Bifunctional Polyene Cyclizations: Synthetic Studies on Pimarane Natural Products

Julian M. Feilner,[a] Immanuel Plangger,[a] Klaus Wurst,[b] and Thomas Magauer*[a]

In memory of Prof. Klaus Hafner

Abstract: Polyene cyclizations generate molecular complexity from a linear polyene in a single step. While methods to initiate these cyclizations have been continuously expanded and improved over the years, the majority of polyene substrates are still limited to simple alkyl-substituted alkenes. In this study, we took advantage of the unique reactivity of higher-functionalized bifunctional alkenes. The realization of a polyene tetracyclization of a dual nucleophilic aryl enol ether involving a transannular endo-termination step enabled the total synthesis of the tricyclic diterpenoid pimara-15-en-3β,8α-diol. The highly flexible and modular route allowed for the preparation of a diverse library of cyclization precursors specifically designed for the total synthesis of the tetracyclic nor-diterpenoid norflickinflimiod C. The tetracyclization of three diversely substituted allenes enabled access to complex pentacyclic products and provided a detailed insight into the underlying reaction pathways.

Introduction

The cyclization of polyenes is one of the most fascinating chemical reactions found in nature. Enabled by terpene synthases (TS) molecular complexity is generated from a linear precursor in a single step. Owing to the variety of cyclization modes a wealth of terpene structures is available.[1] Pimaranes belong to the family of diterpenoids (C20) and share a tricyclic carbon skeleton that is biosynthetically derived from geranylgeranyl diphosphate (1) (Scheme 1 A). A type II terpene synthase initiates a bicyclization by protonation of a double bond followed by deprotonation of the cationic intermediate to provide copalyl diphosphate (2) (Scheme 1 A). Ionization of the allylic diphosphate group in 2 by a type I TS leads to a second cyclization thus forming the tricyclic ring system as found in 3.[2]

Synthetic chemists have mimicked polyene cyclizations with great success[3–5] and have demonstrated their efficiency in a large number of natural product syntheses.[6] For the initiation of the cyclizations, numerous methods have been developed and various functional groups were utilized to activate and terminate the cascade.[4,5] Somewhat surprisingly, modifications of the isoprene subunits are rare.[6] In seminal work by Johnson,[7] it was shown that monofunctional modifications can act as a cation stabilizing auxiliary and serve as a handle for late-stage modifications (Scheme 1 B).

As an example, diene 4 provided the trans-fused tricyclic 5 upon treatment with titanium(IV) chloride. The vinyl group served as a masked carbonyl group, which enabled access to the central lactone of neotripterifordin (6).[8] The cation-stabilizing properties of the fluorine atom in 7 facilitated a tetracyclization reaction in the presence of tin(IV) chloride. The fluorinated product 8 set the stage for the total synthesis of 4β-hydroxyandrosan-17-one (9).[9] For monofunctional modifications as found in 4 and 7, only the alkene participates in the polyene cyclization and the residue is not directly involved in the cyclization. For the synthesis of pimaranes 10 and 11, we envisioned the cyclization of the dual nucleophilic aryl enol ether 13.[10] For this system, the polyene was expected to first undergo a linear cascade cyclization followed by an intramolecular transannular termination of the aryl unit of the aryl enol ether. Hence, we consider the aryl enol ether to be a bifunctional modification of the isoprene pattern. The realization of a tetracyclization featuring a transannular endo-termination of such a bifunctional motif would enable divergent access to pimarane natural products 10 and 11. The nor-diterpenoid norflickinflimiod C (10) was first isolated from the orchid Flickingeria fimбриata in 2014 together with 11 other pimaranes. While 10 was only moderately biologically active, other members of the family exhibited potent anticancer and anti-inflammatory activities.[11]

Retrosynthetically, we envisioned to unmask the lactone motif within the tricyclic trans-fused carbon skeleton of 10.
upon oxidative scission of the bridging arene subunit of 12. The axial secondary alcohol at C-14 would be introduced by transformation of a hydroxy-surrogate (R) for example Tamao–Fleming oxidation of a dimethyl(phenyl)silyl group. From a total of seven stereocenters, six were envisioned to be generated from the tetracyclization of aryl enol ether 13. A pivotal transannular endo-termination step would install one of the two quaternary stereocenters of the natural product. Further C-O and C-C bond disconnections revealed geranyl bromide (14) as the starting point of the synthesis.

Since pimara-15-en-3α,8α-diol (11) features the same tricyclic carbon skeleton as 10 only differing in the oxidation at C-14 and the substituent at C-13, we envisioned its synthesis via a similar tetracyclization strategy. The missing axial secondary alcohol at C-14 would allow for structurally less complex intermediates 12 and 13 with R representing a hydrogen atom.

Results and Discussion

Total synthesis of pimara-15-en-3α,8α-diol

Geranyl bromide (14) provided a valuable starting point to access bromoacetylene 16 via propargylation with lithiated 1-(trimethylsilyl)propyne (15) and subsequent silicon bromine exchange employing N-bromosuccinimide (NBS) in the presence of silver nitrate (AgNO₃) (Scheme 2).

With decagram quantities of 16 in hand, we investigated the phenol alkyne addition for the installation of the aryl enol ether (Table 1). Following the reported conditions, a

Table 1. Investigation of the phenol alkyne addition for the preparation of 17a–e.¹

| Entry | Product  | ArOH (equiv.) | Base (equiv.) | Temp. [°C] | Yield [%] |
|-------|----------|---------------|--------------|-----------|-----------|
| 1     | 17a      | Cs₂CO₃ (1)    | 80           | 12        |
| 2     | 17a      | Cs₂CO₃ (3)    | 80           | 44        |
| 3     | 17a      | Cs₂CO₃ (3)    | 80           | 41        |
| 4     | 17a      | Na₂CO₃ (3)    | 80           | trace     |
| 5     | 17a      | NaH (3)       | 80           | 30        |
| 6     | 17a      | K₂PO₄ (3)     | 80           | 36        |
| 7     | 17b      | Cs₂CO₃ (3)    | 80           | 42        |
| 8     | 17c      | Cs₂CO₃ (3)    | 80           | 44        |
| 9     | 17d      | Cs₂CO₃ (3)    | 80           | 27        |
| 10    | 17e      | Cs₂CO₃ (3)    | 80           | 51        |

¹ DMF = N,N-dimethylformamide.

