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-3α-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] and have demonstrated their efficiency in a large number of natural product syntheses.[4] 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 tricycle **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-hydroxyandrostan-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 fimbriata* 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**

[a] J. M. Feilner, I. Plangger, Prof. Dr. T. Magauer
Institute of Organic Chemistry and
Center for Molecular Biosciences
Leopold-Franzens-University Innsbruck
Innrain 80–82, 6020 Innsbruck (Austria)
E-mail: thomas.magauer@uibk.ac.at

[b] Dr. K. Wurst
Institute of General, Inorganic and Theoretical Chemistry
Leopold-Franzens-University Innsbruck
Innrain 80–82, 6020 Innsbruck (Austria)

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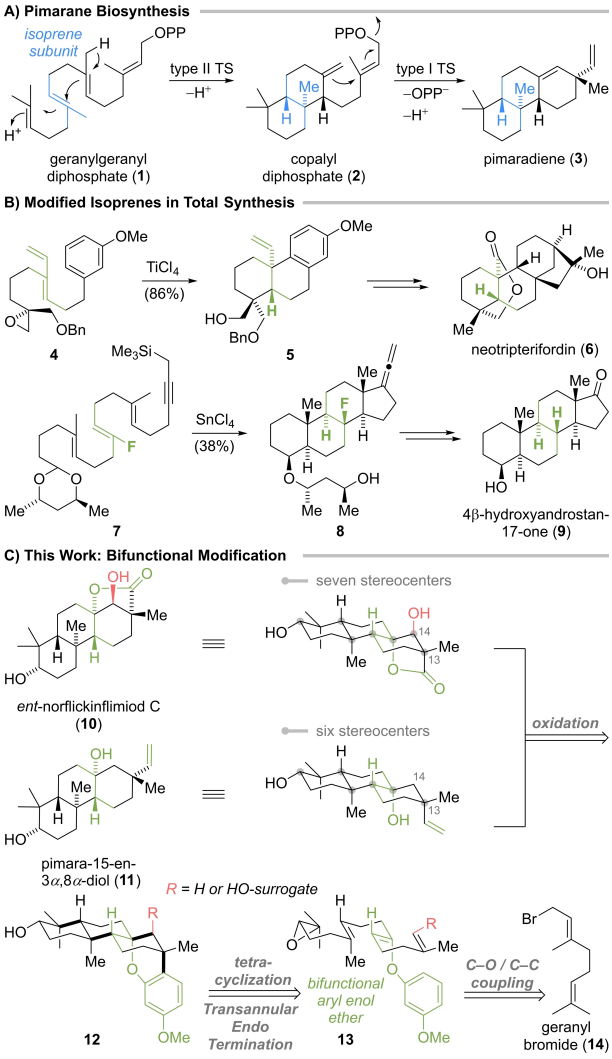


Scheme 1. A) Biosynthesis of **3**. B) Total synthesis of **6** and **9** by polyene cyclization involving modified isoprenes. C) Retrosynthetic analysis of **10** and **11** based on a transannular polyene tetracyclization/*endo*-termination sequence enabled by a bifunctional isoprene modification. Bn = benzyl, OPP = diphosphate ester, TS = terpene synthase.

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.[12] 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.

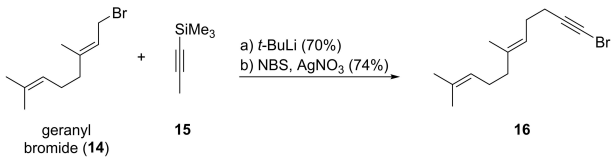
Since pimara-15-en-3α-8α-diol (**11**)[13] features the same tricyclic carbon skeleton as **10** only differing in the oxidation at C-14 and the substituent at C-13, we envisioned its synthesis via a similar tetracyclization strategy. The missing axial secondary alcohol at C-14 would allow for structurally less complex intermediates **12** and **13** with R representing a hydrogen atom. To date, the syntheses of only a few structurally simplified members-all of which lack the axially-oriented tertiary alcohol-have been reported.[14]

Results and Discussion

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

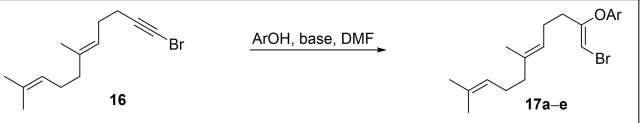
Geranyl bromide (**14**) provided a valuable starting point to access bromoacetylene **16** via propargylation[15] with lithiated 1-(trimethylsilyl)propyne (**15**) and subsequent silicon bromine exchange[16] employing *N*-bromosuccinimide (NBS) in the presence of silver nitrate ($AgNO_3$) (Scheme 2).

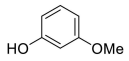
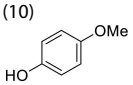
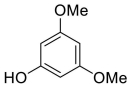
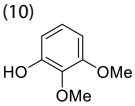
With decagram quantities of **16** in hand, we investigated the phenol alkyne addition for the installation of the aryl enol ether (Table 1). Following the reported conditions,[10b,c] a



Scheme 2. Preparation of bromoacetylene **16** by propargylation of geranyl bromide (**14**). Reagents and conditions: a) 1-(trimethylsilyl)propyne (**15**), *t*-BuLi, THF, −20 °C to −5 °C, 70%; b) NBS, $AgNO_3$, acetone, 0 °C, 74%. NBS = *N*-bromosuccinimide, THF = tetrahydrofuran.

