Short, Divergent, and Enantioselective Total Synthesis of Bioactive ent-Pimaranes

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ABSTRACT: We present the first total synthesis of eight ent-pimaranes via a short and enantioselective route (11–16 steps). Key features of the divergent synthesis are a Sharpless asymmetric dihydroxylation, a Brønsted acid catalyzed cationic bicyclization, and a mild Rh-catalyzed arene hydrogenation for rapid access to a late synthetic branching point. From there on, selective functional group manipulations enable the synthesis of ent-pimaranes bearing different modifications in the A- and C-rings.

Pimarane natural products represent a large class of diterpenoids sharing a common 6,6,6-carbocyclic scaffold and exhibit diverse bioactivities including anti-inflammatory and anticancer properties (e.g., natural products 1–5, Scheme 1A). To date, few total syntheses of pimaranes and the closely related isopimaranes (C13 epimer) have been reported, most of which rely either on condensation reactions (e.g., Robinson annulations) or on Diels–Alder cycloadditions to provide the requisite tricyclic architecture. In 1975, van Tamelen disclosed a hallmark synthesis of the isopimarane araucarol (8) involving a unique head-to-tail/tail-to-head polylene cyclization of racemic carbonate 6 (Scheme 1B). However, the reaction provided tricycle 7 as a mixture of double bond isomers in just 7% yield. To the best of our knowledge, there are only two other total syntheses of pimaranes—one of them by our group—which employ polylene cyclizations to selectively generate the underlying trans-decalin motif. As part of our continuing interest in developing cationic cyclization reactions, we sought to devise a scalable and concise synthetic entry point into the ent-pimarane natural product family. Within this study, we focused on previously inaccessible ent-pimaranes bearing diverse modifications in the A- and C-rings.

From a structural perspective, the targeted ent-pimaranes feature five to seven stereocenters, two of which are quaternary, and further differ by the oxidation pattern around the eastern and western periphery, rendering adversity-oriented total synthesis approach highly attractive (Scheme 1C). Retrosynthetically, we envisioned generation of the A- and C-ring oxidation patterns in a few steps via selective functionalization of advanced key intermediate 9. For the installation of the C13 quaternary center of 9, we identified a substrate-controlled α-alkylation/acylation sequence as the most versatile and strategic bond disconnection. The resulting ketone 10 was anticipated to be accessed through a reductive dearomatization of the structurally simplified tricyclic anisole 11. Enantioselective construction of the requisite 6,6,6-carbocyclic scaffold 11 was envisioned in four steps from commercially available geranyl bromide (14) and 2-methyl anisole (13) involving Sharpless asymmetric dihydroxylation to set the stereochemistry at C3 and a cationic bicyclization of epoxide 12.

Our synthesis commenced with a nucleophilic substitution reaction employing geranyl bromide (14) and the respective benzyl lithium species of 2-methyl anisole (13) to furnish geranyl arene 15 in 80% yield (Scheme 2A). The use of sec-butyllithium along with a slow warm-up from –78 to –20 °C was found to be essential for efficient benzylic lithiation. Subsequent Sharpless asymmetric dihydroxylation employing commercial ligands such as (DHQ)2PHAL and (DHQ)2AQN gave excellent enantioselectivities (91% ee for (DHQ)2PHAL and 93% ee for (DHQ)2AQN). However, those reactions suffered from poor regioselectivity and were also plagued by exhaustive dihydroxylation, resulting in low isolated yields for the desired diol 17 (20–25%, see the Supporting Information). Ultimately, we resorted to the use of the “ent”-Corey–Noe–Lin ligand (16), a diastereomer of the more established Corey–Noe–Lin ligand, which has been shown to exhibit high regioselectivities for sterically less encumbered alkenes.

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Gratifyingly, the use of 16 increased the yield of diol 17 to 65–67% yield while maintaining excellent enantioselectivity (93% ee). The overoxidation was minimized by discontinuing the reaction shortly before complete consumption of alkene 15. Notably, 16 was recovered in 99% yield and was used for up to three cycles without any loss of regio- or enantioselectivity.