(a) To date, the syntheses of only a few structurally simplified members—all of which lack the axially-oriented tertiary alcohol—have been reported.⁷
solution of 16 in N,N-dimethylformamide was heated at 80 °C in the presence of 10 equivalents (equiv) of 3-methoxyphenol and cesium carbonate (1 equiv) for three days. The desired product 17a was isolated as a single isomer, but only in a disappointing 12% yield (Table 1, entry 1). We found that three equivalents of base were crucial to increase the yield for 17a to 44% (Table 1, entry 2). Lowering the excess of 3-methoxyphenol to three equivalents gave 17a in almost identical yield (Table 1, entry 3). Substitution of cesium carbonate by sodium carbonate, sodium hydride or potassium phosphate was detrimental to the reaction and provided 17a in less than 36% yield (Table 1, entry 4–6).

Variation of the aromatic substitution pattern (Table 1, entry 7–10) was also investigated. Similar yields were achieved for 17b (42%) and 17c (44%). While enol ether 17d was obtained in a significant lower yield of 27%, the best yield was achieved for unsubstituted phenol 17e (51%).

For the regioselective installation of the epoxide we resorted to the Corey–Noe–Lin protocol. Standard Sharpless[28] dihydroxylation or direct epoxidation with m-chloroperbenzoic acid were impaired by poor regioselectivity and overoxidation (Scheme 3). The diol intermediate was obtained in 73% yield and 94% ee[19] and converted to epoxide 19 by mesylation of the secondary alcohol followed by intramolecular nucleophilic substitution in the presence of K₂CO₃ in 80% yield. For the completion of the synthesis the cyclization precursor 21, a C(sp³)–C(sp³) Suzuki-coupling reaction proved to be the method of choice.[20] For this purpose, a boron-ate complex was first generated by sequential treatment of alkyl iodide 20 with B-methoxy-9-BBN and t-butyllithium.[21] In the presence of a second-generation SPhos precatalyst (5 mol%) and SPhos (5 mol%), efficient cross-coupling with 19 took place to deliver 21 in 84% yield.[22] For the initiation of the pivotal cyclization, a variety of reaction conditions was investigated. In an attempt to induce a radical cyclization, 21 was treated with the Nugent-RajanBabu reagent (titanocene dichloride, Mn, THF, 22 °C).[23] Unfortunately, under these conditions only a complex mixture of decomposition products was obtained. Diethylaluminum chloride (Et₂AlCl, CH₂Cl₂, −78 °C) did not promote the cyclization at all and unreacted 21 was recovered. The stronger[24] Lewis acid ethylaluminum dichloride[25] (Et₂AlCl₂, CH₂Cl₂, −78 °C) initiated a cationic polyene cyclization, but only traces of the products 22a/b/c/d were observed together with inseparable, unidentified side products. We finally identified tin(IV) chloride (SnCl₄, CH₂Cl₂, −78 °C) as a suitable reagent to initiate the crucial polyene tetracyclization and to promote the challenging transannular C-Si-termination step. A mixture of pentacyclic products 22a/b/c/d was obtained in more than 47% combined yield. The desired products 22a and 22b—two inconsequential regioisomers which only differ in the position of the methoxy group—were isolated after purification by HPLC in 16% and 10% yield, respectively.[26] The structures of 22a and 22b were validated by single-crystal X-ray analysis.

Benzoylation of the remaining product fractions facilitated the isolation of cis-decalin 23 in 9% yield over two steps. The formation of 22c may be attributed to a low π-facial selectivity of the enol ether and accounts for a stepwise mechanism.
Scheme 4. Attempted oxidation of 25a/b and 22b and attempted reduction of 22b. Reagents and conditions: a) RuCl₃, H₂O₂, CCl₄, MeCN, H₂O, 30 °C; b) KMnO₄, acetone, H₂O, 22 °C; c) PIDA, MeCN, H₂O, 22 °C; d) RuCl₃, NaIO₄, CCl₄, MeCN, H₂O, 22 °C; e) MeLi, THF, −78 °C; f) RuCl₃, NaIO₄, CCl₄, MeCN, H₂O, 30 °C; g) Na, NH₄THF, −78 °C; h) Li, NH₄THF, −45 °C; i) Me₅P=CH₂, HOAc, 22 °C, then H₂O₂; j) RuCl₃, H₂O₂, CCl₄, MeCN, H₂O, 30 °C; k) RuCl₃, H₂O₂, CCl₄, MeCN, H₂O, 30 °C; l) KMnO₄, acetone, H₂O, 22 °C; m) PDA = phenylidyne.[I] diacetaate, THF = tetrahydrofuran.

Table 2. Attempted oxidation of 24.³⁶

| Entry | Conditions | Yield [%] |
|-------|------------|-----------|
| 1     | KMnO₄, CCl₄, H₂O, 75 °C | 0         |
| 2     | O₃, MeOH, CH₂Cl₂, −78 °C | 0         |
| 3     | O₃, SiO₂, −78 °C | 0         |
| 4     | RuCl₃, NaIO₄, CCl₄, MeCN, H₂O, 22 °C | traces   |
| 5     | RuCl₃, H₂O₂, CCl₄, MeCN, H₂O, 30 °C | traces   |
| 6     | Ru(bpy)₃Cl₂, NaIO₄, MeCN, H₂O, 22 °C | 0         |
| 7     | Ru(bpy)₃Cl₂, NaIO₄, DCE, H₂O, 80 °C | 24        |

[a] Bpy = 2,2'-bipyridine, Bz = benzoyl, DCE = 1,2-dichloroethane.

Finally, demethylation of 22a/b was accomplished by treatment with sodium ethanethiolate (ETSNa, DMF, 120 °C) yielding phenols 25a/b in excellent yields (94% and 84%).

