Convergent Total Synthesis of (+)-Principinol D, a Rearranged Kaurane Diterpenoid

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Supporting Information Placeholder

ABSTRACT: The total synthesis of principinol D, a rearranged kaurane diterpenoid, is reported. This grayanane natural product is constructed via a convergent fragment coupling approach, wherein the central 7-membered ring is synthesized at a late stage. The bicyclo[3.2.1]octane fragment is accessed by a Ni-catalyzed α-vinylation reaction. Strategic reductions include a diastereoselective SmI_2-mediated ketone reduction with PhSH and a new protocol for selective ester reduction in the presence of ketones. The convergent strategy reported herein may be an entry point to the larger class of kaurane diterpenoids.

The grayanane diterpenoids – well known as the active components in "mad honey" due to inhibition of voltage-gated sodium ion channels[1] – have recently been identified as structurally novel allosteric inhibitors of carbonic anhydrases[2] and phosphatases.[3] Due to the ubiquity of various subtypes of these molecular targets, potential therapeutic development could span numerous different disease areas from neurological dysfunction to cancer.[4,5]

Grayananes are among a broader class of rearranged kauranes that also includes gibberellanes and 6,7-*seco*-kauranes (Figure 1A). The tetracyclic diterpenoid grayananes are formed by rearrangement of the kaurane 6,6-A/B ring system to a 5,7-ring system.[6] The kauranes are derived from rearrangement and cyclization of pimaranes via the beyeranes.[7,8] The first total synthesis of (±)-kaurene was completed in 1962 by Ireland and coworkers,[9] and in recent years several groups have completed elegant syntheses of members of this broader class employing a diverse array of synthetic strategies.[10] Nevertheless, much of the >1000 kaurane diterpenoids that have been isolated remain inaccessible by previously reported synthetic approaches.

Synthetic efforts towards the grayananes have been especially limited[11] despite their compelling biological activities.[12] To address the stereochemical complexities of these compounds, linear cyclization strategies have been employed. We speculated that a convergent retrosynthetic strategy, which isolates the two main constellations of stereocenters, would yield a laboratory route that could enable synthesis of grayanane analogs. Herein, we report the first total synthesis of the grayanane principinol D (**1**).

Similar to other grayanane diterpenoids, the principinols possess a highly oxidized tetracyclic framework, including a bicyclo[3.2.1]octane ring system.[13] As can be seen in Figure 1B, principinol D (**1**) has four stereocenters proximal to the left-most 5-membered ring that are separated spatially from an additional five stereocenters that decorate the bicyclo[3.2.1]octane ring system. In order to provide access to structurally diverse analogs, we designed a convergent strategy wherein two fragments would be joined to assemble the core skeleton and simultaneously merge

