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Natural Products

Biomimetic Total Synthesis of (±)-Pallavicinolide A[**]

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In memory of Nien-chu C. Yang

Liverworts biosynthesize many new skeletons of diterpenoids having interesting biological activities such as antifungal, antimicrobial, cytotoxic, insect antifeedant, insecticidal, and muscle relaxant.[1],[2] In 1998, three diterpenes [herein called pallavicinolide A (**1**), B (**2**), and C (**3**)] were isolated for the first time from the Japanese liverwort *Pallavicinin subciliata* (Figure 1).[3] The novel tetracyclic fused skeletons having seven or eight contiguous stereocenters make them particularly challenging targets from a chemical synthesis viewpoint. Interestingly, in compounds **1** and **2**, the four neighboring bridgehead protons point to the same face, resulting in a bowl-like three-dimensional structure. To the best of our knowledge, these frameworks have rarely been found in naturally occurring molecules. The intriguing molecular architecture and the potential bioactivities of **1**, **2**, and **3** have attracted our attention. Herein we report the first total synthesis of (±)-pallavicinolide A (**1**) using a biomimetic approach.

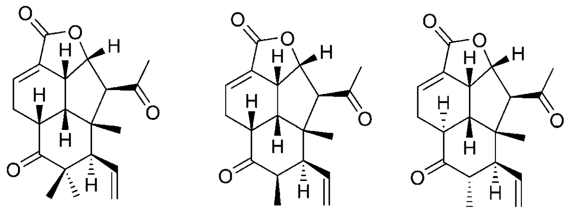
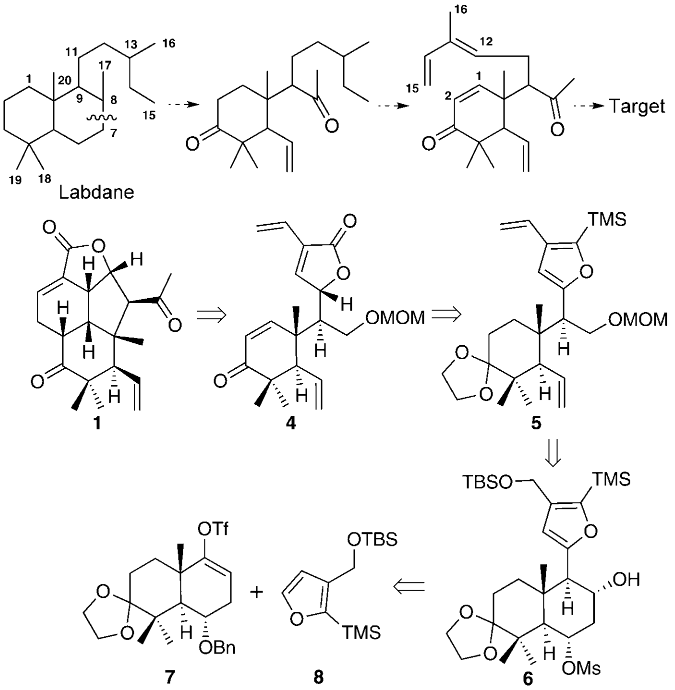

Pallavicinolide A (**1**) Pallavicinolide B (**2**) Pallavicinolide C (**3**)

Figure 1. Structure of pallavicinolides.

Pallavicinolide A (**1**) is a modified labdane-type diterpene, and its proposed biosynthetic pathway includes a C7–C8 bond cleavage of labdane, and then a bond reconstruction of the C15–C2 and C12–C1 segments (Scheme 1).[3] Encouraged by our recent success in the syntheses of natural molecules starting from furan species[4] and the aforementioned biogenetic hypothesis, we envisioned that the molecular complexity of **1** could be achieved through an intramolecular Diels–Alder (IMDA) cycloaddition[5] of butenolide **4**, in which the three new stereogenic centers could be formed stereoselectively in one step. Butenolide **4**, in turn, can be produced by the oxidation of furan **5**, which can be formed through a Grob fragmentation[6] of the bicyclic mesylate **6**; **6** can be disconnected to the known triflate **7**[4a,7] and the furan subunit **8** (Scheme 1).