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



Entry	Product	ArOH (equiv.)	Base (equiv.)	Temp. [°C]	Yield [%]
1	**17a**	 (10)	Cs_2CO_3 (1)	80	12
2		(10)	Cs_2CO_3 (3)	80	44
3		(3)	Cs_2CO_3 (3)	80	41
4		(10)	Na_2CO_3 (3)	80	trace
5		(10)	NaH (3)	80	30
6		(10)	K_3PO_4 (3)	80	36
7	**17b**	 (10)	Cs_2CO_3 (3)	80	42
8	**17c**	 (10)	Cs_2CO_3 (3)	80	44
9	**17d**	 (3)	Cs_2CO_3 (3)	80	27
10	**17e**	 (8)	Cs_2CO_3 (3)	80	51

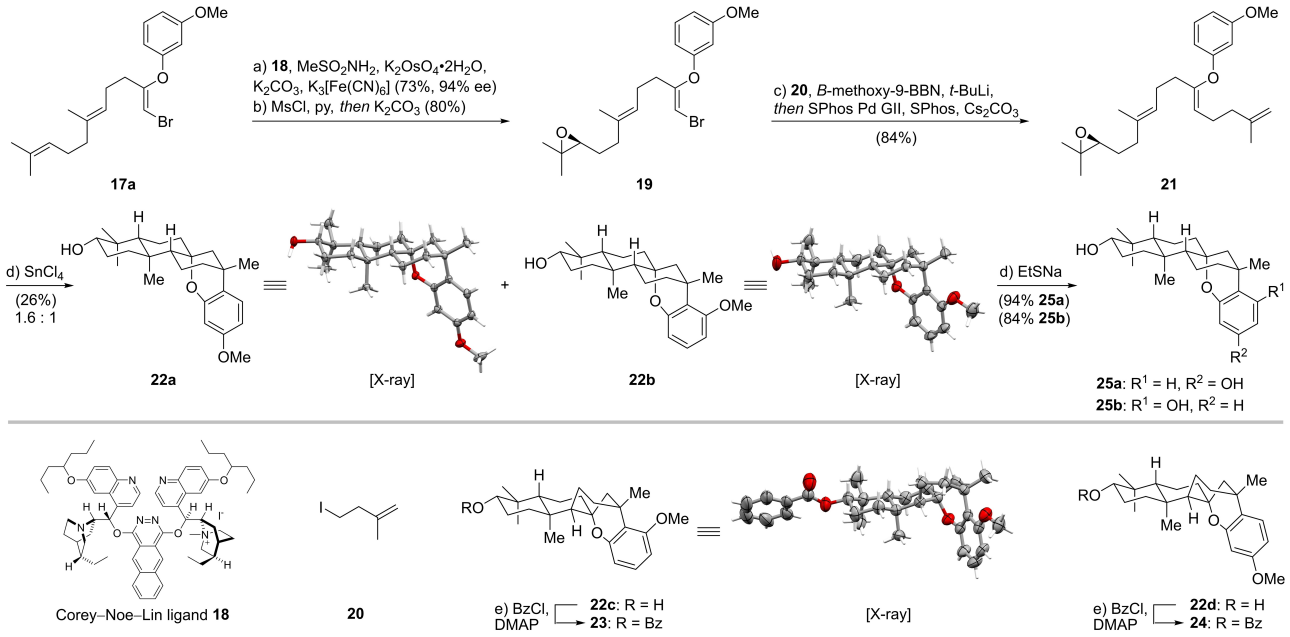
[a] DMF = *N*,*N*-dimethylformamide.

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[17] protocol. Standard Sharpless[18] dihydroxylation or direct epoxidation with *m*-chloroperoxybenzoic 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 K_2CO_3 in 80% yield. For the completion of the synthesis of the cyclization precursor **21**, a C(sp^2)–C(sp^3) Suzuki cross-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 (Et_2AlCl, CH_2Cl_2, −78 °C) did not promote the cyclization at all and unreacted **21** was recovered. The stronger[24] Lewis acid ethylaluminum dichloride[25] ($EtAlCl_2$, CH_2Cl_2, −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 ($SnCl_4$, CH_2Cl_2, −78 °C) as a suitable reagent to initiate the crucial polyene tetracyclization and to promote the challenging transannular *endo*-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

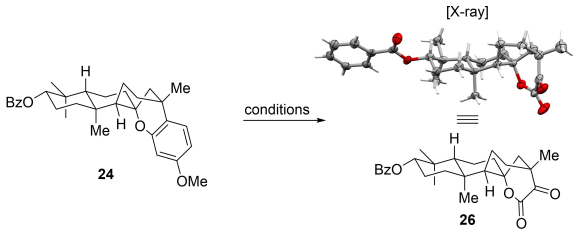


Scheme 3. Synthesis of **25a/b** via polyene tetracyclization of **21**. Reagents and conditions: a) Corey–Noe–Lin ligand **18**, $MeSO_2NH_2$, $K_2OsO_4 \cdot 2H_2O$, K_2CO_3, $K_3[Fe(CN)_6]$, *t*-BuOH, H_2O, 0 °C, 73%, 94% *ee*; b) MsCl, pyridine, CH_2Cl_2, 22 °C, *then* K_2CO_3, MeOH, 22 °C, 80%; c) **20**, *t*-BuLi, *B*-methoxy-9-BBN, THF, −78 °C to 22 °C, *then* SPhos Pd GII, SPhos, Cs_2CO_3, DMF, H_2O, 40 °C, 84%; d) $SnCl_4$, CH_2Cl_2, −78 °C, 16% **22a**, 10% **22b**; d) EtSH, NaH, DMF, 120 °C, 94% of **25a**, 84% of **25b**; e) BzCl, DMAP, py, 22 °C, 9% **23** over two steps, 12% **24** over two steps. *B*-methoxy-9-BBN = 9-methoxy-9-borabicyclo[3.3.1]nonane, Bz = benzoyl, DMAP = *N*,*N*-dimethylpyridin-4-amine, DMF = *N*,*N*-dimethylformamide, ee = enantiomeric excess, MsCl = methanesulfonyl chloride, py = pyridine, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, SPhos Pd GII = chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)] palladium(II), THF = tetrahydrofuran.

involving a boat-type transition state for the second ring closure.[27] Isomerization of the (Z)-enol ether **21** prior to cyclization, which would also explain the formation of **22c**, was found to be unlikely, as treatment of a model system lacking the epoxide (see Supporting Information for details) with tin(IV) chloride did not lead to any detectable isomerization. The constitution of **24** (12% yield over two steps) was fully supported by extensive 2D NMR studies, but the depicted stereochemistry could not be validated at this point. NOE experiments were inconclusive and crystals for single-crystal X-ray analysis were not obtained.[28]

We also explored the impact of the aryl substitution pattern on the cyclization reaction to further improve the yield and diastereoselectivity of the process. The modular route allowed to exchange the aryl group and investigate the tetracyclization of several related aryl enol ethers. To our surprise, all derivatives investigated proved to be inferior to **21**, providing lower yields and unidentified product mixtures.