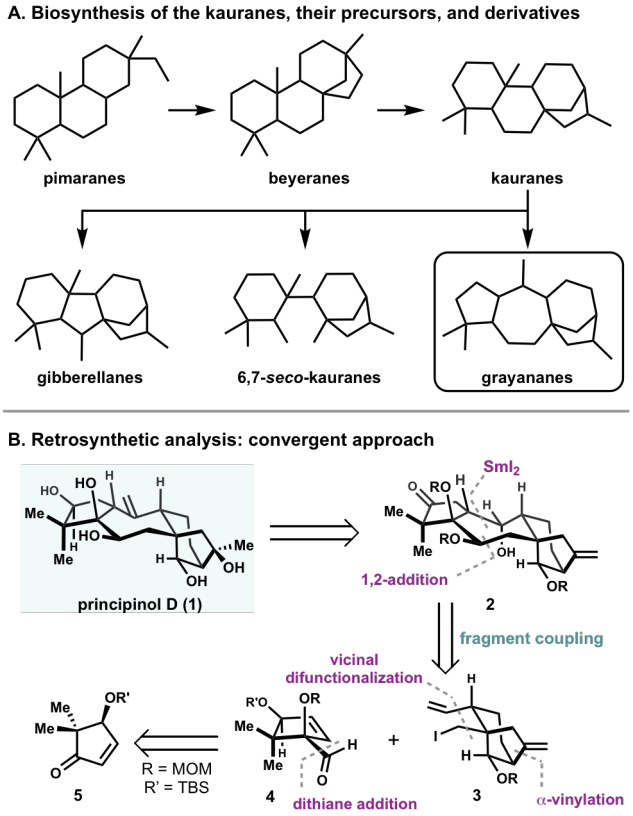
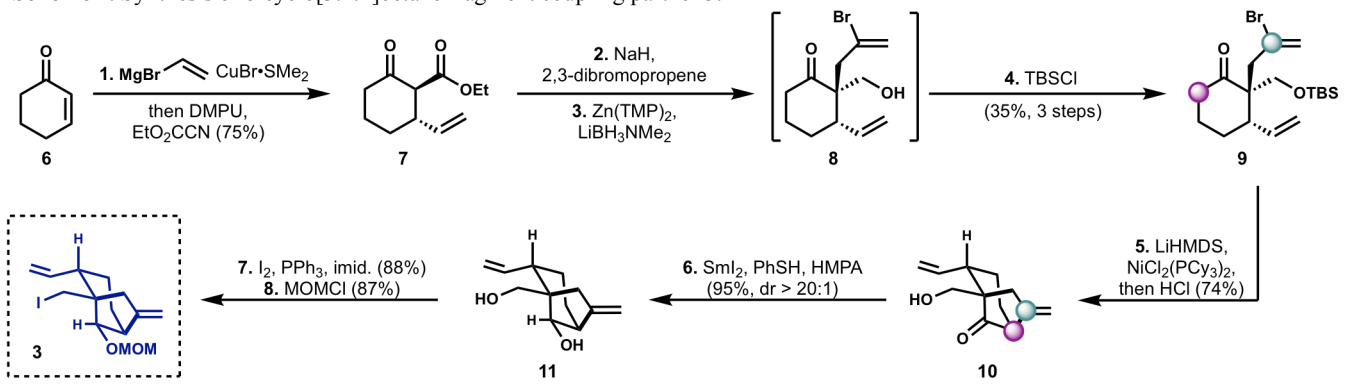


Figure 1. A. Precursors and derivatives of the kaurane diterpenes. B. Retrosynthetic analysis of principinol D (**1**).

the two constellations of stereocenters. This topological simplification to mark external rings for preservation differs significantly from prior work in the grayanane class, but is a powerful strategy in diterpenoid synthesis.[14]

We planned to utilize two robust C–C bond-forming reactions to merge the fragments, as this would maximize success for creating derivatives for SAR investigations: fragment union via a 1,2-addition reaction between a cyclopentyl fragment (**4**) and a bicyclo[3.2.1]octane fragment (**3**), and subsequent reductive cyclization using SmI_2. Dissection of the bicyclic fragment by an exendo bond using a Ni-catalyzed α-vinylation reaction would reveal a 6-membered ring that could be obtained by vicinal difunctionalization of cyclohexenone. Compound **4** was readily obtained from the known compound **5**[15] by dithiane addition, MOM protection, and dithiane deprotection (not depicted, see Supporting Information for details).

Scheme 1. Synthesis of bicyclo[3.2.1]octane fragment coupling partner **3**.[a]



[a](1) $CH_2CHMgBr$ (1.1 equiv), $CuBr{\cdot}SMe_2$ (0.1 equiv), DMPU (3.5 equiv), EtO_2CCN (1.1 equiv), THF (0.6 M), –50 → –72 → 23 °C, 6 h, 75%; (2) NaH (1.3 equiv), 2,3-dibromopropene (1.2 equiv), DMF (0.4 M), 0 → 23 °C, 13 h; (3) $Zn(TMP)_2$ (1.1 equiv), $LiBH_3NMe_2$ (1.0 equiv) THF (0.1 M), 0 → 23 °C, 1 h; (4) TBSCl (5.1 equiv), imid. (10.0 equiv), DMAP (0.3 equiv), DMF (0.1 M), 40 °C, 16 h, 35% (3 steps); (5) LiHMDS (2.0 equiv), $NiCl_2(PCy_3)_2$ (0.3 equiv), THF (0.2 M), –40 → 50 °C, 4 h, then 6 N HCl, 74%; (6) SmI_2 (3.0 equiv), PhSH (6.0 equiv), HMPA (10.0 equiv), THF (0.1 M), 0 °C, 1 h, 95%, >20:1 dr; (7) I_2 (1.5 equiv), PPh_3 (2.0 equiv), imid. (4.0 equiv), C_6H_6/MeCN/CH_2Cl_2, (4:1:1, 0.2 M), 0 → 23 °C, 90 h, 88%; (8) MOMCl (5.0 equiv), *i*-Pr_2NEt (5.0 equiv), CH_2Cl_2 (0.2 M), 0 → 23 °C, 72 h, 87%.

