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First total synthesis of (+)-pentandranoic acid A

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ABSTRACT

The first total synthesis of (+)-pentandranoic acid A (**1**) was accomplished in 14 steps, starting from alcohol **3**. Our synthesis features several key transformations, such as an ozonolysis-aldol cyclization-dehydration ring contraction sequence and a selective 1,4-diol oxidation, and provides an efficient synthetic route to this rare clerodane diterpenoid.

The isolation of (+)-pentandranoic acid A (**1**), a structurally novel diterpenoid from the leaf extracts of the *Callicarpa pentandra*, was first reported by Goh et al. in 2000.[1] Plants of the genus *Callicarpa* are known to have medicinal properties for the treatment of rheumatism, stomach disorders, and intestinal troubles.[2] The Malaysian species *Callicarpa pentandra* Roxb. (Verbenaceae), as a liquid, is used for the treatment of the common cold in traditional Malaysian folk medicine.[3] On the basis of a combination of NMR and mass spectrometry studies, the structure of (+)-pentandranoic acid A was proposed as **1** with the relative and absolute stereochemistry shown (Fig. 1).[1]

The natural product is a *trans*-clerodane diterpenoid (**2**) with a rare contraction of ring A. In addition to the novel scaffold, (+)-pentandranoic acid A (**1**) features four contiguous chiral centers, two of which are quaternary, as well as several sensitive functionalities, which can pose additional synthetic challenges. Its intriguing structure and important biological activities make (+)-pentandranoic acid A (**1**) an attractive target. The Piers laboratory previously developed a general synthetic route to the enantiomerically pure *cis*- and *trans*-clerodane family of diterpenoids via annulation sequences using bifunctional trialkylstannylcopper reagents.[4] Although this strategy was successfully applied to clerodanes with a 6,6-fused decalin framework (**2**), its utility in the construction of a 5,6-fused hydrindane has yet to be demonstrated. In this Letter, we wish to report the application of this methodology to the hydrindane scaffold and the first total synthesis of (+)-pentandranoic acid A (**1**).

The presence of sensitive functional groups, such as an aldehyde and an enone in (+)-pentandranoic acid A (**1**), required careful planning at the onset of our campaign. For example, the C-2 formyl group can easily be oxidized or reduced under a variety of conditions and would limit the choice of synthetic transformations if introduced early. Furthermore, the unique enone moiety, a potential Michael acceptor, is a cause for greater concern (vide infra). In addition to its perceived reactivity towards nucleophiles, the alkene can readily isomerize to a thermodynamically more favorable isomer (between C-13 and C-14) in the presence of a base. Based on these considerations, it was decided that the enone functionality should be unveiled late in the synthesis.

It was envisioned that the enone precursor, allylic alcohol **A**, could be prepared from addition of an appropriately functionalized vinyl anion, such as **B**, to aldehyde **C** (Scheme 1). The C-2 formyl group in (+)-pentandranoic acid A (**1**) was masked as a protected alcohol at this stage which could be revealed at the end of the synthesis. Construction of the *trans*-fused hydrindane framework was envisioned to arise from ring contraction of a suitably decorated decalin such as **D**. A series of manipulations, starting with oxidative cleavage of the double bond between C-3 and C-4, followed by an intramolecular aldol cyclization and dehydration were planned for this key transformation.

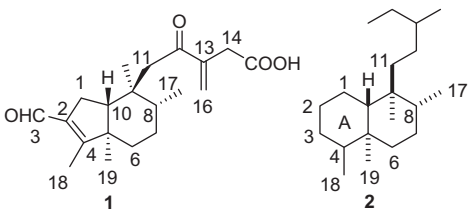

Figure 1. (+)-Pentandranoic acid A (**1**) and general carbon skeleton of *trans*-clerodane diterpenoids (**2**).