Table 2. Attempted oxidation of **24**.[a]



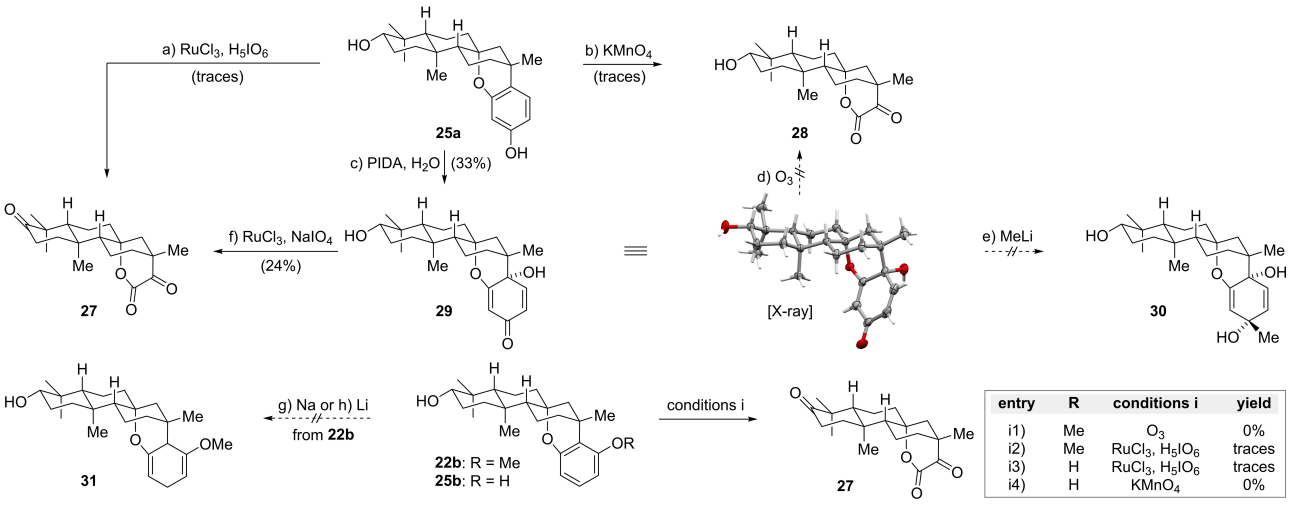
Entry	Conditions	Yield [%]
1	$KMnO_4$, CCl_4, H_2O, 75 °C	0
2	O_3, MeOH, CH_2Cl_2, −78 °C	0
3	O_3, SiO_2, −78 °C	0
4	$RuCl_3$, $NaIO_4$, CCl_4, MeCN, H_2O, 22 °C	traces
5	$RuCl_3$, H_5IO_6, CCl_4, MeCN, H_2O, 30 °C	traces
6	$Ru(bpy)_2Cl_2$, $NaIO_4$, MeCN, H_2O, 22 °C	0
7	$Ru(bpy)_2Cl_2$, $NaIO_4$, DCE, H_2O, 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.[29] By applying the method of Sharpless ($RuCl_3$, $NaIO_4$, CCl_4, MeCN, H_2O, 22 °C), only traces of ketolactone **26** were formed together with a complex mixture of decomposition products (Table 2, entry 4).[30] While periodic acid was described as a powerful substitute for sodium periodate in the literature, we did not observe any improvement (Table 2, entry 5).[31] Subjecting pentacycle **24** to a solution of *cis*-bis-(2,2′-bipyridine)-dichlororuthenium(II) and sodium periodate in a mixture of acetonitrile and water at 22 °C did not lead to any transformation (Table 2, entry 6).[32] 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 ($RuCl_3$, H_5IO_6, CCl_4, MeCN, H_2O), traces of ketone **27** were isolated. While most of **25a** decomposed in the presence of potassium permanganate ($KMnO_4$, acetone, H_2O), the for-



Scheme 4. Attempted oxidation of **25a/b** and **22b** and attempted reduction of **22b**. Reagents and conditions: a) $RuCl_3$, H_5IO_6, CCl_4, MeCN, H_2O, 30 °C, traces; b) $KMnO_4$, acetone, H_2O, 22 °C, traces; c) PIDA, MeCN, H_2O, 22 °C, 33%; d) O_3, CH_2Cl_2, MeOH, −78 °C, *then* dimethylsulfide; e) MeLi, THF, −78 °C; f) $RuCl_3$, $NaIO_4$, CCl_4, MeCN, H_2O, 30 °C, 24%; g) Na, NH_3, THF, *t*-BuOH, −78 °C; h) Li, NH_3, THF, *t*-BuOH, −45 °C; i1) O_3, EtOAc, HOAc, 22 °C, *then* H_2O_2; i2) $RuCl_3$, H_5IO_6, CCl_4, MeCN, H_2O, 30 °C, traces; i3) $RuCl_3$, H_5IO_6, CCl_4, MeCN, H_2O, 30 °C, traces; i4) $KMnO_4$, acetone, H_2O, 22 °C. Ac = acetyl, PIDA = phenyliodine(III) diacetate, THF = tetrahydrofuran.

mation of traces of **28** was indicated by ^{1}H NMR. Exposing a solution of **25a** in acetonitrile and water to phenyliodine(III) diacetate (PIDA) led to dearomatization. Dienone **29**, whose structure was verified by single-crystal X-ray analysis, was isolated in 33% yield. The dienone motif proved to be resistant to ozonolysis and only slow partial oxidation of the secondary alcohol in **29** was observed.

