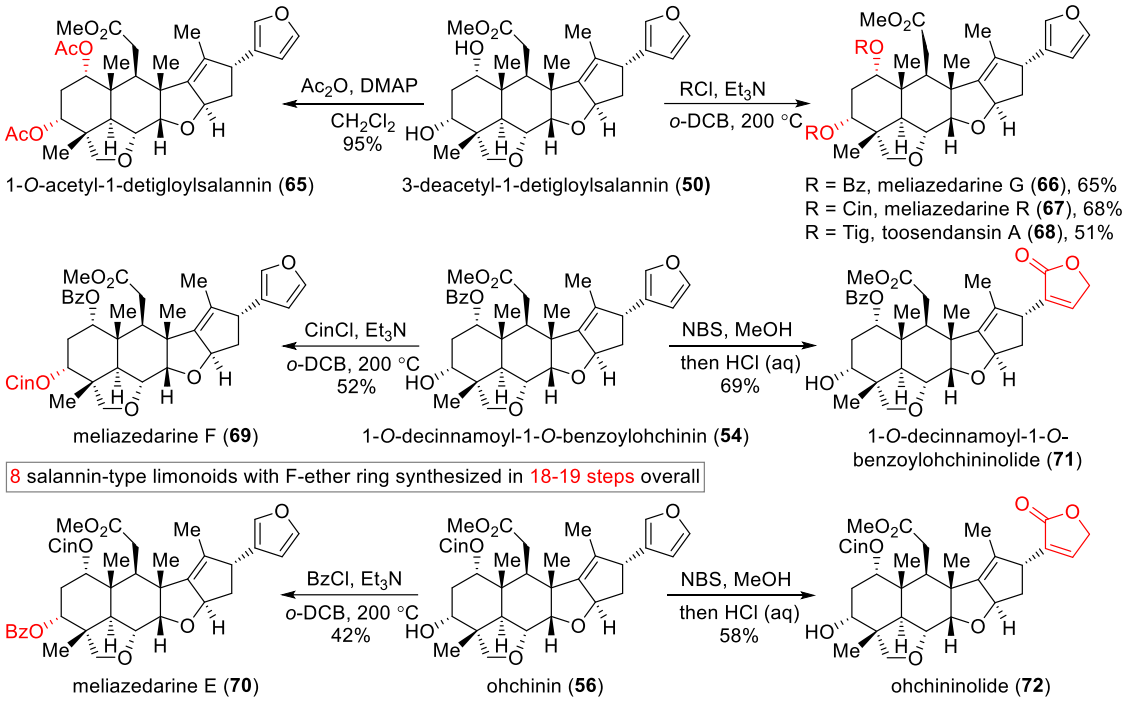


Scheme 5. Divergent total syntheses of salannin-type ring C-*seco* limonoids with F-ether ring. Ms = Methanesulfonyl, *L*-selectride = lithium tri-*sec*-butylborohydride, LDA = lithium diisopropylamide, NBS = *N*-bromosuccinimide, DIPEA = *N*, *N*-diisopropylethylamine, Tinton B = benzyl trimethylammonium hydroxide, TBHP = *tert*-butyl hydroperoxide, DMAP = 4-dimethylaminopyridin, Bz = benzoyl, Tig = (*E*)-2-methylbut-2-enoyl, Cin = (2*E*)-3-phenyl-2-propenoyl, *i*-Val = isovaleryl, Ren = 3-methyl-2-butenoyl, Met = methacryloyl.

obtained from **23** in the same manner. Further oxidation of **26** with NBS and a subsequent acidic work-up delivered the 3-deacetyl-28-oxosalannolactone (**27**) featuring an unsaturated butyrolactone unit.[46] Thus, efficient syntheses of 8 salannin-type ring C-*seco* limonoids with F-lactone ring were accomplished in 12–16 steps from 4-bromo-4-pentenal.