For the installation of the axial vinyl group of 11, oxidative scission of the aryl group was required. For initial studies, we subjected cis-decalin 24 to a variety of oxidation protocols. While potassium permanganate appeared to be ineffective to promote any oxidation (Table 2, entry 1), ozonolysis of a solution of 24 in methanol and chloroform (Table 2, entry 2) or as adsorbate on silica gel (Table 2, entry 3) led to complete decomposition of the material.³⁵ By applying the method of Sharpless (RuCl₃, NaIO₄, CCl₄, MeCN, H₂O, 22 °C), only traces of ketolactone 26 were formed together with a complex mixture of decomposition products (Table 2, entry 4).³⁶ While period acid was described as a powerful substitute for sodium periodate in the literature, we did not observe any improvement (Table 2, entry 5).³⁷ Subjecting pentacycle 24 to a solution of cis-bis(2,2'-bipyridine)-dichlororuthenium(II) and sodium peridode in a mixture of acetonitrile and water at 22 °C did not lead to any transformation (Table 2, entry 6).³⁸ The poor solubility of 24 was addressed by replacing acetonitrile with 1,2-dichloroethane (DCE). Heating to 80 °C facilitated the oxidative scission of the aromatic ring and 26 was isolated in 24% yield (Table 2, entry 7). The structure of 26 was verified by single-crystal X-ray analysis and also allowed for confirmation of the proposed stereochemistry of 24. Since no satisfactory results were achieved, we turned our focus on the oxidation of phenol 25a (Scheme 4).

By treating phenol 25a with in situ generated ruthenium tetroxide (RuCl₃, H₂O₂, CCl₄, MeCN, H₂O), traces of ketone 27 were isolated. While most of 25a decomposed in the presence of potassium permanganate (KMnO₄, acetone, H₂O), the for-
mation of traces of 28 was indicated by $^1$H NMR. Exposing a solution of 25a in acetonitrile and water to phenyldiiodine(III) diacetate (PIDA) led to deamination. Dienone 29, whose structure was verified by single-crystal X-ray analysis, was isolated in 33% yield. The diene motif proved to be resistant to ozonolysis and only slow partial oxidation of the secondary alcohol in 29 was observed.

We attempted to increase the reactivity of the diene by breaking the conjugation with the carbonyl group. However, 1,2-addition of methylithium to 29 to give 30 was not observed but a complex mixture was obtained instead. Finally, Sharpless oxidation (RuCl$_3$, NaIO$_4$, CCl$_4$, MeCN, H$_2$O) of dienone 29 afforded the desired carbon skeleton 27, albeit in low yield (24%). Due to the difficulties with the oxidative degradation, we planned a Birch reduction of 22b to diene 31, as the latter was envisioned to be more readily oxidized.[30] Unfortunately, treatment of a solution of 22b in a mixture of ammonia, tetrahydrofuran and t-butanol with sodium or lithium metal did not provide diene 31 and solely 22b was reisolated. Ozonolysis of 22b resulted in the formation of a complex product mixture. Ruthenium catalyzed oxidation of 22b or 25b (RuCl$_3$, H$_2$O, CCl$_4$, MeCN, H$_2$O) led to decomposition and only traces of ketone 27 were isolated. We were unable to isolate any products from the oxidation of phenol 25b with potassium permanganate (KMnO$_4$, acetonitrile, H$_2$O). We speculated that the secondary alcohol might play a crucial role in the decomposition and therefore opted for selective acetylation of the secondary alcohol. Transesterification with ethyl acetate catalysis and therefore afforded the desired carbon skeleton 27, albeit in low yield (24%). Due to the difficulties with the oxidative degradation, we planned a Birch reduction of 22b to diene 31, as the latter was envisioned to be more readily oxidized.[30] Unfortunately, treatment of a solution of 22b in a mixture of ammonia, tetrahydrofuran and t-butanol with sodium or lithium metal did not provide diene 31 and solely 22b was reisolated. Ozonolysis of 22b resulted in the formation of a complex product mixture. Ruthenium catalyzed oxidation of 22b or 25b (RuCl$_3$, H$_2$O, CCl$_4$, MeCN, H$_2$O) led to decomposition and only traces of ketone 27 were isolated. We were unable to isolate any products from the oxidation of phenol 25b with potassium permanganate (KMnO$_4$, acetonitrile, H$_2$O). We speculated that the secondary alcohol might play a crucial role in the decomposition and therefore opted for selective acetylation of the secondary alcohol. Transesterification with ethyl acetate catalyzed by p-toluenesulfonic acid was indeed selective for the formation of 33 and 34 with potassium permanganate (20 equiv) for 3.5 d, keto-lactone 33 was isolated in 19% yield along with lactone 34 in 18% yield (Table 3, entry 1).[31] To prevent stalling of the reaction, an aqueous solution of potassium permanganate had to be added continuously to the reaction mixture via syringe pump. Decreasing the concentration in the organic layer from 100 mM to 24 mM shifted the product ratio towards the desired keto-lactone 33 (27% yield, Table 3, entry 2). Increasing the temperature to 70°C allowed for a shorter reaction time (24 h) and significantly improved the yield of 33 (38%) and provided lactone 34 in 7% yield (Table 3, entry 3). We also found that a shorter (Table 3, entry 4) or longer (Table 3, entry 5) reaction time was detrimental to the reaction. Further increasing the temperature (100°C in chlorobenzene) led to decomposition and only traces of 33 and 34 were isolated (Table 3, entry 6).

The other regioisomer 32b turned out to be even more reluctant to oxidation. Employing the optimized reaction conditions and extending the reaction time to 48 h allowed for the isolation of 33 in 20% yield along with 34 (7%) (Scheme 5). Efforts to convert the lactone 34 into 11 by reduction to the corresponding lactol and subsequent methylation were unsuccessful.