The synthesis of bicyclo[3.2.1]octane fragment **3** began with a vicinal difunctionalization of cyclohexenone with vinylmagnesium bromide in the presence of DMPU and catalytic $CuBr{\bullet}SMe_2$, followed by trapping with Mander's reagent.[16,17] β-Ketoester **7** underwent allylation with 2,3-dibromopropene. It was hoped that reduction of the ester could occur in the presence of the ketone in order to eliminate unnecessary redox fluctuations.[18] Common protocols that protect the ketone in situ via nucleophilic addition with metal amides[19] or phosphines[20] failed. Likewise, initial efforts masking the ketone as an enolate (LiHMDS, KHMDS, NaHMDS, or LDA) and treatment with a reductant ($LiAlH_4$, DIBAL-H, AlH_3, $LiBH_4$, or $LiEt_3BH$) led to base-mediated decomposition.[21] More mild and selective conditions were identified, wherein an enolate formed by deprotonation with the weaker base $Zn(TMP)_2$ underwent reduction with commercially available $LiBH_3NMe_2$[22] to form the base-sensitive keto-alcohol **8**. It is our expectation that this procedure will find additional application in the selective reduction of esters in the presence of enolizable carbonyl compounds, especially in the case of base-sensitive substrates. Protection of the resultant primary alcohol as the TBS ether provided the vinylation precursor **9** in 35% yield as a single diastereomer over 3 steps.

In order to form the bicycle **10** from the halide **9**, a variety of α-vinylation substrates and conditions were investigated. We found that the analogous β-ketoester (not depicted, the product of step 2) was not a viable substrate for the vinylation reaction. This may be due to the preference for the ester-containing compound to adopt the chair conformation wherein the ester is axial and the allyl group is equatorial, thus disfavoring the formation of the C-vinylation product, which is only accessible for the conformation wherein the allyl group is axial. We hypothesized that replacing the ester with a larger substituent would predispose the intermediate to adopt the necessary chair conformer in which the allyl substituent is axial, and thus lead to higher degrees of C-vinylation—this is indeed what we observed. Vinylation was ultimately performed using $NiCl_2(PCy_3)_2$ as a pre-catalyst and LiHMDS as base. These conditions proved to be more successful than either Pd-catalyzed conditions,[23] wherein cross-coupling can be problematic on such 1,1-disubstituted alkenes, or Ni-catalyzed conditions employing NHC ligands as recently reported by Helquist.[24]