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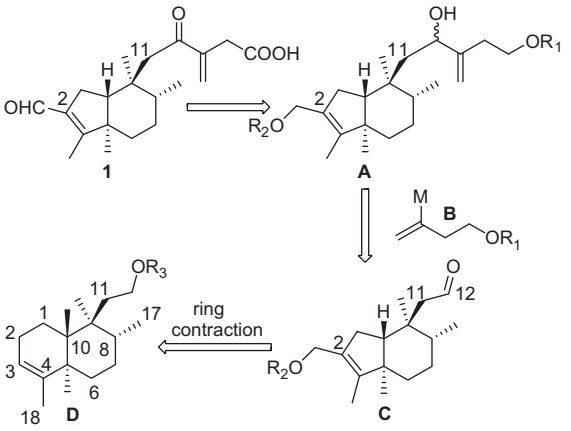
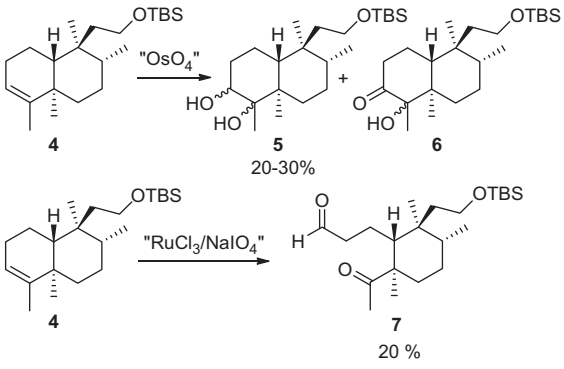


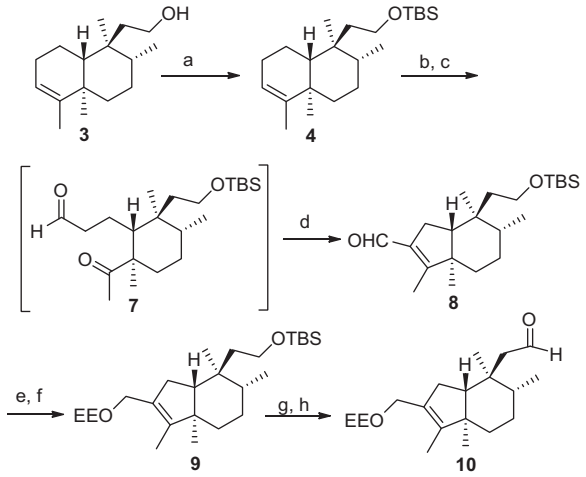
Scheme 1. Retrosynthetic analysis of (+)-pentandranoic acid A.

The synthesis of (+)-pentandranoic acid A (**1**) began with the known alcohol **3**, an advanced intermediate used in the total synthesis of (−)-kolavenol and (−)-agelasine B[4a] (Scheme 3). Protection of alcohol **3** with TBSCl afforded the corresponding silyl ether **4** in quantitative yield. Next, oxidation of the alkene was evaluated. Treatment of alkene **4** with OsO_4 under a variety of conditions gave the desired diol **5** in low yield (20–30%), along with decomposition of the starting material. In some cases, hydroxyl ketone **6** was isolated as a minor product (Scheme 2). The formation of ketone byproduct was observed in the dihydroxylation of sterically hindered olefins.[5] Direct cleavage of alkene **4** using $RuCl_3$/$NaIO_4$[6] was also attempted. Unfortunately, the desired ketoaldehyde **7** was obtained in low yield (20%) together with **6** as a byproduct. These initial results highlighted the challenges associated with our plan to use the alkene as a synthetic handle for ring contraction.

Ozonolysis was reported as an effective protocol for alkenes oxidation in congested systems.[7] To our delight, under the conditions reported by Ward,[8] the desired ketoaldehyde **7** was obtained efficiently (Scheme 3). The unstable intermediate was immediately subjected to an aldol condensation/dehydration sequence following conditions reported by Corey and Tanabe to give aldehyde **8** in 52% overall yield.[9] With the hydrindane core in hand, attaching the enone side chain became the next focus. Towards this end, the C-2 aldehyde was first reduced with DIBAL and the resulting allylic alcohol was protected with an ethoxyethyl ether to afford **9** as an inconsequential 1:1 mixture of diastereomers which were inseparable by column chromatography.[10] The judicious choice of the ethoxyethyl ether as a C-3 hydroxyl protecting group was based on considerations that it could be removed with mild acids, conditions most likely to be compatible with the sensitive enone moiety



Scheme 2. Initial ring contraction attempts.