Furthermore, we explored the syntheses of the diverse nimbin-type ring C-*seco* limonoids from the common advanced intermediate nimbolide (**1**) via late-stage functional group manipulations. As shown in Scheme 4, alcoholysis of **1** with EtONa and MeONa generated 6-homodeacetylnimbin (**28**)[47] and 6-deacetylnimbin (**29**),[48] respectively. Subsequent acetylation of **29** provided nimbin (**30**),[48] which was converted into isonimbinolide (**31**)[49] through the same photochemical oxidation. Likewise, oxidation of **29** with NBS and a subsequent acidic work-up delivered the 6-deacetylnimbinolactone (**32**).[47] Next, we continued to focus on the syntheses of these diverse family members bearing different substituents at C4. To this end, hydrolysis and subsequent decarboxylation of **1** with LiOH·H_2O afforded 6-deacetylnimbinene (**33**),[50] which underwent a copper-catalyzed vinylogous aerobic oxidation developed by Newhouse and Yin group[51] to give nimbandiol (**34**).[50] Meanwhile, transformation of **33** into the conjugated enone was accomplished with DBU in dichloromethane, producing 4-dehydroxynimbandiol (**35**) as a single isomer.[52] Additionally, acylation of **33** furnished nimbinene (**36**),[50] which was subjected to LDA and O_2 to afford 4-α-hydroperoxy-6-*O*-acetylnimbandiol (**37**) with a γ-peroxy unit through a vinylogous oxidation.[53] Similarly, 6-*O*-acetylnimbandiol (**38**) was obtained via a copper-catalyzed vinylogous aerobic oxidation of **36**.[50] Subsequent regioselective dehydration of the allylic alcohol **38** with MsCl and Et_3N provided morenolide (**39**).[54] With **33** and **36** in hand, we moved on to investigate another synthetic challenge, that is, utilization of vinylogous aldol reaction or vinylogous alkylation to install the hydroxymethyl group of nimbinol (**44**).[48] However, treatment of **33** or **36** with various bases and electrophiles (HCHO or iodide) resulted in the direct aldol or alkylation at C2 rather than C4, which indicated that it was difficult to construct the all-carbon quaternary center at C4 in a vinylogous manner. Therefore, we decided to explored the selective reduction of **1** to complete the syntheses of **42**-**44** with the F-lactone ring opening. To our delight, although the C2–C3 olefin of **1** was innately more reactive toward reductants than the lactone ring, reduction of **1** with DIBAL-H in THF provided the aldehyde **41**, along with the alcohol **40** as the minor product. Subsequently, according to Ley's conditions,[44] dehydrogenation of **41** was achieved by selenenylation and elimination of the resulting selenium with Davis' oxidant,[55] yielding 6-deacetylnimbinal (**42**).[48] Further treatment of **42** with Ac_2O generated nimbanal (**42**),[56] which was chemoselectively reduced with $Zn(BH_4)_2$ to give nimbinol (**44**). Thus, diverse syntheses of 15 nimbin-type ring C-*seco* limonoids were accomplished in one to five steps from nimbolide (**1**) (that is, 13–17 steps from 4-bromo-4-pentenal).

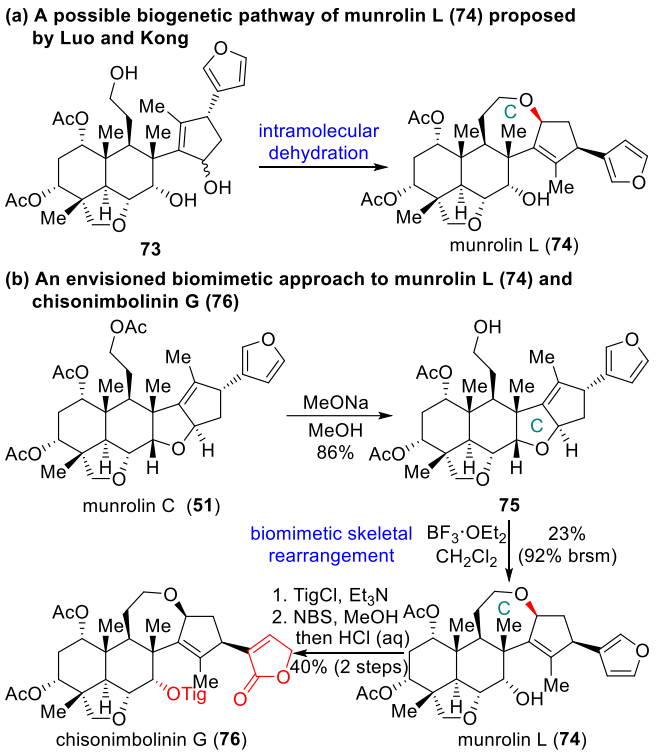
Next, we shifted our attention to the divergent syntheses of salannin-type ring C-*seco* limonoids bearing a F-ether ring, planning to construct the ether ring by means of an intramolecular *O*-alkylation of **40** (Scheme 5). Gratifyingly, the desired intramolecular *O*-alkylation of **40** proceeded smoothly to provide