With diol 17 in hand, a selective one-pot mono-mesylation of the more accessible secondary alcohol followed by an intramolecular nucleophilic substitution in the presence of potassium carbonate and methanol furnished epoxide 12 in excellent yield (97%). Our screening of the key bicyclization commenced with established literature conditions for similar systems employing a variety of Lewis acids (i.e., SnCl₂, Et₂AlCl, EtAlCl₂, BF₃·Et₂O, Bi(OTf)₃, InBr₃, FeCl₃). Surprisingly, under these conditions, tricycle 11 only resulted in the formation of equimolar amounts of tricycle 11 and 19 (36–37% NMR yield). Based on this result, we set out to screen alternative Bronsted acids in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). Following careful optimization, methanesulfonic acid was found to efficiently catalyze the conversion of 12 to the desired bicyclization product 11 in 50–58% yield on a decagram scale. In addition, oxabicyclo[2.2.1]heptane 19 (0–7%) and tricycle 18 (10–12%) featuring an axially oriented secondary alcohol were isolated from this reaction. The relative stereochemistry of 11 and 18 was confirmed by single crystal X-ray analysis. After recrystallization from diethyl ether, tricycle 11 was obtained in enantiopure form (>99% ee). We then moved on to investigate reductive deamortization of the C-ring (Scheme 2B). Initial attempts to employ a Birch reduction protocol using a huge excess of lithium (>600 equiv)₁₀ resulted in poor yields (<20%) and left us with considerable safety concerns due to the handling of liquid ammonia at −40 °C, close to its boiling point. Notably, Birch reductions of electron-rich anisoles requiring protonation at a site bearing alkyl substituents have been reported as exceptionally challenging.¹³ Unfortunately, established methodologies such as a modification by Wilds, fourteen an electroreduction method developed by Baran, and as well as an ammonia-free Birch reduction by Koide failed to deliver the desired products in satisfactory yields. Therefore, we proceeded to investigate alternative reduction protocols. While hydrogenation of structurally related arenes typically requires harsh reaction conditions,²⁰,¹⁰,¹⁷ we found that exposure of 11 to Rh on alumina under a hydrogen atmosphere (12 bar) in isopropanol (65 °C) allowed for the formation of the corresponding cyclohexane under relatively mild conditions.¹⁸ After removal of isopropanol under reduced pressure, the inseparable mixture of diastereomeric alcohols was directly protected using tert-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in the presence of 2,6-lutidine. Several methods for selective methyl ether oxidation to the corresponding ketone 10 were examined (see the Supporting Information). Extensive investigations revealed a combination of calcium hypochlorite and acetic acid in acetone:water (9:1 v/v) as the ideal oxidation method to yield 10 in 72% NMR yield on a 24 μmol scale.¹⁹ Unexpectedly, large scale oxidation (18 mmol) suffered from stalling of the reaction after partial conversion. Therefore, unreacted starting material was recovered and resubjected to the reaction conditions. After three cycles, the ketone 10 was obtained in 56% yield over two steps. Deprotonation of 10 using lithium bis(trimethylsilyl)-amide (LiHMDS) at cryogenic temperatures (−55 to −38 °C) followed by addition of methyl iodide afforded α-methylated epimers 20 and 21 as an inconsequential 1:1 diastereomeric mixture in excellent combined yield (96%). Interestingly, the use of tetrahydrofuran as solvent was essential, as diethyl ether led to undesired double methylation through enolate equilibration (see the Supporting Information). Next, C-acylation of 20 and 21 was investigated via regioselective deprotonation and subsequent trapping of the enolate with Mander’s reagent. In accordance with Mander’s findings, competitive O-acylation was completely suppressed through the use of diethyl ether instead of tetrahydrofuran and strictly avoiding coordinating agents such as N,N,N′,N′-tetramethyl ethylenediamine (TMEDA).²⁰ Employing only a slight excess of Mander’s reagent and performing the acylation at −78 °C was found to be essential to prevent the emergence of side products.
products via cyanohydrin formation. Under optimized conditions, we obtained the β-ketoester 22 in 76% yield.

Formation of the potassium enolate of 22 through deprotonation with potassium bis(trimethylsilyl)amide (KHMDS) in tetrahydrofuran (0 °C, 100 min) followed by trapping with phenyl triflimide (PhNTf₂) at −78 °C furnished triflate 23 in 86% yield. Subsequent reduction of 23 was best performed employing SPhos Pd G3 catalyst (5 mol %), formic acid, and triethylamine to provide the key intermediate 9 in 92% yield (10-step LLS).