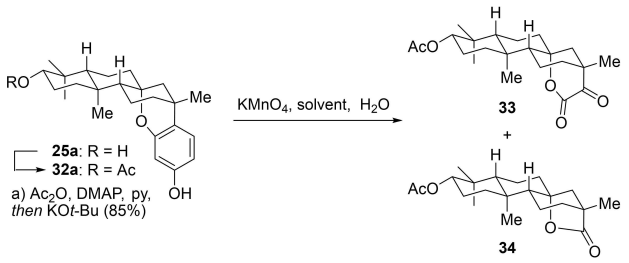
We attempted to increase the reactivity of the diene by breaking the conjugation with the carbonyl group. However, 1,2-addition of methyllithium to **29** to give **30** was not observed but a complex mixture was obtained instead. Finally, Sharpless oxidation ($RuCl_3$, $NaIO_4$, CCl_4, MeCN, H_2O) of 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.[33] 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_5IO_6, CCl_4, MeCN, H_2O) 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 ($KMnO_4$, acetone, H_2O). 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_2O, DMAP, pyridine) and subsequent selective deprotection of the phenol (KO*t*-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, ketolactone **33** was isolated in 19% yield along with lactone **34** in 18% yield (Table 3, entry 1).[35] 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 ketolactone **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 methylenation were unsuccessful.

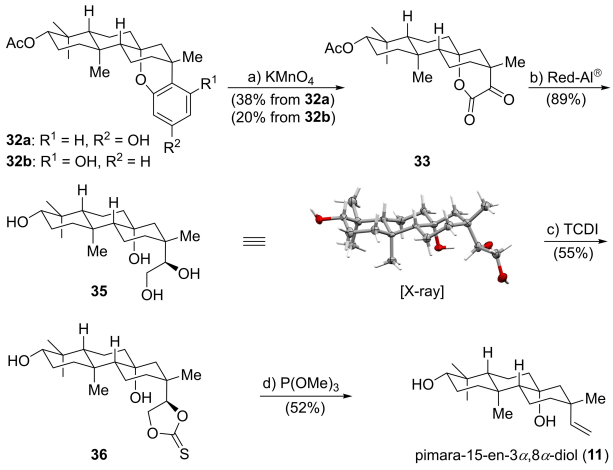
For the deprotection and reduction of **33** we initially investigated a lithium aluminum hydride reduction. In this case, we only observed incomplete reduction. In contrast, treatment with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®) reproducibly afforded tetraol **35** in excellent yield (89%). For the final installation of the axial vinyl unit, direct vanadium[36] or rhenium[37] catalyzed deoxydehydration (Bu_4NReO_4, P(*o*-tolyl)$_3$; H_4NReO_4, P(*o*-tolyl)$_3$; $MeReO_4$, P(*o*-tolyl)$_3$) led to decomposition. When employing Nicholas conditions (Bu_4NReO_4, Na_2SO_3, 15-crown-5 or H_4NReO_4, indoline), traces of the diterpenoid **11** were obtained, but as an inseparable mixture with side products.[38] Finally, the Corey–Winter protocol was found to be the best option.[39] Thiocarbonate **36** was initially accessed by

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_6H_5Cl	24	100	12	traces	traces

[a] Reagents and conditions: a) Ac_2O, DMAP, pyridine, CH_2Cl_2, 22 °C, *then* KO*t*-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-3α,8α-diol (**11**). Reagents and conditions: a) $KMnO_4$, ethyl acetate, H_2O, 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(OMe)$_3$, 110 °C, 52%. Ac = acetyl, DMF = *N*,*N*-dimethylformamide, Red-Al® = sodium bis(2-methoxyethoxy)aluminum hydride, TCDI = 1,1′-thiocarbonyldiimidazole, THF = tetrahydrofuran.

treating a solution of tetraol **35** in chloroform with thiophosgene 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 phosphite to 110 °C, the final elimination was induced to complete the first total synthesis of pimara-15-en-3α,8α-diol (**11**, 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 enantiomer in the literature.[13]