Scheme 1. Biogenetic hypothesis and retrosynthetic analysis of pallavicinolide A (**1**). MOM = methoxymethyl, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl, Bn = benzyl, TBS = *tert*-butyldimethylsilyl, Ms = methanesulfonyl.

Our synthesis began with vinyl triflate **7**, which was prepared by a known synthetic route starting from 2-methyl-1,3-cyclohexanedione.[4a,7] Building block **8** was prepared in three steps from the commercially available 3-furoic acid (Scheme 2). Thus, 3-furoic acid preferentially underwent 2-lithiation and subsequent silylation[8] to give compound **9**. The reduction of **9** using $LiAlH_4$ and subsequent protection, gave silylfuran **8** in a high yield.

As shown in Scheme 3, the Negishi coupling[9] between **7** and **8** afforded the pivotal compound **10** in good yield. After a highly diastereoselective hydroboration/oxidation (d.r. > 20:1),[10] **11**, which contained an equatorial furyl group

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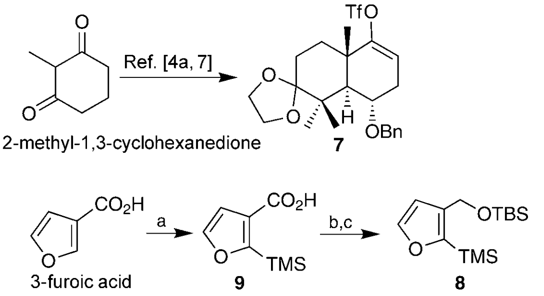
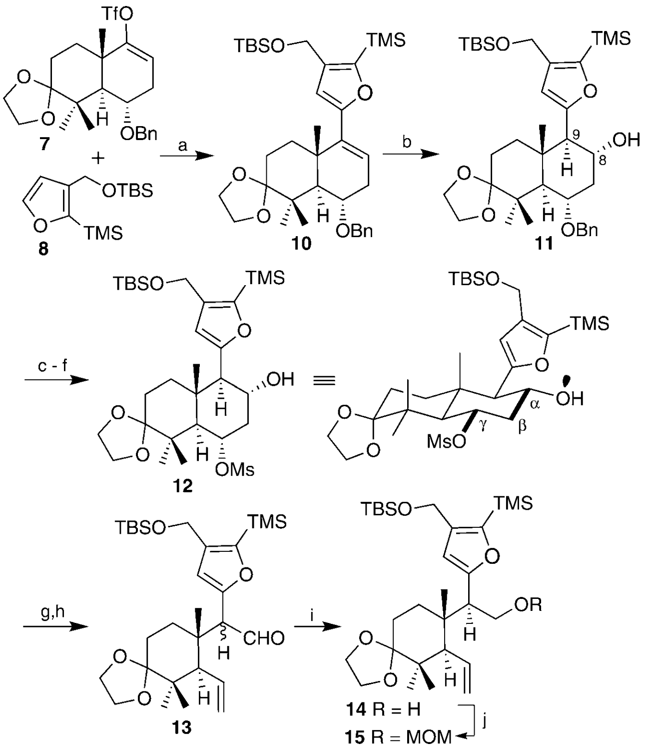