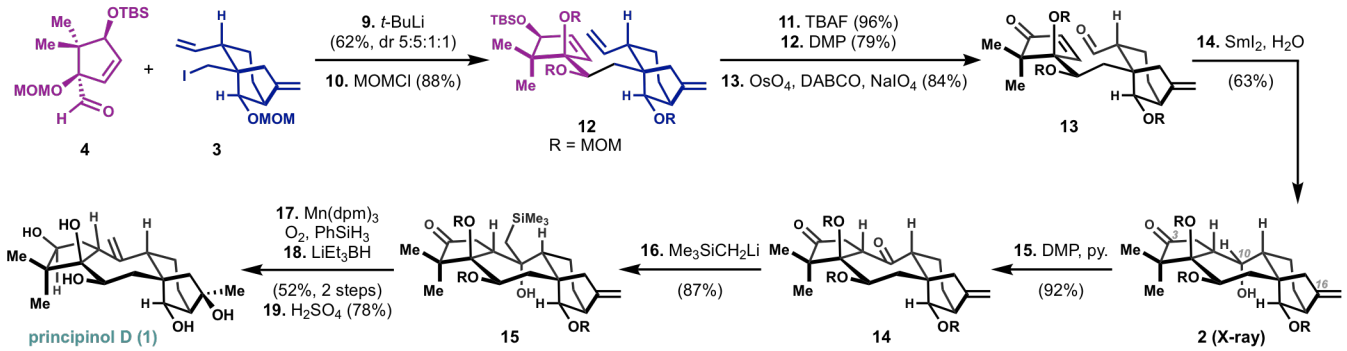
Following deprotection of the TBS-protected keto-alcohol, we required a diastereoselective reduction of ketone **10**. Unfortunately, reduction with boron or aluminum hydrides ($NaBH_4$, $Et_2BOMe/NaBH_4$, $NaBH_4/CeCl_3$, DIBAL, $Al(O\text{-}i\text{-}Pr)_3$) produced predominantly the undesired diastereomer. With use of SmI_2 in the presence of H_2O the product was still disfavored (dr = 1:2). Addition of HMPA and PhSH,[25] which may act as an H-atom donor,[26] provided the desired product in an excellent yield (95%, >20:1 dr). The use of HMPA was required for the reaction to proceed to full conversion, presumably because it increases the reduction potential of the samarium complex.[27,28] After the development of this protocol, it was successfully employed in the context of a different natural product synthesis and found to be similarly effective for the reduction of 1,3-diketones.[6] These modified conditions of classic SmI_2-mediated thermodynamic reduction may find additional utility in multistep synthesis.

Conversion of the primary alcohol in the presence of a secondary alcohol to the primary alkyl iodide occurred smoothly by the Appel reaction using a trisolvent system of C_6H_6/MeCN/CH_2Cl_2 in a ratio of 4:1:1. It is noteworthy that this trisolvent system proved to be uniquely effective for this transformation: experiments with a single solvent or combinations thereof resulted in prohibitively low yields. After MOM protection of the remaining secondary alcohol, the bicycle **3** necessary for fragment coupling was obtained.

To link the two fragments, the racemic bicyclo[3.2.1]octane **3** was treated with *tert*-butyllithium, followed by addition of enantioenriched cyclopentyl aldehyde **4** (er = 93:7), which provided the adduct as a separable mixture of diastereomers in 5:5:1:1 dr with a combined yield of 62%. Proceeding forward with the single desired diastereomer that was formed in 26% yield, protection of the secondary alcohol with MOMCl formed **12**; due to the steric hindrance at this center, introduction of other protecting groups such as TBS and TES was not feasible. The allylic silyl ether could be converted to an enone, and selective oxidative cleavage of the monosubstituted alkene in the presence of the 1,1-disubstituted alkene afforded enone-aldehyde **13**. To obtain the observed selectivity, DABCO was a key additive, whereas NMO, 2,6-lutidine, methanesulfonamide, and various two-step procedures were less effective.[29]

At this stage, closure of the seven-membered ring using SmI_2 was attempted.[30, 31] After extensive optimization, it was found that treatment of enone-aldehyde **13** with SmI_2 in the presence of water provided the desired tetracycle **2** in 63% yield as a single diastereomer. The structure and stereochemistry of this compound were determined by NOESY NMR and eventually confirmed by X-ray crystallography.

Scheme 2. Total synthesis of principinol D (**1**) via fragment coupling and reductive cyclization[a]