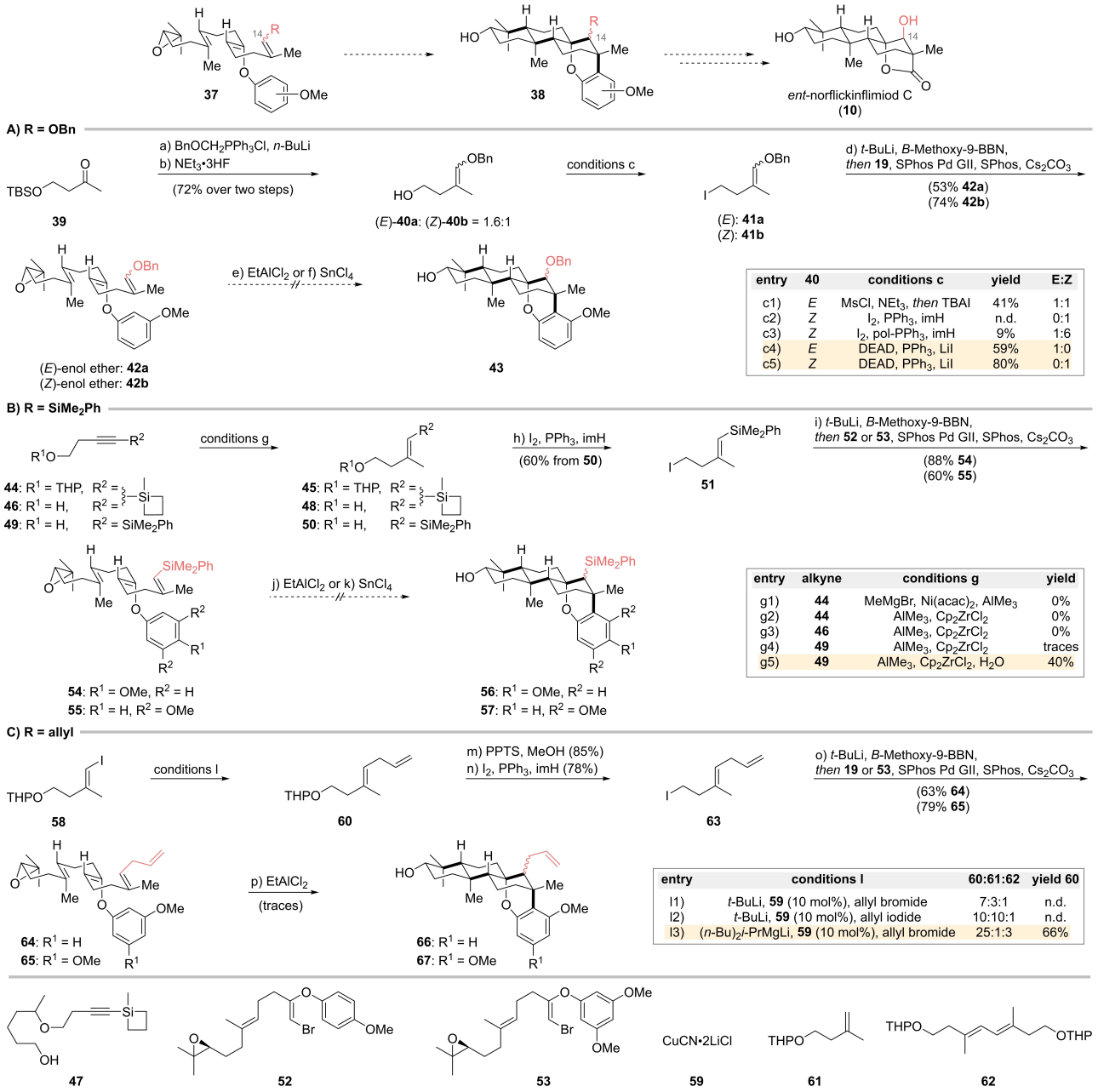
Towards *ent*-Norflickinflimiod C

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 ((benzyloxy)methyl) triphenylphosphonium chloride ($BnOCH_2PPh_3Cl$) and *n*-butyllithium.[40] Deprotection of the primary alcohol with triethylamine trihydrofluoride afforded alcohol **40** in 72% yield as a separable 1.6:1 mixture of **40a**:**40b**. 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.[41] 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–polystyrene (pol–PPh_3), a polymer-bound variant.[42] This enabled the isolation of **41** as a mixture of isomers (**41a**:**41b** = 1:6) in 9% yield. Finally, a modified Mitsunobu reaction (DEAD, PPh_3, LiI) was able to deliver isomerically pure **41a** in 59% and **41b** in 80% yield, respectively.[43] Fragments **41a/b** were converted into a boron–ate complex by treatment with *t*-butyllithium in the presence of *B*-methoxy-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 ($EtAlCl_2$) or tin(IV) chloride ($SnCl_4$) 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).[12,44] We expected that the β-silicon effect would ensure the formation of a six-membered carbocycle during the third ring-closure.[45]

We first planned the installation of a silacyclobutane unit due to its small size and its capability to undergo the Tamao–Fleming oxidation.[46] For the preparation of **45**, we attempted carbometallation of tetrahydropyranyl ether **44** (conditions g). In the presence of methylmagnesium bromide and catalytic amounts of nickel(II) bis(acetylacetonate) ($Ni(acac)_2$) and trimethylaluminum ($AlMe_3$) decomposition occurred.[47] Treatment of **44** with trimethylaluminum and zirconocene dichloride (Cp_2ZrCl_2) led to the formation of **46** and **47** via nucleophilic ring-opening of the tetrahydropyranyl group.[48] When alcohol **46** was treated under the same conditions, slow decomposition over six days was observed. When silacyclobutane **46** was exchanged with dimethyl(phenyl)silane **49**, formation of traces of **50** occurred upon treatment with Cp_2ZrCl_2 and $AlMe_3$. 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.[49] 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 CH_2Cl_2 was treated with ethylaluminum dichloride ($EtAlCl_2$) or tin(IV) chloride ($SnCl_4$) 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 l).[50] 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 protodemetallation product **61** and dimer **62** in a 7:3:1 ratio, which was determined by ^{1}H NMR analysis of the crude reaction mixture. The use of allyl iodide instead of allyl bromide resulted in an even larger amount of the protodemetallation product **61**. We found that the mixed magnesate (n-Bu)$_2i$-PrMgLi was capable of suppressing the formation of **61** (**60:61:62** = 25:1:3) and the desired product **60** was isolated in 66% yield.[51] Deprotection of the tetrahydropyranyl ether with pyridinium *p*-toluenesulfonate (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 ($EtAlCl_2$) or tin(IV) chloride ($SnCl_4$) at −78 °C led to the formation of a complex product mixture. Treatment of **65** with tin(IV) 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



entry	40	conditions c	yield	E:Z
c1)	*E*	MsCl, NEt_3, *then* TBAI	41%	1:1
c2)	*Z*	I_2, PPh_3, imH	n.d.	0:1
c3)	*Z*	I_2, pol-PPh_3, imH	9%	1:6
c4)	*E*	DEAD, PPh_3, LiI	59%	1:0
c5)	*Z*	DEAD, PPh_3, LiI	80%	0:1

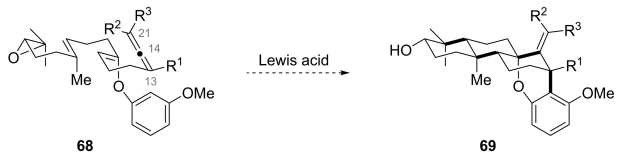
entry	alkyne	conditions g	yield
g1)	**44**	MeMgBr, $Ni(acac)_2$, $AlMe_3$	0%
g2)	**44**	$AlMe_3$, Cp_2ZrCl_2	0%
g3)	**46**	$AlMe_3$, Cp_2ZrCl_2	0%
g4)	**49**	$AlMe_3$, Cp_2ZrCl_2	traces
g5)	**49**	$AlMe_3$, Cp_2ZrCl_2, H_2O	40%

entry	conditions l	60:61:62	yield 60
l1)	*t*-BuLi, **59** (10 mol%), allyl bromide	7:3:1	n.d.
l2)	*t*-BuLi, **59** (10 mol%), allyl iodide	10:10:1	n.d.
l3)	$(n\text{-Bu})_2i\text{-PrMgLi}$, **59** (10 mol%), allyl bromide	25:1:3	66%