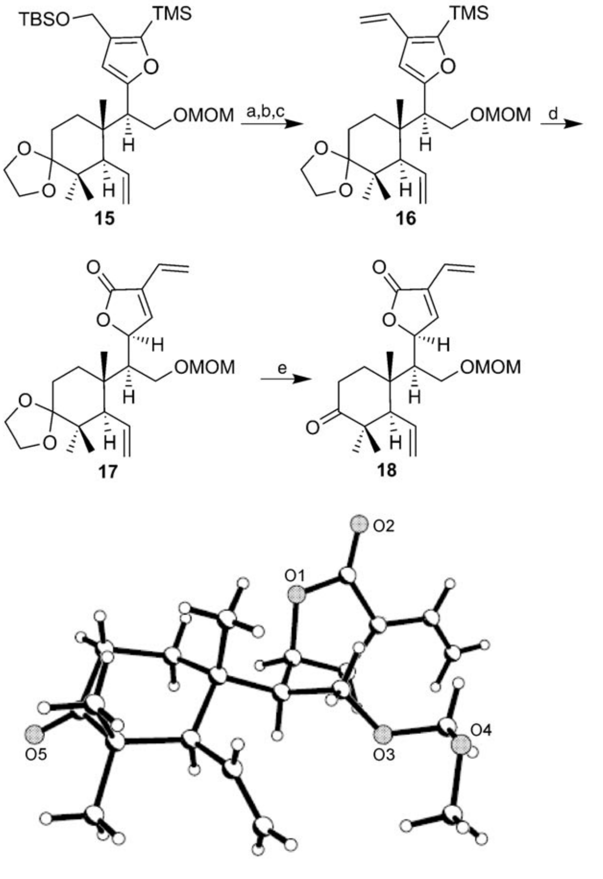
Scheme 2. Syntheses of **7** and **8**. a) 1) LDA, THF, −78 °C, 30 min; 2) TMSCl, −78 °C→RT, 1 h, 65 %; b) $LiAlH_4$, THF, 0 °C→RT, 1 h, 95 %; c) TBSCl, imidazole, DMF, RT, 12 h, 92 %. LDA = lithium diisopropylamide, DMF = *N*,*N*-dimethylformamide.



Scheme 3. Synthesis of **15**. a) 1) **8**, *n*BuLi, $ZnCl_2$, 0 °C→RT, 1 h; 2) **7**, $[Pd(PPh_3)_4]$, THF, 50 °C, 20 min, 82 %; b) $BH_3{\cdot}Me_2S$, THF, 0 °C→RT, 15 h, H_2O_2, NaOH, 70 %; c) Ac_2O, pyridine, DMAP, RT, 2 h, 91 %; d) Pd/C, H_2, ethyl acetate, RT, 2 h, 95 %; e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, 94 %; f) NaOMe, MeOH, RT, 3 h, 93 %; g) *t*BuOK, *t*BuOH, RT, 10 min; h) DBU, THF, RT, 3.5 h; i) $NaBH_4$, THF/H_2O (10:1 v/v), 0 °C, 1 h, (d.r. 1:1), 70 % yield over three steps; j) MOMCl, DIPEA, CH_2Cl_2, RT, 15 h, 90 %. DMAP = dimethylaminopyridine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, d.r. = diastereomeric ratio, DIPEA = diisopropylethylamine.

and an equatorial hydroxy group, was obtained. The stereochemistry could be observed by an *anti* axial–axial correlation in **11** ($J_{8H,9H} = 10.8$ Hz). Therefore, the usual stereochemical requirement for the Grob fragmentation was assembled, in which the oxygen lone pair is oriented anti-periplanar to the C(α)−C(β) bond and the C(γ)−OMs bond. The fragmentation precursor **12** was then prepared after several steps, that is, formation of an acetate, hydrogenolysis, and mesylation to introduce a leaving group, and removal of the acetyl group. After extensive investigation, we found that the deprotonation of **12** using *t*BuOK in *t*BuOH at room temperature smoothly afforded the crude aldehyde **13**, but with an unfavorable diastereoselectivity (d.r. ca. 1:5). Subsequent base-mediated equilibration, using DBU, improved the ratio to 1:1. Aldehyde **13** was then reduced with $NaBH_4$ to deliver the desired alcohol **14** after column chromatography, which was then protected as a MOM ether (**15**). Although the diastereoselectivity of the Grob fragmentation was modest, the undesired alcohol isomer could be recycled by oxidation, equilibration, and subsequent reduction.