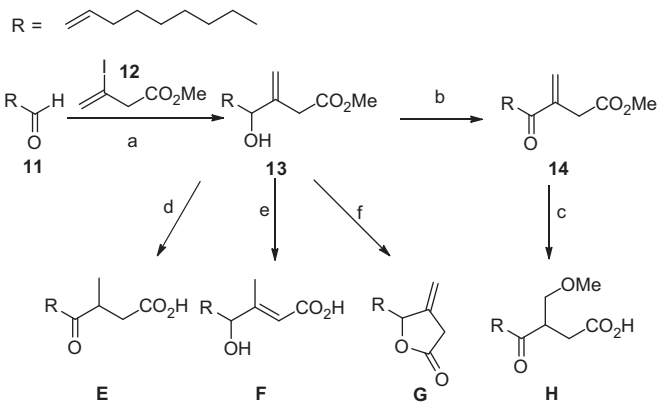


Scheme 3. Reagents and conditions: (a) TBSCl, imidazole, DCM, 99%; (b) O_3, Sudan II, −78 °C, DCM/MeOH (9:1); (c) pyridine, Me_2S, 0 °C; (d) neutral alumina, 4A molecular sieves, 52%; (e) DIBAL, −78 °C, ether, 92%; (f) vinyl ethyl ether, PPTS, DCM, 99%; (g) TBAF, THF, 98%; (h) Dess–Martin periodinane, DCM, 95%.

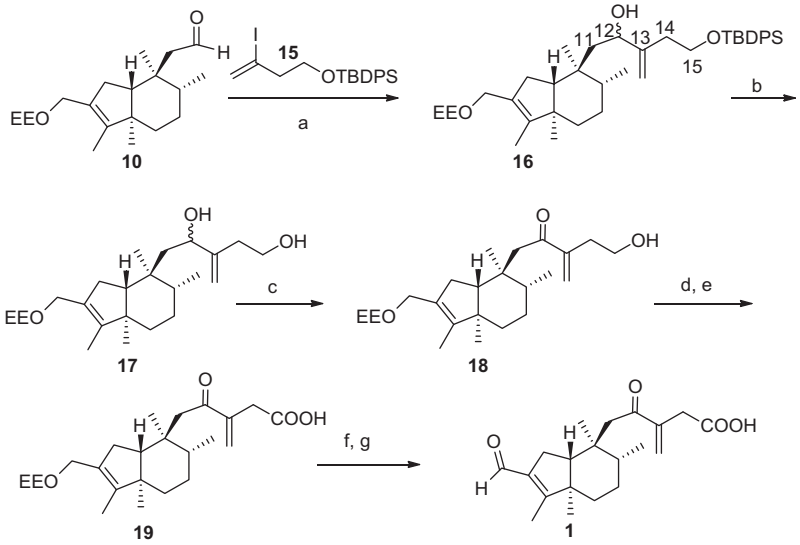
on the side chain. The requisite C-12 aldehyde **10** was obtained via a two-step procedure, first removal of the TBS protecting group with TBAF, followed by subsequent oxidation using Dess–Martin periodinane.[11]

Originally, we planned to attach the side chain via a $NiCl_2$/$CrCl_2$ mediated Nozaki–Kishi reaction. (Scheme 4).[12] Vinyl iodide **12** with a pendant methyl ester, which could be converted to the desired acid by hydrolysis, was deemed to be a suitable coupling partner. The feasibility of this strategy was tested with a model compound **11**. The coupling reaction proceeded reasonably well and gave alcohol **13** in moderate yield (51%), which was oxidized to enone **14** in 95% yield. Unfortunately, attempts to hydrolyze the methyl ester of either **13** or **14** under a variety of conditions failed, due to the various decomposition pathways shown in Scheme 4. For example, saponification of **14** in the presence of a base gave the Michael adduct (**H**) as predicted. Although this can be avoided with alcohol **13**, byproducts stemming from isomerization (**E**), alkene migration (**F**) and lactonization (**G**) became predominate. Furthermore, vinyl iodides with more labile acid protecting groups such as TBS or OCH_2CCl_3, failed to participate in the Nozaki–Kishi coupling. These observations showcased the delicate nature of this particular side chain.