For the deprotection and reduction of 33 we initially investigated a lithium aluminum hydride reduction. In this case, we only observed incomplete reduction. In contrast, treatment with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®) reproducibly afforded tetraol 35 in excellent yield (89%). For the final installation of the axial vinyl unit, direct vanadium(IV) redox[36] or rhenium[37] catalyzed deoxydehydration (Bu$_3$SnH, sodium or lithium metal did not provide diene 31 and solely 22b was reisolated. Ozonolysis of 22b resulted in the formation of a complex product mixture. Ruthenium catalyzed oxidation of 22b or 25b (RuCl$_3$, H$_2$O, CCl$_4$, MeCN, H$_2$O) led to decomposition and only traces of ketone 27 were isolated. We were unable to isolate any products from the oxidation of phenol 25b with potassium permanganate (KMnO$_4$, acetonitrile, H$_2$O). We speculated that the secondary alcohol might play a crucial role in the decomposition and therefore opted for selective acetylation of the secondary alcohol. Transesterification with ethyl acetate catalyzed by p-toluenesulfonic acid was indeed selective for the secondary alcohol but was outcompeted by substrate decomposition. Therefore, we developed a one-pot procedure for double acetylation (Ac$_2$O, DMAP, pyridine) and subsequent selective deprotection of the phenol (KOH-Bu, t-BuOH) to provide 32a in 85% yield (Table 3).[34]

When a solution of 32a in a biphasic mixture of ethyl acetate and water was heated to 50°C in the presence of an excess of potassium permanganate (20 equiv) for 3.5 d, keto-lactone 33 was isolated in 19% yield along with lactone 34 in 18% yield (Table 3, entry 1).[31] To prevent stalling of the reaction, an aqueous solution of potassium permanganate had to be added continuously to the reaction mixture via syringe pump. Decreasing the concentration in the organic layer from 100 mM to 24 mM shifted the product ratio towards the desired keto-lactone 33 (27% yield, Table 3, entry 2). Increasing the temperature to 70°C allowed for a shorter reaction time (24 h) and significantly improved the yield of 33 (38%) and provided lactone 34 in 7% yield (Table 3, entry 3). We also found that a shorter (Table 3, entry 4) or longer (Table 3, entry 5) reaction time was detrimental to the reaction. Further increasing the temperature (100°C in chlorobenzene) led to decomposition and only traces of 33 and 34 were isolated (Table 3, entry 6).

The other regioisomer 32b turned out to be even more reluctant to oxidation. Employing the optimized reaction conditions and extending the reaction time to 48 h allowed for the isolation of 33 in 20% yield along with 34 (7%) (Scheme 5). Efforts to convert the lactone 34 into 11 by reduction to the corresponding lactol and subsequent methylation were unsuccessful.

For the deprotection and reduction of 33 we initially investigated a lithium aluminum hydride reduction. In this case, we only observed incomplete reduction. In contrast, treatment with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®) reproducibly afforded tetraol 35 in excellent yield (89%). For the final installation of the axial vinyl unit, direct vanadium(IV) redox[36] or rhenium[37] catalyzed deoxydehydration (Bu$_3$SnH, sodium or lithium metal did not provide diene 31 and solely 22b was reisolated. Ozonolysis of 22b resulted in the formation of a complex product mixture. Ruthenium catalyzed oxidation of 22b or 25b (RuCl$_3$, H$_2$O, CCl$_4$, MeCN, H$_2$O) led to decomposition and only traces of ketone 27 were isolated. We were unable to isolate any products from the oxidation of phenol 25b with potassium permanganate (KMnO$_4$, acetonitrile, H$_2$O). We speculated that the secondary alcohol might play a crucial role in the decomposition and therefore opted for selective acetylation of the secondary alcohol. Transesterification with ethyl acetate catalyzed by p-toluenesulfonic acid was indeed selective for the secondary alcohol but was outcompeted by substrate decomposition. Therefore, we developed a one-pot procedure for double acetylation (Ac$_2$O, DMAP, pyridine) and subsequent selective deprotection of the phenol (KOH-Bu, t-BuOH) to provide 32a in 85% yield (Table 3).[34]

Table 3. Optimization of the oxidation of 32a.[a]

| Entry | Solvent | Concentration (mM) | Temp (°C) | Time (h) | 33 | 34 |
|-------|---------|--------------------|-----------|----------|----|----|
| 1     | EtOAc   | 100                | 50        | 84       | 19 | 18 |
| 2     | EtOAc   | 24                 | 50        | 72       | 27 | 12 |
| 3     | EtOAc   | 24                 | 70        | 24       | 38 | 7  |
| 4     | EtOAc   | 24                 | 70        | 12       | 25 | 3  |
| 5     | EtOAc   | 24                 | 70        | 48       | 29 | 13 |
| 6     | C$_2$H$_5$Cl | 24               | 100       | 12       | traces | traces |

[a] Reagents and conditions: a) Ac$_2$O, DMAP, pyridine, CH$_2$Cl$_2$, 22°C, then KOH-Bu, THF, t-BuOH, 22°C, 85%. Ac = acetyl, DMAP = N,N-dimethylpyridin-4-amine, py = pyridine, THF = tetrahydrofuran.

Scheme 5. Completion of the synthesis of pimara-15-en-3β,8β-diol (11). Reagents and conditions: a) KMnO$_4$, ethyl acetate, H$_2$O, 70°C, 38% from 32a, 20% from 32b; b) Red-Al®, toluene, 22°C, then 80°C, 89%; c) TCDI, DMF, 60°C, 55%; d) P(OEt)$_2$, 110°C, 52%. Ac = acetyl, DMF = N,N-dimethylformamide, Red-Al® = sodium bis(2-methoxyethoxy)aluminum hydride, TCDI = 1,1'-thiocarbonyldiimidazole, THF = tetrahydrofuran.
treatment of the tetralin 35 in chloroform with thiophosphate and 4(N,N-dimethylamino)pyridine. However, this procedure was not reproducible and led to variable yields (0–58%). We attribute this observation to the poor solubility of 35 in chlorinated solvents. Performing the reaction with 1,1’-thiocarbonyldiimidazole (TCDI) in N,N-dimethylformamide at elevated temperature (60 °C) reproducibly afforded 36 in 55% yield. Upon heating a solution of 36 in trimethyl phosphate to 110 °C, the final elimination was induced to complete the first total synthesis of pimara-15-en-3-ol α, 52% in 0.2% overall yield. The NMR and mass-spectroscopic data obtained for synthetic 11 were in full agreement with those reported for the natural analog in the literature.\textsuperscript{[13]}