Scheme 6. Synthesis of cyclization precursors **42 a/b**, **54**, **55**, **64** and **65**. Reagents and conditions: a) $BnOCH_2PPh_3Cl$, *n*-BuLi, THF, −78 °C to 22 °C; b) $NEt_3 \cdot 3HF$, MeCN, 22 °C, 72 % over two steps; c1) MsCl, NEt_3, CH_2Cl_2, 0 °C to 22 °C, *then* TBAI, benzene, 80 °C, 41 % of **41 a/b** (1 : 1); c2) I_2, PPh_3, imH, CH_2Cl_2, 0 °C, inseparable mixture of **41 b** with PPh_3; c3) I_2, pol–PPh_3, imH, CH_2Cl_2, 0 °C to 22 °C, 9 % of **41 a/b** (1 : 6); c4) DEAD, PPh_3, LiI, THF, 0 °C, 59 %; c5) DEAD, PPh_3, LiI, THF, 0 °C, 80 %; d) *t*-BuLi, *B*-methoxy-9-BBN, THF, −78 °C to 22 °C, *then* **19**, SPhos Pd GII, SPhos, Cs_2CO_3, DMF, H_2O, 40 °C, 53 % of **42 a**, 74 % of **42 b**; e) $EtAlCl_2$, CH_2Cl_2, −78 °C; f) $SnCl_4$, CH_2Cl_2, −78 °C; g1) **44**, MeMgBr, $Ni(acac)_2$, $AlMe_3$, THF, 22 °C; g2) **44**, $AlMe_3$, Cp_2ZrCl_2, CH_2Cl_2, 0 °C to 22 °C; g3) **46**, $AlMe_3$, Cp_2ZrCl_2, CH_2Cl_2, 0 °C to 22 °C; g4) **49**, $AlMe_3$, Cp_2ZrCl_2, CH_2Cl_2, 22 °C to 40 °C, traces; g5) **49**, $AlMe_3$, Cp_2ZrCl_2, H_2O, CH_2Cl_2, −40 °C to 40 °C, 40 %; h) I_2, PPh_3, imH, CH_2Cl_2, 0 °C, 60 %; i) *t*-BuLi, *B*-methoxy-9-BBN, THF, −78 °C to 22 °C, *then* **52** or **53**, SPhos Pd GII, SPhos, Cs_2CO_3, DMF, H_2O, 40 °C, 88 % of **54**, 60 % of **55**; j) $EtAlCl_2$, CH_2Cl_2, −78 °C; k) $SnCl_4$, CH_2Cl_2, −78 °C; l1) *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; l2) *t*-BuLi, CuCN·2LiCl (10 mol%), allyl iodide, THF, −78 °C, **60/61/62** (10 : 10 : 1) determined by ^1H NMR analysis of the crude reaction mixture; l3) *i*-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, *B*-methoxy-9-BBN, THF, −78 °C to 22 °C, *then* **19** or **53**, SPhos Pd GII, SPhos, Cs_2CO_3, DMF, H_2O, 40 °C, 63 % of **64**, 79 % of **65**; p) $EtAlCl_2$, CH_2Cl_2, −78 °C, traces. Acac = acetylacetone, *B*-methoxy-9-BBN = 9-methoxy-9-borabicyclo[3.3.1]nonane, Bn = benzyl, Cp = cyclopentadienyl, DEAD = diethyl azodicarboxylate, DMF = *N*,*N*-dimethylformamide, imH = imidazole, MsCl = methanesulfonyl chloride, n.d. = not determined, pol–PPh_3 = diphenylphosphino–polystyrene, PPTS = pyridinium *p*-toluenesulfonate, py = pyridine, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, SPhos Pd GII = chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II), TBAI = tetrabutylammonium iodide, TBS = *t*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, THP = tetrahydropyranyl.

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.[52] As a result, verification of the proposed structure **67** was not possible and we discontinued our efforts on this approach.

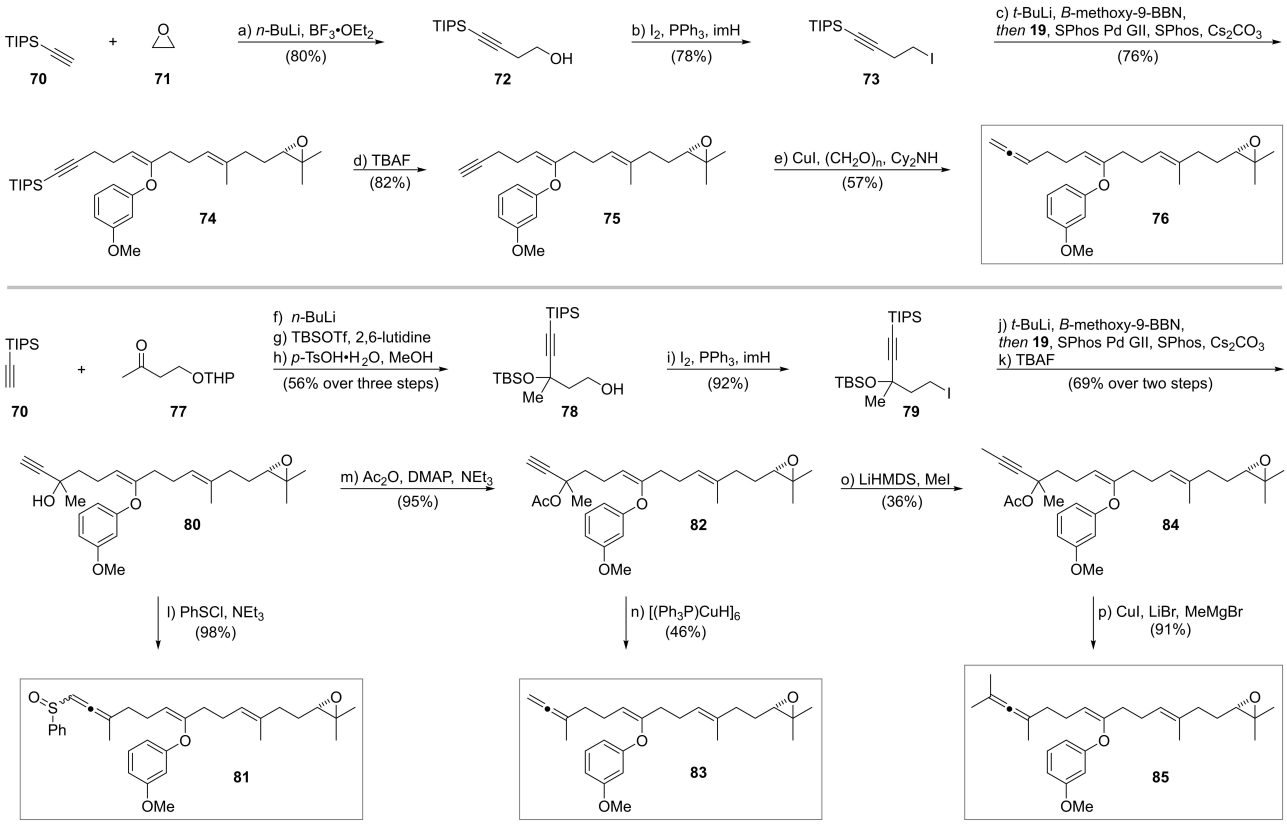
Due to the results obtained for **65** and the lessons learned from the alternative substrates, we planned a new route avoiding additional heteroatoms in the cyclization precursor. We decided to investigate the application of allenes as hydroxy-surrogates, which are an underrepresented functional group in the field of polyene cyclization (Scheme 7).[53]