Scheme 6. Divergent total syntheses of salannin-type ring C-*seco* limonoids **65-72** with F-ether ring. DMAP = 4-dimethylaminopyridin, *o*-DCB = 1, 2-dichlorobenzene, NBS = *N*-bromosuccinimide, Bz = benzoyl, Tig = (*E*)-2-methylbut-2-enoyl, Cin = (2*E*)-3-phenyl-2-propenoyl.

28-deoxo-2, 3-dihydronimbolide (**45**)[57] in excellent yield when MsCl and pyriding were used. Stereoselective reduction of **45** with *L*-selectride afforded 3-deoxymethylnimbidate (**46**).[37] Alternatively, treatment of **45** with LDA generated the corresponding lithium enolate, which was then treated with *N*-*tert*-butylphenylsulfinimidoyl chloride to inudce a Mukaiyama dehydrogenation,[58] delivering desired 28-deoxonimbolide (**47**).[59] Under the previously same oxidation conditions, 1-*O*-decinnamoyl-1-*O*-benzoylohchininolide (**48**)[41] and 17-defurano-17-(2ξ-2,5-dihydro-2-hydroxy-5-oxofuran-3-yl)-28-de oxonimbolide (**49**)[47] were obtained from **47**. Meanwhile, 3-deacetyl-1-detigloylsalannin (**50**)[60] could be prepared from **47** via the same two-step protocol involving epoxidation and SmI_2-mediated reductive ring opening of the resulting epoxide. Further reduction of **50** with $LiAlH_4$ followed by global acylation provided munrolin C (**51**).[23] Next, selective acylation of the C1 hydroxy group of **50** was still a challenge. Although Ley reported the acylation of **50** with AcCl, affording 1-*O*-acetyldeacetyldetigloylsalannin,[61] we found that subjecting **50** to the same condition yielded **52** with the acetyl group at C3, whose ^1H NMR data and specific rotation were in good agreement with that reported by Ley. To further confirm the structures of **52** and 2', 3'-dihydrosalannin (**53**)[62] with an uncertain configuration of the α-carbon of the acyl group, we treated **52** with commercially available (*S*)-2-methylbutyric anhydride to generate **53**. To our delight, the spectroscopic data for the synthetic 2', 3'-dihydrosalannin (**53**) were identical to those reported for the natural isolate. Therefore, the acylation product of **50** was revised as detigloylsalannin (**52**) instead of 1-*O*-acetyldeacetyldetigloylsalannin, a structure originally proposed by Ley. Additionally, the *S* configuration of the α-carbon of the acyl group within 2', 3'-dihydrosalannin (**53**) was clarified though chemical synthesis. To continue the synthesis, we carried out the previous condition (RCl, Et_3N, toluene, 100 ºC) that was used for the syntheses of **24-26**. However, treatment of **50** with BzCl resulted in the major product with the acylated C3 hydroxy group, and only a trace amount of the desired acylation product **54** was obtained. We speculated that this change from **23** to **50** increased the nucleophilicity of the hydroxy group at C3 by removing the electron-withdrawing ester group of **23**, making it more difficult to introduce the acetyl group at C1. Gratifyingly, under the dynamic condition (KHMDS, BzCl, THF), 1-*O*-decinnamoyl-1-*O*-benzoylohchinin (**54**)[41] could be obtained from **50**. In addition to **54**, 3-deacetylsalannin (**55**),[63] ohchinin (**56**),[64] salannol (**57**),[63] 3-deacetyl-4'-demethylsalannin (**58**)[42] and 2', 3'-dehydrosalannol (**59**)[65] were synthesized using similar protocols. Further acylation of **54-58** with Ac_2O furnished 1-*O*-decinnamoyl-1-*O*-benzoylohchinin acetate (**60**),[41] salannin (**61**),[66] ohchinin acetate (**62**),[67] salannol acetate (**63**)[68] and 1-detigloyl-1-*O*-methacryloylsalannin (**64**).[57]