Towards ent-Norflickinflimiod C

After the successful total synthesis of 11, we envisioned to extend the application of the polyene tetracyclization/transannular endo-termination step to the synthesis of ent-norflickinflimiod C (10). For the introduction of the secondary alcohol at C-14, we attached various hydroxy-surrogates (=R) at the corresponding C-14 position of the general cyclization precursor 37 (Scheme 6). Despite the potential propensity to form a 5-membered ring during the third ring-closure, we wanted to study the behavior of bis enol ether 42 under Lewis-acidic conditions (Scheme 6A). Benzyl enol ether 40 was prepared by Wittig olefination of ketone 39 employing (benzyl oxy)methyltriphenylphosphonium chloride (BnOCH₂PH₃Cl) and n-butyllithium.\textsuperscript{[19]} Deprotection of the primary alcohol with triethylamine trihydrofluoride afforded alcohol 40 in 72% yield as a separable 1:6:1 mixture of 40a:40b:40. For the formation of alkyl iodides 41a/b, a screen of reaction conditions was performed (conditions c). Mesylation of 40a followed by treatment with tetrabutylammonium iodide afforded alkyl iodides 41a/b in 41% yield as a 1:1 mixture of double bond isomers.\textsuperscript{[40]} No isomerization was observed when 40b was treated with iodine, triphenylphosphine and imidazole (imH), but the product 41b was inseparable from residual triphenylphosphine. Therefore, triphenylphosphine was replaced by diphenylphosphino-poly styrene (pol–PPh₃), a polymer-bound variant.\textsuperscript{[40]} This enabled the isolation of 41 as a mixture of isomers (41a:41b = 1:6) in 9% yield. Finally, a modified Mitsunobu reaction (DEAD, PPh₃, LiI) was able to deliver isomERICALLY pure 41a in 59% and 41b in 80% yield, respectively.\textsuperscript{[40]} Fragments 41a/b were converted into a boron–octa complex by treatment with t-butyllithium in the presence of B-methylxy-9-BBN. This enabled a Suzuki cross-coupling reaction with vinyl bromide 19 to obtain polyenes 42a/b in 53% and 74% yield, respectively. Treatment of a solution of 42a or 42b in dichloromethane with either ethylaluminum dichloride (EtAlCl₂) or tetravinyl chloride (SnCl₄) at –78°C resulted in the formation of a complex mixture of unidentified decomposition products.

In the second approach, we decided to replace the benzyl enol ether by a more stable vinyl silane, which would allow for a late-stage Tamao–Fleming oxidation (Scheme 6B).\textsuperscript{[14,44]} We expected that the β-silicon effect would ensure the formation of a six-membered carbocycle during the third ring-closure.\textsuperscript{[45]}

We first planned the installation of a silacyclobutane unit due to its small size and its capability to undergo the Tamao–Fleming oxidation.\textsuperscript{[146]} For the preparation of 45, we attempted carbometallation of tetrahydropyraneryl ether 44 (conditions g). In the presence of methylmagnesium bromide and catalytic amounts of nickelll(i) bis(acetylefetionate) (Ni(acac)₂) and trimethylaluminunum (AlMe₃) decomposition occurred.\textsuperscript{[47]} Treatment of 44 with trimethylaluminun and zirconocene dichloride (Cp₂ZrCl₂) led to the formation of 46 and 47 via nucleophilic ring-opening of the tetrahydropyranyl group.\textsuperscript{[48]} When alcohol 46 was treated under the same conditions, slow decomposition over six days was observed. When silacyclobutane 46 was exchanged with dimethylphenylsilane 49, formation of traces of 50 occurred upon treatment with Cp₂ZrCl₂ and AlMe₃. In contrast to 46, 49 proved to be stable under these conditions, as unreacted 49 was reisolated. We found that the addition of water (1 equiv) was crucial to promote the carbometallation and to obtain vinyl silane 50 in 40% yield.\textsuperscript{[146]} Alcohol 50 was converted to alkyl iodide 51 in the presence of iodine, triphenylphosphine and imidazole (60% yield). Borylation and Suzuki cross-coupling with vinyl bromide 52 or 53 afforded the cyclization precursors 54 (88% yield) and 55 (60% yield). When a solution of precursor 54 or 55 in CH₂Cl₂ was treated with ethylaluminum dichloride (EtAlCl₂) or tetravinyl chloride (SnCl₄) at –78°C, a complex mixture of unidentified decomposition products was formed.