Scheme 4 shows the five-step protocol for the conversion of **15** into ketone **18**. After selective removal of the TBS group (TBAF, 0 °C) with subsequent PDC oxidation and a standard Wittig reaction,[11] alkene **16** was formed in a good yield. With **16** in hand, we then focused on the oxidation of the furan into an α,β-butenolide. All of our attempts to oxidize **16** using a peroxy acid [12] only gave the undesired β,γ-butenolide or a decomposition residue. Gratifyingly, we found that the desired α,β-butenolide **17** was furnished after using singlet



Scheme 4. Synthesis of butenolide **18**. X-ray crystallographic structure of **18** shown (thermal ellipsoids at 30% probability). a) TBAF, THF, 0 °C, 2.5 h; b) PDC, 4-Å M.S., CH_2Cl_2, RT, 5 h, two steps: 78 %; c) PPh_3CH_3I, *n*BuLi, THF, −10→0 °C, 1 h, 88 %; d) 1) O_2, TPP (cat.), *hν*, CH_2Cl_2/MeOH, −78 °C, 40 min; 2) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 30 min (d.r. 4:1); e) PPTS, acetone/H_2O (20:1 v/v), reflux, 24 h, two steps: 45 %. TBAF = tetra-*n*-butylammonium fluoride, PDC = pyridinium dichromate, M.S. = molecular sieves, TPP = tetraphenylporphyrin, PPTS = pyridium *para*-toluenesulfonate.

oxygen,[13] and a subsequent Luche reduction.[14] The d.r. value was found to be 4:1 in favor of the desired stereochemistry as determined by NMR analysis. Although the two isomers were inseparable by column chromatography, isolation of the product could be achieved after the next step. Therefore, the ketal was unmasked to give the desired ketone **18**, which was isolated after careful column chromatography. The structure of **18** was confirmed by an X-ray crystallographic analysis.[15] Notably, there is an abundance of ground-state molecular dioxygen in nature, which, in the presence of a natural photosensitizer (such as porphyrin) and sunlight, can easily generate the more reactive singlet oxygen. Furthermore, the aqueous cellular environments in plants might facilitate the oxidation using singlet oxygen. In the literature, there have been many reports on biogenetic syntheses employing oxidation with singlet oxygen.[16] This step also lends its support to the proposed biosynthetic pathway.

The final stage of the synthesis of **1** is summarized in Scheme 5. Firstly, we needed to set a double bond between C1 and C2 to form the IMDA precursor **19**. After extensive investigations, we found that when **18** was exposed to an acidic version of Nicolaou's IBX reaction conditions[17] (PPTS, IBX) at 65 °C for 3.5 hours, the Diels–Alder cycloaddition adduct **20** was obtained as the only product in modest yield (42% yield based on 80% conversion of **18** through a tandem enone formation/IMDA cycloaddition sequence). We presumed that only the *endo*-product **20** was formed because of the more favorable *cis*-fused bicyclo[3.3.0] system and the steric hindrance of the methyl group. The result was also in accord with our preliminary computational studies.[18] After removing the MOM group with PPTS/NaI in refluxing 2-butanone, alcohol **21** was obtained in 75% yield. The stereochemistry of the IMDA adduct was confirmed by an X-ray crystallographic analysis on bromobenzoate **22** (Figure 2)[15]. Finally, oxidation of alcohol **21**, subsequent addition of MeLi, and then PDC oxidation afforded our synthetic target **1**. The ^{1}H and ^{13}C NMR spectroscopic and MS spectrometric data of synthetic **1** are in agreement with those reported in the literature.[3]

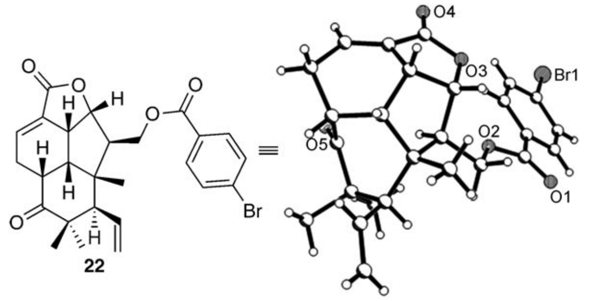


Figure 2. ORTEP view of **22** (thermal ellipsoids at 30% probability).