[a]Reagents and conditions: (9) *t*-BuLi (2.0 equiv), pentane:Et_2O (3:2, 0.1 M), –70 → 0 °C, 2.5 h, 62%; (10) MOMCl (10 equiv), DMAP (2.2 equiv), *i*-Pr_2NEt (15 equiv), $(CH_2Cl)_2$ (0.2 M), 80 °C, 17 h, 88%; (11) TBAF (5.0 equiv), THF (0.1 M), 23 °C, 3 h, 96%; (12) DMP (5.0 equiv), CH_2Cl_2 (0.1 M), 23 °C, 30 h, 79%; (13) OsO_4 (0.1 equiv), DABCO (3.0 equiv), $NaIO_4$ (3.0 equiv), THF/H_2O (2:1, 0.01 M), 0 °C, 15 h, 84%; (14) SmI_2 (25 equiv), H_2O (2.6 equiv), THF (0.01 M), –72 → 0 °C, 2.5 h, 63%; (15) DMP (5.0 equiv), pyridine:CH_2Cl_2 (1:2, 0.07 M), 23 °C, 20 h, 92%; (16) Me_3SiCH_2Li (10 equiv), THF (0.01 M), 0 °C, 0.3 h, 87%; (17) $Mn(dpm)_3$ (0.15 equiv), $PhSiH_3$ (2.2 equiv), O_2, EtOH (0.02 M), 23 °C, 1.5 h; (18) $LiEt_3BH$ (14 equiv), THF (0.01 M), 0 → 65 °C, 16 h, 52% over 2 steps; (19) 2 M H_2SO_4:1,4-dioxane (1:2, 0.02 M), 23 °C, 5 d.

After completion of the synthesis of the carbocyclic core structure **2**, significant challenges stood ahead: installation of the secondary alcohol at C3, alkene at C10, and tertiary alcohol at C16. Several sequences of events were investigated and it was found that intermediate **14**, prepared by oxidation of **2** using Dess-Martin periodinane buffered with pyridine, was a viable substrate to navigate chemoselectivity challenges. A selective olefination of the ketone on the seven-membered ring was attempted in the presence of the five-membered ring ketone. Standard olefination conditions (e.g. Wittig, Tebbe, Petasis, Nysted, etc.) were unable to form the desired exocyclic olefin. However, it was found that treatment with Me_3SiCH_2Li was efficient in producing Peterson adduct **15**.[32] Thus, the three sites (C3, C10, C16) were differentiated in a synthetically productive way.

Mukaiyama hydration of the exocyclic olefin with $Mn(dpm)_3$, $PhSiH_3$, and O_2 installed the tertiary alcohol at C16. Reduction of cyclopentyl ketone **15** at C3 produced predominantly the undesired α-alcohol under most conditions that were attempted (e.g. DIBAL, LAH, $NaBH_4$, $NaBH_4$, $CeCl_3$•$7H_2O$, Na^0, $LiBH_4$, $Zn(BH_4)_2$, SmI_2, etc.). Reaction with $LiEt_3BH$ resulted in the exclusive formation of the desired alcohol at C3. Upon heating, concomitant elimination of the Peterson adduct released the methylidene at C10, providing the product as one diastereomer in 52% yield over 2 steps. Global MOM deprotection occurred smoothly using H_2SO_4 in 1,4-dioxane, furnishing principinol D (**1**). The NMR spectral data was identical to those reported.[13]

The work described herein represents the first total synthesis of principinol D (**1**) by a 19-step approach. This synthesis features a convergent fragment coupling strategy, and a SmI_2-mediated reductive cyclization to form the central seven-membered ring of the grayanane skeleton. In addition, α-vinylation conditions are reported to form the bicyclo[3.2.1]octane, as well as a diastereoselective SmI_2-mediated reduction of a bicyclic ketone. This synthetic route is expected to lead to laboratory access to a variety of derivatives, including ones which selectively act on phosphatases, carbonic anhydrases, or voltage-gated sodium ion channels, all known targets of the grayananes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

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Notes

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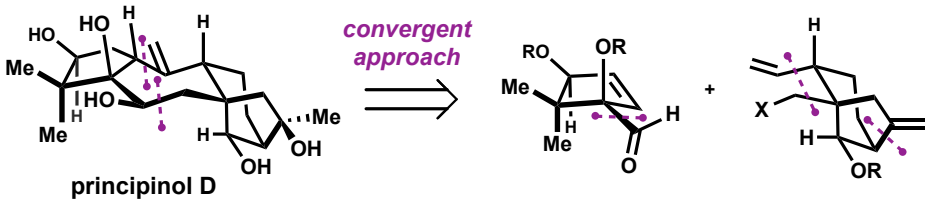
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