Since additional heteroatoms proved to be incompatible in the tetracyclization reaction, we opted for an allyl group as a hydroxy-surrogate in our third attempt (Scheme 6C). We prepared 60 by allylation of vinyl iodide 58 (conditions I).\textsuperscript{[14]} Halogen lithium exchange was induced by treatment with t-butyllithium. Upon addition of copper(i) cyanide di(lithium chloride) complex 59 and allyl bromide, allylation was observed and diene 60 was formed along with protodemetaUation product 61 and dimer 62 in a 7:3:1 ratio, which was determined by ¹H NMR analysis of the crude reaction mixture. The use of allyl iodide instead of allyl bromide resulted in an even larger amount of the protodemetaUation product 61. We found that the mixed magnesate (n-Bu₂)₂PtMe₂Li was capable of suppressing the formation of 61 (60:61:62 = 25:1:3) and the desired product 60 was isolated in 66% yield.\textsuperscript{[35]} Deprotection of the tetrahydropyranyl ether with pyridinium p-toluensulfoUate (PPTS) in methanol (85% yield) and treatment of the resulting primary alcohol with iodine, triphenylphosphine and imidazole afforded alkyl iodide 63 in 78% yield. Borylation and Suzuki cross-coupling with either 19 or 53 yielded the cyclization precursors 64 (63%) and 65 (79%). Exposing a solution of 64 to ethylaluminum dichloride (EtAlCl₂) or tetravinyl chloride (SnCl₄) at –78°C led to the formation of a complex product mixture. Treatment of 65 with tetravinyl chloride or ethylaluminum dichloride under the same conditions led to a complex mixture as well, but three major products were isolated, which were inseparable from each other by normal phase high performance liquid chromatography (HPLC). Extensive NMR studies of the mixture indicated the formation of the
Scheme 6. Synthesis of cyclization precursors 42a/b, 54, 55, 64 and 65. Reagents and conditions: a) BnOCH_2PPh_2Cl, n-BuLi, THF, –78 °C to 22 °C; b) NEt_3, 3HF, MeCN, 22 °C, 72% over two steps; c1) MeCl, NEt_3, CH_2Cl_2, 0 °C to 22 °C, then TBAI, benzene, 80 °C, 41% of 41a/b (1:6); c2) I_2, PPh_3, imH, CH_2Cl_2, 0 °C, inseparable mixture of 41b with PPh_3; c3) t-Bu-poly-PPh_3, imH, CH_2Cl_2, 0 °C to 22 °C, 9% of 41a/b (1:6); c4) DEAD, PPh_3, LiCl, THF, 0 °C, 59%; c5) DEAD, PPh_3, LiCl, THF, 0 °C, 80%; d) t-BuLi, 8-methoxy-9-BBN, THF, –78 °C to 22 °C, then 19, SPhos Pd Cl, SPhos, Cs_2CO_3, DMF, H_2O, 40 °C, 53% of 42a, 74% of 42b; e) EIAACL_2, CH_2Cl_2, –78 °C; f) SnCl_2, CH_2Cl_2, –78 °C; g1) 44, MeMgBr, N(acac)_2, AlMe_3, THF, 22 °C; g2) 44, AlMe_3, CpZrCl_2, CH_2Cl_2, 0 °C to 22 °C; g3) 46, AlMe_3, CpZrCl_2, CH_2Cl_2, 0 °C to 22 °C; g4) 49, AlMe_3, CpZrCl_2, CH_2Cl_2, 22 °C to 40 °C, traces; g5) 49, AlMe_3, CpZrCl_3, H_2O, CH_2Cl_2, 40 °C to 40 °C, 40%; g6) I_2, PPh_3, imH, CH_2Cl_2, 0 °C, 60%; g7) t-BuLi, 8-methoxy-9-BBN, THF, –78 °C to 22 °C, then 52 or 53, SPhos Pd Cl, SPhos, Cs_2CO_3, DMF, H_2O, 40 °C, 88% of 54, 60% of 55; j) EIAACL_2, CH_2Cl_2, –78 °C; k) SnCl_2, CH_2Cl_2, –78 °C; II) t-BuLi, CuCN-2LiCl (10 mol%), allyl bromide, THF, –78 °C, 60/61/62 (7:3:1); determined by 1H NMR analysis of the crude reaction mixture; d) t-BuLi, CuCN-2LiCl (10 mol%), allyl iodide, THF, –78 °C, 60/61/62 (10:1:1) determined by 1H NMR analysis of the crude reaction mixture; e) t-PrMgBr, n-BuLi, CuCN-2LiCl (10 mol%), allyl bromide, THF, –78 °C to 0 °C, 60/61/62 (25:1:3) determined by 1H NMR analysis of the crude reaction mixture, 66% of 60; m) PPTS, MeOH, 22 °C, 85%; n) I_2, PPh_3, imH, CH_2Cl_2, 0 °C, 78%; o) t-BuLi, 8-methoxy-9-BBN, THF, –78 °C to 22 °C, then 19 or 53, SPhos Pd Cl, SPhos, Cs_2CO_3, DMF, H_2O, 40 °C, 63% of 64, 79% of 65; p) EIAACL_2, CH_2Cl_2, –78 °C, traces. Acac = acetylacetone, 8-methoxy-9-BBN = 9-methoxy-9-boracyclo[3.3.1]nonane.
putative pentacycle 67 as a mixture of diastereomers (1:1) along with equimolar amounts of an unidentified incomplete cyclization product. Variation of the temperature and reaction time did neither alter the product ratio nor could the yield of 67 be improved. Oxidation of the product mixture by ozone or osmium tetroxide and sodium periodate led to inseparable mixtures as well.\[32\] As a result, verification of the proposed structure 67 was not possible and we discontinued our efforts on this approach.

Due to the results obtained for 65 and the lessons learned from the alternative substrates, we planned a new route towards the total synthesis of osmium tetroxide and sodium periodate. Oxidation of the product mixture by ozone or time did neither alter the product ratio nor could the yield of cyclization product. Variation of the temperature and reaction along with equimolar amounts of an unidentified incomplete putative pentacycle mixtures as well.

From the alternative substrates, we planned a new route structure 67 from the alternative substrates, we planned a new route

Realization of a tetracyclization/endo-termination sequence of an allene with the general structure 68 would give access to pentacycle 69 via attack of C-14 and termination of the arene at C-13. Oxidative cleavage of the exo-methylene group would allow for unmasking of the hydroxy group at C-14. Alternatively, exo-termination might occur at C-21, as a formal allylic cation would be formed during the third ring-closure at C-14. Due to the two electrophilic positions of the allylic cation, we decided to investigate the impact of electronic and steric parameters on the allene. For this purpose, we chose the four differently substituted allenes 76, 81, 83 and 85, three of which differ only in their alkyl substitution degree. The allene 81 features an electron-withdrawing group to destabilize the developing positive charge at the undesired C-21 position (Scheme 8).

Attempts to directly couple allene fragments with vinyl bromide 19, failed (see Supporting Information for details).
Thus, we decided to install the allene after the C(sp³)–C(sp³) coupling. The synthesis of allene 76 commenced with the addition of lithiated allene 70 to oxirane (71) in the presence of boron trifluoride diethyl etherate (BF₃·OEt₂) yielding primary alcohol 72 in 80% yield (Scheme 8). Treatment of 72 with iodine, triphenylphosphine and imidazole afforded alky iodide 73 in 78% yield.