In summary, we have accomplished the first total synthesis of (±)-pallavicinolide A in a linear sequence of 20 steps from vinyl triflate **7** or 32 steps from 2-methyl-1,3-cyclohexanedione. Our synthetic route featured the following three biomimetic transformations as key steps: a) Grob fragmentation, b) singlet-oxygen oxidation, and c) intramolecular Diels–Alder cycloaddition. Efforts towards the syntheses of the other two related natural products, **2** and **3**, are currently underway in our laboratory.

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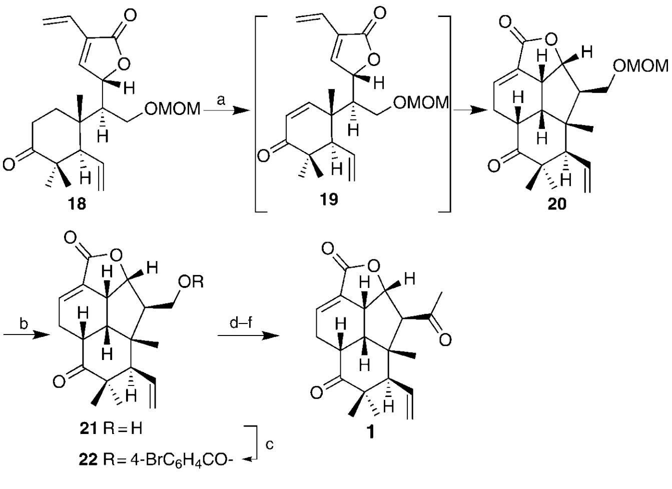

Scheme 5. Completion of the total synthesis of pallavicinolide A. a) IBX, *p*-TsOH, DMSO, 65 °C, 3.5 h, 42% (80% brsm); b) PPTS, NaI, 2-butanone, reflux, 12 h, 75%; c) 4-bromobenzoyl chloride, DMAP, pyridine, RT, 3 h, 94%, d) PDC, 4-Å M.S., CH_2Cl_2, RT, 1.5 h, 92%; e) CH_3Li, THF, −78 °C, 40 min, −10 °C, 40 min; f) PDC, 4 Å M.S., CH_2Cl_2, RT, 2 h, 50% yield over two steps. IBX = *o*-iodoxybenzoic acid, DMSO = dimethylsulfoxide, brsm = based on recovered starting material.

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[15] CCDC 714884 (**18**) and CCDC 714885 (**22**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[18] Initially, we chose **23** as a model to study the cycloaddition. From theory, this step could produce four possible isomers **1**, **1'**, **1''**, and **1'''**. **1''** and **1'''** cannot be formed because of the *trans*-fused bicyclic [3,3,0] system. The calculations (optimization and thermal correction at the HF/6-31G(d) level and single point calculation at the B3LYP/6-31G(d) level) showed that the *endo*-cycloaddition leading to **1** ($\Delta H = -123.9\ \mathrm{kJ\,mol^{-1}}$, $\Delta S = -79.0\ \mathrm{kJ\,mol^{-1}}$, $\Delta G = -100.4\ \mathrm{kJ\,mol^{-1}}$) is more favorable by $72.8\ \mathrm{kJ\,mol^{-1}}$ than that for the formation of **1'** ($\Delta H = -49.6\ \mathrm{kJ\,mol^{-1}}$, $\Delta S = -73.8\ \mathrm{kJ\,mol^{-1}}$, $\Delta G = -27.6\ \mathrm{kJ\,mol^{-1}}$). The activation energies computed for the transition states of *endo*-down **1** and *exo*-up **1'** are $79.0\ \mathrm{kJ\,mol^{-1}}$ and $152.1\ \mathrm{kJ\,mol^{-1}}$, respectively. It therefore appears that *endo*-down **1** should be the most favorable adduct from the IMDA cycloaddition.