Scheme 7. Envisioned tetracyclization/*endo*-termination sequence of allene **68** towards the total synthesis of *ent*-norflickinflimiod C (**10**).

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).



Scheme 8. Synthesis of cyclization precursors **76**, **81**, **83** and **85**. Reagents and conditions: a) *n*-BuLi, $BF_3 \cdot OEt_2$, THF, −78 °C to 0 °C, 80%; b) I_2, PPh_3, imH, Et_2O, MeCN, 22 °C, 78%; c) *t*-BuLi, *B*-methoxy-9-BBN, THF, −78 °C to 22 °C, *then* **19**, SPhos Pd GII, SPhos, Cs_2CO_3, DMF, H_2O, 40 °C, 76%; d) TBAF, THF, 0 °C to 22 °C, 82%; e) CuI, $(CH_2O)_n$, Cy_2NH, 1,4-dioxane, 103 °C, 57%; f) *n*-BuLi, THF, −78 °C to 22 °C; g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; h) *p*-TsOH·H_2O, MeOH, 22 °C, 56% over three steps; i) I_2, PPh_3, imH, Et_2O, MeCN, 22 °C, 92%; j) *t*-BuLi, *B*-methoxy-9-BBN, THF, −78 °C to 22 °C, *then* **19**, SPhos Pd GII, SPhos, Cs_2CO_3, DMF, H_2O, 40 °C; k) TBAF, THF, 0 °C to 22 °C, 69% over two steps; l) PhSCl, NEt_3, THF, −78 °C to 22 °C, 98%; m) Ac_2O, DMAP, NEt_3, 22 °C, 95%; n) $[(Ph_3P)CuH]_6$, toluene, 22 °C, 46%; o) LiHMDS, MeI, THF, −78 °C to 22 °C, 36%; p) CuI, LiBr, MeMgBr, THF, 0 °C to 22 °C, 91%. Ac = acetyl, *B*-methoxy-9-BBN = 9-methoxy-9-borabicyclo[3.3.1]nonane, Cy = cyclohexyl, DMAP = *N*,*N*-dimethylpyridin-4-amine, DMF = *N*,*N*-dimethylformamide, imH = imidazole, LiHMDS = lithium hexamethyldisilazide, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, SPhos Pd GII = chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II), TBAF = tetra-*n*-butylammonium fluoride, TBS = *t*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, THP = tetrahydropyranyl, TIPS = tri-*iso*-propylsilyl, Ts = toluenesulfonyl.

Thus, we decided to install the allene after the $C(sp^2)$–$C(sp^3)$ coupling. The synthesis of allene **76** commenced with the addition of lithiated alkyne **70** to oxirane (**71**) in the presence of boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$) yielding primary alcohol **72** in 80% yield (Scheme 8).[54] Treatment of **72** with iodine, triphenylphosphine and imidazole afforded alkyl iodide **73** in 78% yield.

Borylation of **73** by exposure to *t*-butyllithium 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 precatalyst (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 Crabbé homologation (CuI, $(CH_2O)_n$, Cy_2NH) to provide the cyclization precursor **76** in 57% yield.[55]

The higher substituted allenes **81**, **83** and **85** were prepared by a divergent strategy. Addition of lithiated alkyne **70** to ketone **77** was followed by silylation of the resulting tertiary alcohol under Corey's conditions (TBSOTf, 2,6-lutidine).[56] Cleavage of the tetrahydropyranyl ether under acidic conditions (*p*-TsOH, MeOH) afforded primary alcohol **78** in 56% yield over three steps. Alkyl 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 dienyne **80** in 69% yield over two steps. Upon treatment of **80** with phenylsulfenyl chloride[57] (PhSCl) in the presence of triethyl amine a Mislow-Evans rearrangement[58] was induced to complete the synthesis of cyclization precursor **81** in almost quantitative yield.[59] Acetylation of tertiary alcohol **80** (Ac_2O, DMAP, NEt_3) gave ester **82** in 95% yield. Employing Stryker's reagent ($[(Ph_3P)CuH]_6$) to a solution of **82** in degassed toluene delivered allene **83** in 46% yield.[60] 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 S_N2' reaction of the propargylic acetate. By subjecting **84** to a mixture of copper(I) iodide, lithium bromide and methylmagnesium bromide in tetrahydrofuran **85** was formed in 91% yield.[61]

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**.