Borylation of 73 by exposure to t-butyl lithium in the presence of B-methoxy-9-BBN enabled a Suzuki cross-coupling reaction with vinyl bromide 19. In the presence of a second-generation SPhos precatatst (5 mol%) and SPhos (5 mol%), 74 was obtained in 76% yield. Deprotection of alkynyl silane 74 was accomplished by treatment with tetra-n-butylammonium fluoride in 82% yield. The resulting alkyne 75 underwent a modified Crabbe homologation ([Cu, (CH₂O)₃, Cy,NH] to provide the cyclization precursor 76 in 57% yield. The higher substituted allenes 81, 83 and 85 were prepared by a divergent strategy. Addition of lithiated allene 70 to ketone 77 was followed by silylation of the resulting tertiary alcohol under Corey’s conditions (TBSOTf, 2,6-lutidine). Cleavage of the tetrahydropyranyl ether under acidic conditions (TsOH, MeOH) afforded primary alcohol 78 in 56% yield over three steps. Alky iodide 79 was provided in 92% yield by treatment with iodine, triphenylphosphine and imidazole. Borylation of 79 followed by a Suzuki cross-coupling reaction with vinyl bromide 19 and subsequent desilylation of the alkynyl silane and the silyl ether in the presence of tetra-n-butylammonium fluoride afforded diene 80 in 69% yield over two steps. Upon treatment of 80 with phenylsulfonyl chloride (PhSCl) in the presence of triethyl amine a Mislow-Evans rearrangement was induced to complete the synthesis of cyclization precursor 81 in almost quantitative yield. Acetylation of tertiary alcohol 80 (Ac₂O, DMAP, NEt₃) gave ester 82 in 95% yield. Employing Stryker’s reagent ([Ph₃P]CuH)₂ to a solution of 82 in degassed toluene delivered allene 83 in 46% yield.

Alkyne 82 was lithiated by treatment with lithium bis(trimethylsilyl)amide and alkylated with methyl iodide to give 84 in 36% yield. The low yield for 84 results from competing alkylation of the acetyl group to form a propionyl group. Introduction of the missing methyl group and completion of the synthesis of allene precursor 85 was accomplished via a S₈2 reaction of the propargyl acetate. By subjecting 84 to a mixture of copper(I) iodide, lithium bromide and methyl magnesium bromide in tetrahydrofuran 85 was formed in 91% yield.

Upon treatment of a solution of tetrasubstituted allene 85 in dichloromethane with tin(iv) chloride at −78 °C (conditions a), four tetracyclization products were isolated in 69% overall yield. Trans-fused pentacycle 86a was obtained in 15% yield along with regioisomer 86b (20% yield), which only differs in the position of the methoxy group. The structure of 86b was verified by single-crystal X-ray analysis. The cis-fused structures 86c and 86d were isolated in 13% and 21% yield, respectively and represent epimers of 86a and 86b.

We assume that the formation of cis- and trans-fused products can be attributed to a low π-facial selectivity of the enol ether involved in the second ring-closure (Scheme 9B). Formation of a chair-chair conformation 86a leads to the generation of the trans-fused oxocarbenium ion 90. Subsequent attack of the central carbon atom of the allene provides the allyl cation 91a/b. A transannular endo-termination would afford the desired product of the general structure 92. Unfortunately, cyclization precursor 85 underwent an exo-termination pathway via 91b to give pentacyclic products of the general structure 92 (highlighted in green). The formation of cis-fused products 86c/d (general structure 96) might be explained by a chair-boat conformation 86b of the first two rings at the beginning of the cyclization reaction (Scheme 9B).

A subsequent ring-flip results in the formation of oxocarbenium ion 94a/b residing in a chair-chair conformation. The formation of cis-fused [6,6,6,6]-pentacycles 96 (highlighted in red) is consistent with an attack of the central carbon atom (C-14) of the allene 94a followed by an exo-termination step of the resulting allylic cation 95.

Owing to recent applications of HFIP as a cosolvent for cationic polycycle cyclization reactions, we decided to include it in our screening. Changing the solvent from dichloromethane to a 17:1 mixture of dichloromethane and HFIP (conditions b) and increasing the temperature to −15 °C led to a higher overall yield of tetracyclization products (79%) and a change in the product composition (Scheme 9A). The temperature had to be increased from −78 °C up to −15 °C to prevent freezing of HFIP. Instead of 86a and 86b, the regiosomers 86e and 86f were formed in 14% and 25% yield. The structure of 86e was verified by single-crystal X-ray analysis. The yield of cis-decalins 86c and 86d slightly increased to 17% and 23%, respectively. The formation of the isomers 86e/f (general structure 93 highlighted in blue, Scheme 9B) is explained by the same cyclization pathway as for 92 with a subsequent 1,3-phenolene shift, which alleviates the unfavorable 1,3-diaxial interactions. This reactivity was exclusively observed for the trans-decalins but not for the cis-decalins.

DFT calculations revealed that exo-termination products are considerably thermodynamically favored over the desired endo-termination products ($\Delta G = 10.0$ kcal/mol for 86b). Nevertheless, we intended to investigate if the endo-termination product could be obtained by variation of the stereoelectronic properties of the allene.

Exposure of a solution of disubstituted allene 83 in dichloromethane to tin(iv) chloride at −78 °C (conditions a) afforded a mixture of four tetracyclization products in 59% overall yield. The regiosomers 87a and 87b were isolated in 15% yield each, which both originate from the undesired exo-termination. Control experiments indicated that higher temperatures during the work-up procedure caused the 1,3-phenolene shift see (Supporting Information for details). Analysis of the 2D NMR data revealed the opposite stereoechemistry at C-13 when compared to 86a and 86f. This was supported by single-crystal X-ray analysis of 87b. The cis-fused regiosomers 87c and 87d were isolated in 13% and 16% yield, respectively.

Addition of tin(iv) chloride to a solution of monosubstituted allene 76 in dichloromethane at −78 °C (conditions a) afforded only 32% of tetracyclization products and secondary products thereof. Unfortunately, the decreased steric demand at C-13 did
not facilitate the formation of endo-termination products. Instead, the trans-fused pentacyclic product 88a was isolated in 5% yield. The formation of regioisomer 88b was supported by detailed NMR-studies of a sample containing copolar impurities.
Surprisingly, we observed the formation of cis-fused [6,6,5,6,6]-pentacycle 88c, which was isolated as a mixture of double bond isomers in 11% yield. For the exo-methylene unit, we observed spontaneous isomerization to the endo-isomer in deuterated chloroform. The structure of 88c was verified by single crystal X-ray analysis. The formation of regioisomer 88d was supported by NMR analysis of a sample containing copolar imurities.