With ample amounts of key intermediate 9 in hand, we proceeded to investigate the anticipated diversifications of the
A- and C-rings (Scheme 3). With regard to the A-ring, we performed a silyl protection of 9 using aqueous hydrofluoric acid, directly followed by oxidation with Dess–Martin periodinane (DMP) to yield ketone 24 in 97% over two steps. For the conversion of 24 to the α-hydroxylated ketone 25, we opted for a robust Rubottom oxidation protocol that allowed us to obtain 25 as a single diastereomer.22 Reduction of α-hydroxy ketone 25 with sodium borohydride provided trans-diol 26 as the main product (66%) along with cis-diol 28 (19%) and, unexpectedly, also cis-diol 27 (3%). We hypothesize that isomerization of 25 via its enediol tautomer and subsequent reduction of the regioisomeric α-hydroxy ketone explains the formation of cis-diol 27. Ester hydrolysis of 26 and 28 with aqueous sodium hydroxide was high yielding (97%) for both substrates and afforded 2,3-dihydroxy-16-nor-ent-pimar-8(14)-en-15-oic acid (DHPA, 29) (17 mg) and norflickinflimiod A (2) (5.6 mg).23

Having prepared natural products bearing modifications in the A-ring, we turned our attention toward diversification of the C-ring. According to the biosynthetic hypothesis,24 the γ-lactone of norflickinflimiod C (5) is formed via a sequence that involves epoxidation of the C8/C14 alkene and intramolecular cyclization. In practice, exposure of 9 to meta-chloroperbenzoic acid (m-CPBA) followed by the addition of para-toluene sulfonic acid (p-TsOH) and desilylation using aqueous hydrofluoric acid directly afforded norflickinflimiod C (5) in 77% yield (57 mg). Single crystal X-ray analysis validated the depicted relative stereochemistry. Double acetylation with acetic anhydride and catalytic amounts of 4-(dimethylamino)-pyridine (DMAP) gave 3,14-diacetoxy-16-nor-ent-pimar-15α,8-olide (DAP, 30) in 73% yield (15 mg). Sequential desilylation with tetrabutylammonium fluoride (TBAF) and ester hydrolysis of 9 using sodium hydroxide furnished the 2-hydroxy-16-nor-ent-pimar-8(14)-en-15-oic acid (HPA, 1) in excellent yield (96%, 17 mg). For the conversion of the ester at C15 into an α-hydroxy ketone, we turned to the Taber modification of the Fehr procedure.25 First, ester 9 was treated with lithium diisopropylamide (LDA) and methyl lithium and the resulting lithium enolate was trapped with triethylsilyl chloride (TESCl). The crude silyl enol ether was treated with m-CPBA at low temperatures (−30 °C) to prevent oxidation of the C8/C14 alkene. Excess m-CPBA was removed by addition of anylene, and silyl deprotection with aqueous hydrofluoric acid yielded lonesphyllobid B (3) (50 mg). Reduction of lonesphyllobid B (3) with sodium borohydride gave 3,15,16-trihydroxy-ent-pimar-8(14)-ene (THP, 4) (60%, 21 mg) and darutigenol (31) (29%, 9.9 mg). The spectroscopic data for the eight synthetic natural products matched the literature reports; however, the sign of the optical rotation values for norflickinflimiod A (2) (αD20 = +65.1 vs αD20(literature) = −48.4), norflickinflimiod C (5) (αD20 = +3.4 vs αD20(literature) = −13.3), and lonesphyllobid B (3) (αD20 = +6.2 vs αD20(literature) = −9.93) was inverted. Validation of the absolute stereochemistry was finally possible by comparison of the ECD spectra with the literature and allowed us to confirm the configuration of all three natural products.

In summary, we have accomplished the first enantioselective total synthesis of eight ent-pimarane natural products in 11–16 steps (1.0–7.8% overall yield) from commercially available starting materials. The developed strategy enabled rapid access to diverse substitution patterns in the A-ring ((3R)-hydroxy, (2S,3S)-trans-diol, and (2S,3R)-cis-diol) and C-ring (γ-lactone, C15 carboxylic acid, α-hydroxy ketone, and C15/C16-diols). Salient features of our synthetic strategy encompass a scalable and robust four-step sequence allowing access to the tricyclic carbon scaffold through Sharpless asymmetric dihydroxylation in combination with a powerful Brønsted acid catalyzed bicyclization. A mild rhodium catalyzed arene hydrogenation served as an entry to the fully saturated 6,6,6-carbocyclic ring systems en route to a late synthetic branching point. Application of the key findings of this study may drive the development of scalable syntheses for other pimaranes and related diterpenoids and are currently underway in our laboratories.

## ASSOCIATED CONTENT

*Supporting Information*

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02843.

**Experimental details, spectroscopic data, and X-ray data (PDF)**

## Accession Codes

CCDC 2194515—2194517 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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**Notes**

The authors declare no competing financial interest.

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