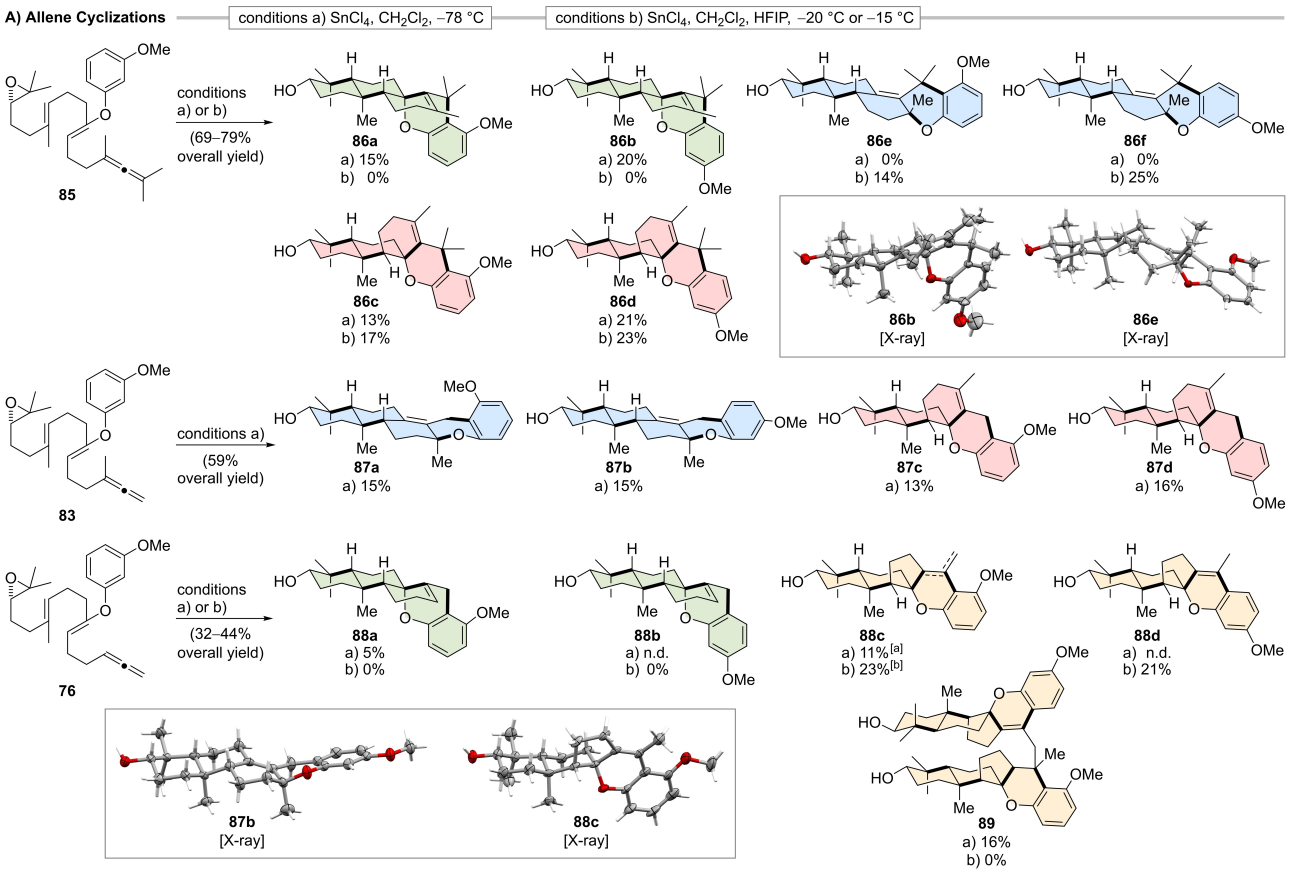
We assume that the formation of *cis*- and *trans*-fused products can be attributed to a low π-facial selectivity of the enol ether involved in the second ring-closure (Scheme 9B). Formation of a chair-chair conformation **68a** leads to the generation of the *trans*-fused oxocarbenium ion **90**. Subsequent 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 **69**. 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 **68b** 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 [6,6,6,6,6]-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 polyene cyclization reactions, we decided to include it in our screening.[62] 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 regioisomers **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-phenolate 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 regioisomers **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-phenolate shift (see Supporting Information for details). Analysis of the 2D NMR data revealed the opposite stereochemistry at C-13 when compared to **86e** and **86f**. This was supported by single-crystal X-ray analysis of **87b**. The *cis*-fused regioisomers **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



Scheme 9. A) Cyclization of precursors **85**, **83** and **76**. B) Observed cyclization pathways. [a]: a mixture of double bond isomers was obtained, and the major *exo*-methylene isomer spontaneously isomerized in a solution of $CDCl_3$ to the *endo*-isomer while standing at 22 °C; [b] only the *endo*-isomer was isolated. Reagents and conditions: a) $SnCl_4$, CH_2Cl_2, −78 °C; b) $SnCl_4$, CH_2Cl_2, HFIP, −15 °C for **85**, −20 °C for **76**. HFIP = hexafluoro-*iso*-propanol.

not facilitate the formation of *endo*-termination products. Instead, the *trans*-fused pentacyclic product **88 a** was isolated in 5% yield. The formation of regioisomer **88 b** 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 impurities.

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 9B). DFT calculations suggest kinetic reaction control, as the theoretical *cis*-fused [6,6,6,6,6]-product (of the general structure **96**) originating from an *exo*-termination of an allylic cation would be thermodynamically favored ($\Delta G = 3.3$ 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 nucleophilic attack of the *exo*-methylene isomer of **88d** at the intermediary tertiary benzylic carbocation (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 polyene tetracyclization/transannular *endo*-termination sequence involving a dual nucleophilic aryl enol ether. Four carbon–carbon bonds and five stereocenters were formed from a readily available polyene by the key cyclization assembling the pimarane carbon skeleton in a single step. Oxidative cleavage of the aryl group enabled the first total synthesis of the diterpenoid pimara-15-en-3α-8α-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 polyene backbone. A library of cyclization precursors aimed at the total synthesis of the *nor*-diterpenoid *ent*-norflickinflimiod C (**10**) was prepared. Polyene tetracyclization of three alkyl-substituted allenes delivered novel pentacyclic 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.

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Conflict of Interest

The authors declare no conflict of interest.

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

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