The formation of cis-fused [6,6,5,6,6]-pentacycles 98 (highlighted in orange) originates from an unusual attack of C-13 of the allene 94b and proceeds via an exo-termination at the intermediary vinyl cation 97 (Scheme 98). DFT calculations suggest kinetic reaction control, as the theoretical cis-fused [6,6,5,6,6]-product (of the general structure 96) originating from an exo-termination of an allylic cation would be thermodynamically favored (ΔG = 3.3 kcal/mol compared to exo-88c). While the decreased steric demand of allene 76 furnished exo-88c as a kinetic reaction product, still no endo-termination products were observed. Additionally, we also isolated heterodimer 89 in 16% yield. We assume its formation by protonation of the exo-methylene group of exo-88c followed by a nucelophilic attack of the exo-methylene isomer of 88d at the intermediary tertiary benzylc cation (conditions a).

When the cyclization reaction was conducted in a 21:1 mixture of dichloromethane and HFIP (conditions b) and at elevated temperature (−20 °C), the formation of 88a and 88b was not observed. Detailed NMR-studies of a sample containing copolar impurities indicated the formation of 1,3-phenolate shifted tetracyclization products of the general structure 93. The yield of cis-fused [6,6,5,6,6]-pentacycle endo-88c was more than doubled (23%) and exo-88c was not isolated due to quantitative isomerization of the exo-methylene group subsequent to the cyclization event. Regioisomer 88d was obtained in 21% yield. The presence of HFIP also prevented the formation of heterodimer 89, which explains the higher yield of the corresponding monomers 88c and 88d. We assume, that at elevated temperatures (>−20 °C) in presence of tin(IV) chloride and HFIP (conditions b) isomerization of exo-88c/d is faster than dimerization and therefore the formation of 89 was not observed.

Sulfinyl allene 81 proved to be unreactive under conditions a. However, under conditions b, sulfinyl allene 81 decomposed to a complex product mixture and formation of tetracyclization products was not observed.

In conclusion, we accomplished a polyyne tetracyclization/transannular endo-termination sequence involving a dual nucleophilic allyl enol ether. Four carbon–carbon bonds and five stereocenters were formed from a readily available polyyne by the key cyclization assembling the pimarane carbon skeleton in a single step. Oxidative cleavage of the allyl group enabled the first total synthesis of the diterpenoid pimara-15-en-3β-sulfo-L-diol (11) in 13 steps from commercially available geranyl bromide. The highly flexible and modular synthesis allowed for rapid structural modifications of the substitution pattern along the polyyne backbone. A library of cyclization precursors aimed at the total synthesis of the nor-diterpenoid ent-norflickinflimiod C (10) was prepared. Polyyne tetracyclization of three alkyl-substituted allenes delivered novel pentacycle structures, which allowed insight into the underlying cyclization pathways. The investigated allenes underwent an exo-termination pathway instead of the transannular endo-termination pathway required for the synthesis of ent-norflickinflimiod C (10). The use of alternative cyclization precursors is currently investigated in our laboratories and will be reported in due course.

Experimental Section

Crystal-structure analysis: Deposition Numbers 1987621 (for 22a), 1987622 (for 22b), 1987623 (for 23), 2082138 (for 26), 2082139 (for 29), 1987624 (for 35), 2082140 (for 86b), 2082141 (for 86e), 2082142 (for 87b) and 2082143 (for endo-88c) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Acknowledgements

This work was supported by the Tyrolean Science Fund TWF (F.166466/5-2019 to J.M.F.), and the Center for Molecular Biosciences CMBl. We are grateful to Assoc. Prof. Dr. Christoph Kreutz, Assoc. Prof. Dr. Thomas Müller, and Dr. Christina Meisenbichler (University of Innsbruck) for help with NMR and HRMS studies. Furthermore, we thank Prof. Dr. Ulrich Grieser, Larissa Feilner, Tobias Taibon and Elias Schmidhammer for experimental support. T.M. acknowledges the European Research Council under the European Union’s Horizon 2020 research and innovation program (grant agreement No 101000060).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: cationic cascades · natural products · polyyne cyclization · terpenoids · total synthesis

[1] a) F. Chen, D. Tholl, J. Bohlmann, E. Pichersky, Plant J. 2011, 66, 212–229; b) E. Oldfield, F.-Y. Lin, Angew. Chem. Int. Ed. 2012, 51, 1124–1137; Angew. Chem. 2011, 124, 1150–1163; c) F. Zhou, E. Pichersky, Curr. Opin. Plant Biol. 2020, 55, 1–10.
[2] a) D. E. Hall, P. Zerbe, S. Jancsik, A. L. Quesada, H. Dullat, L. L. Madilao, M. Yuen, J. Bohlmann, Plant Physiol. 2013, 161, 600–616; b) F. Chen, D. Tholl, J. Bohlmann, E. Pichersky, Plant J. 2011, 66, 212–229.
[3] a) G. Stork, A. W. Burgstahler, J. Am. Chem. Soc. 1955, 77, 5068–5077; b) A. Eschenmoser, L. Ruzicka, O. Jeger, D. Arigoni, Helv. Chim. Acta 1955, 38, 1890–1904.
[4] a) R. A. Yoder, J. N. Johnston, Chem. Rev. 2005, 105, 4730–4756; b) W. S. Johnson, Biorg. Chem. 1976, 5, 51–98; c) C. N. Ungarean, C. N. Ungarean, E. H. Southgate, D. Sarlah, Org. Biomol. Chem. 2016, 14, 5454–5467; d) A. Banett, T.-K Ma, T. Mies, Synthesis 2019, 51, 67–82; e) M. Baunach, J. Fraenze, C. Hertweck, Angew. Chem. Int. Ed. 2015, 54, 2604–2626; Angew. Chem. 2015, 127, 2640–2664.