Encouraged by the above-described results, we moved on to the preparation of the related salannin-type limonoids **65-72**, as shown in Scheme 6. Although 1-*O*-acetyl-1-detigloylsalannin (**65**)[69] was readily obtained through the direct acylation of **50** with Ac_2O, syntheses of **66-70** proved to be a formidable task, especially in the introduction of the second acyl group. To address this issue, we screened various reaction parameters, including temperature, solvents, bases and acylating agents. Eventually, we were pleased that treatment of **50** with Et_3N and the corresponding acyl chloride in *o*-DCB at 200 °C gave the expected products meliazedarine G (**66**), [70] meliazedarine R (**67**)[71] and toosendansin A (**68**).[72] Likewise, meliazedarine F (**69**)[70] and meliazedarine E (**70**)[70] could be prepared from **54** and **56** in the same manner. Alternatively, oxidation of **54** and **56** with NBS and a subsequent acidic work-up delivered the 1-*O*-decinnamoyl-1-*O*-benzoylohchininolide (**71**)[41] and ohchininolide (**72**),[41] respectively. Notably, divergent syntheses of 27 salannin-type ring C-*seco* limonoids with F-ether ring were accomplished in 13–19 steps from 4-bromo-4-pentenal.



Scheme 7. Total syntheses of nimbolinin-type ring C-*seco* limonoids munrolin L (**74**) and chisonimbolinin G (**75**). NBS = *N*-bromosuccinimide, Tig = (*E*)-2-methylbut-2-enoyl.

Finally, we focused on the syntheses of munrolin L (**74**)[23] and chisonimbolinin G (**76**),[73] two nimbolinin-type ring C-seco limonoids that possess a common seven-membered ether ring system, through an envisioned biomimetic skeletal rearrangement reaction (Scheme 7). On the basis of the isolation of 17 ring C-*seco* limonoids with diverse oxidative patterns at C12, Kong and Luo proposed a possible biogenetic pathway that munrolin L (**74**) might be derived from **73** through intramolecular dehydration, resulting in the formation of the seven-membered ether ring (Scheme 7a).[23] Given the unavailability of **73** in nature, we proposed an alternative biomimetic pathway. We envisioned that **75** could be transformed to munrolin L (**74**) through a Lewis acid-mediated skeletal rearrangement,[74] achieving the conversion of the salannin-type skeleton to the nimbolinin-type skeleton (Scheme 7b). To confirm our proposal, we treated **51** with MeONa to generate **75**, a key precursor for the rearrangement reaction. After examining a variety of Lewis acids, we found that munrolin L (**74**) could be obtained by using $BF_3{\cdot}Et_2O$. However, our result did not allow us to rule out the possibility that **73** was the intermediate of this rearrangement reaction. Further acylation of **74** with TigCl followed by oxidation with NBS and a subsequent acidic work-up furnished chisonimbolinin G (**76**).

Conclusion

In summary, we have developed a concise and scalable approach for the preparation of nimbolide (**1**), which can be divergently elaborated into three classes of ring C-seco limonoids with diverse structures. In this study, we accomplished a unified, protecting-group-free synthesis of 52 ring C-*seco* limonoids in only 12–23 longest linear steps from a commercially available starting material (4-bromo-4-pentenal). The challenging polycyclic framework was rapidly installed in a stereocontrolled manner by means of four strategic bond forming reactions: a TADDOL-catalyzed asymmetric intermolecular Diels-Alder reaction, a Pd-catalyzed reductive Heck reaction, a sulfonyl hydrazone-mediated etherification, and a 5-*exo*-trig radical cyclization. Based on our total synthesis, the originally proposed structure of 1-*O*-acetyldeacetyldetigloylsalannin was revised and the *S* configuration of the α-carbon of the acyl group within 2', 3'-dihydrosalannin (**53**) was clarified. More importantly, our work provides experimental evidence for the possible biogenetic pathway of munrolin L (**74**) from **75** and the interrelationships between the salannin-type and the nimbolinin-type. Further investigations on the synthesis of more analogues of ring C-*seco* limonoids and their in-depth structure−activity relationship are actively pursued in our laboratory and the results will be disclosed in due course.

Acknowledgements

The authors are grateful to the National Natural Science Foundation of China (grant 21831009 and 21991110) for financial support.

Keywords: total synthesis, ring C-*seco* limonoids, reductive heck reaction, biomimetic skeletal rearrangement

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