Since an ester was not a viable precursor for the desired acid in this case, other alternatives were explored. Vinyl iodide **15** with a



Scheme 4. Reagents and conditions: (a) $NiCl_2$, $CrCl_2$, DMF, 51%; (b) TPAP, NMO, DCM, 95%; (c) K_2CO_3, MeOH; (d) $Ba(OH)_2$; MeOH; (e) NaSMe, DMPU; (f) BBr_3, DCM.



Scheme 5. Reagents and conditions: (a) *t*-BuLi, **15**, −78 to −40 °C, then **10**, ether, 94%; (b) TBAF, THF, 99%; (c) MnO_2, ether, 65%; (d) Dess–Martin periodinane, DCM, 92%; (e) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, 2-methyl-2-butene, 90%; (f) PPTS, MeOH, 95%; (g) Dess–Martin periodinane, DCM, 99%.

TBDPS protected homoallylic alcohol eventually served as the appropriate precursor to the side chain of (+)-pentandranoic acid A (**1**) (Scheme 5). Addition of the vinyl lithium reagent derived from metal-halide exchange between **15** and *tert*-butyl lithium gave **16** as a 1:1 mixture of diastereomers at C-12 in 94% yield.[13] Although alcohol **16** was produced in a non-selective manner, all isomers were used in the synthesis of (+)-pentandranoic acid A (**1**) as the newly generated chiral center was removed in the subsequent oxidation step.

At this stage, the remaining transformations to complete the side chain included oxidizing the secondary alcohol at C-12 as well as deprotecting and converting the primary alcohol at C-15 to the corresponding acid. Again, these seemingly trivial transformations turned out be quite challenging in the context of our target. Fist, the order of these two events was critical for success. It was determined that the C-12 hydroxyl group should be oxidized first to circumvent formation of the five-membered ring lactone byproduct such as G during the conversion of the C-15 alcohol to the corresponding acid. Thus, an effective protocol for converting **16** to the hydroxyl enone **18** was needed. The most straight forward way to accomplish this would be oxidation followed by silyl deprotection. Although the oxidation step occurred in high yield**,** removal of the TBDPS protecting group under standard conditions (TBAF, HF/pyridine, bases) led to decomposition, likely due to the sensitivity of the enone moiety.

Our backup strategy was to remove the silyl protecting group first and then selectively oxidize the secondary C-12 hydroxyl group in the presence of the primary C-15 hydroxyl group (Scheme 5). It is recognized that the C-12 hydroxyl group is an allylic alcohol and can be oxidized preferentially with a unique set of oxidants.[14] In practice, alcohol **16** was first treated with TBAF to give **17** in quantitative yield. To our delight, stirring a solution of diol **17** in ether with MnO_2 at room temperature overnight afforded the desired hydroxyl enone **18** in 65% yield.[15] It was also interesting to note that other oxidants such as, TPAP/NMO, PDC and Dess–Martin periodinane, oxidized the primary hydroxyl group (C-15) first which inevitably led to the formation of lactol and lactone as major byproducts. With **18** in hand, the remaining steps of the synthesis proceeded smoothly. Oxidation of the primary alcohol to the carboxylic acid was accomplished by sequential treatment with Dess–Martin periodinane and $NaClO_2$[16] to produce acid **19** in 83% yield over two steps. The ethoxyethyl ether protecting group was removed with a mild acid (PPTS)[10] and the resulting alcohol was oxidized to the aldehyde using Dess–Martin periodinane to afford (+)-pentandranoic acid A (**1**).

The ^1H NMR and ^{13}C NMR spectra of the synthetic (+)-pentandranoic acid A (**1**) were identical with those of the natural product. Furthermore, the optical rotation value of our synthetic material ($[\alpha]_D^{21}$ +47.2, c 0.5, $CHCl_3$) agreed very well with the reported value of the natural substance ($[\alpha]_D$ +44.9, c 0.86, $CHCl_3$). Thus, our synthesis has confirmed the correct assignment of both the relative and absolute configuration of (+)-pentandranoic acid A (**1**).

In summary, the first total synthesis of (+)-pentandranoic acid A (**1**) was accomplished in 14 steps, starting from alcohol **3**. This synthetic procedure, which employs an ozonolysis-aldol cyclization-dehydration ring contraction sequence and a selective 1,4-diol oxidation as key steps, offers a concise and efficient synthetic route to this rare clerodane diterpenoid.

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