Synthetic Studies towards an Advanced Precursor of the Jatrophane Diterpene Pl-4

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Abstract: Jatrophane diterpenes, isolated from members of the Euphorbiaceae plant family, constitute a class of biologically and structurally intriguing natural products. Herein, different strategies for the preparation of an advanced intermediate towards the total synthesis of the jatrophane diterpene Pl-4 are described. Key strategies for the elaboration of the jatrophane precursors include hydrometalation and radical reactions.

Key words: Euphorbiaceae, jatrophane diterpene, hydrometalation, samarium diiodide, Reformatsky reaction

When Juba II of Mauretania, one of the most loyal client kings of the Roman Empire and contemporary of Emperor Augustus, was troubled by a swollen belly, Euphorbus applied herbal remedies to cure his ailments. In appreciation of his healing and relief, and in honor of his Greek physician, Juba named the succulent and strongly laxative plant, which helped to improve his conditions, Euphorbia. Much later, Carl Linnaeus, one of the most important botanists in the 18th century, assigned the name *Euphorbia* to the entire genus.

The application of spurges, as members of the Euphorbiaceae plant family are commonly referred to, in the treatment of cancerous conditions, swellings, and warts in traditional herbal folk medicine, is historically documented from different cultures around the globe.[1] Since the isolation of jatrophone by Kupchan in 1970,[2] phytochemists have shown increasing interest in the isolation of active ingredients from plants of the Euphorbiaceae family. To date, numerous natural products, possessing different core frameworks, such as the tigliane, ingenane, daphnane, and jatrophane skeleton have been isolated. These terpene-based natural products were explored in extensive biological studies and demonstrated a wide range of pharmacologically promising properties, including anti-proliferation, cytotoxic, antimicrobial, anti-inflammatory, as well as antiviral activity.[3] Additionally, jatrophane diterpenes were identified to bind and selectively inhibit the ATP-dependent efflux pump P-glycoprotein (Pgp).[4] This is probably the most interesting biological activity of this class of natural products, as overexpression of Pgp and the resulting multidrug resistance (MDR) are commonly observed in cancer cells. Therefore, jatrophane diterpenes might serve as lead compounds in the development of co-therapeutics for cancer chemotherapy. Despite these promising biological properties and the challenging structural features, only few synthetic routes to jatrophane diterpenes have been reported.[5]

Pl-4 (**1**) was isolated in 2003 from a Hungarian sample of *Euphorbia platyphyllos*, an annual herbaceous plant.[6] The natural product belongs to the jatrophane-type family of diterpenes. As shown in Figure 1, jatrophanes are characterized by a highly functionalized cyclopentane ring, which is annulated to a twelve-membered macrocycle. In most jatrophanes, the two rings are *trans* fused, however, a few derivatives, such as Pl-4, were isolated that possess a double bond at the ring junction. In addition to its promising biological properties, Pl-4 represents an exciting target for synthetic chemists, which inspired us to develop a strategy towards this terpenoid natural product.

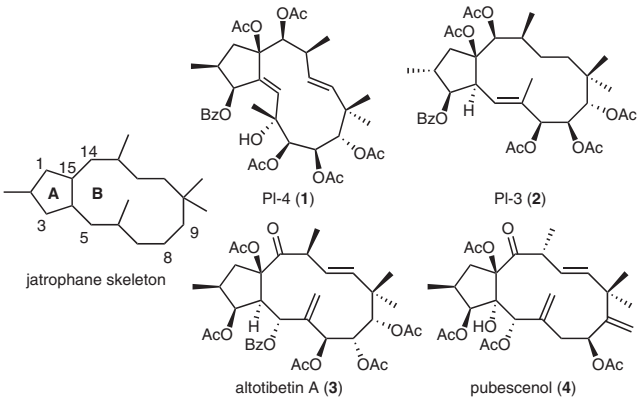

Figure 1 Jatrophane skeleton and representative jatrophane diterpenes

Recently, we reported the preparation of an advanced intermediate towards the synthesis of Pl-4 (**1**).[5o] The key strategy of this approach relied on a regioselective chelation-controlled lithiation/alkylation sequence of the more hindered bromide in the requisite vinyl dibromide as outlined in Scheme 1.[7] However, before the preparation of vinyl bromide **5** was achieved via the aforementioned dibromide coupling approach, several routes were investigated. With the intrinsic potential of jatrophane diterpenes as co-therapeutics for modern cancer chemotherapy, we also wish to describe unsuccessful approaches to accelerate the development of future synthetic routes towards members of the jatrophane family. The following section summarizes unsuccessful attempts to ac-

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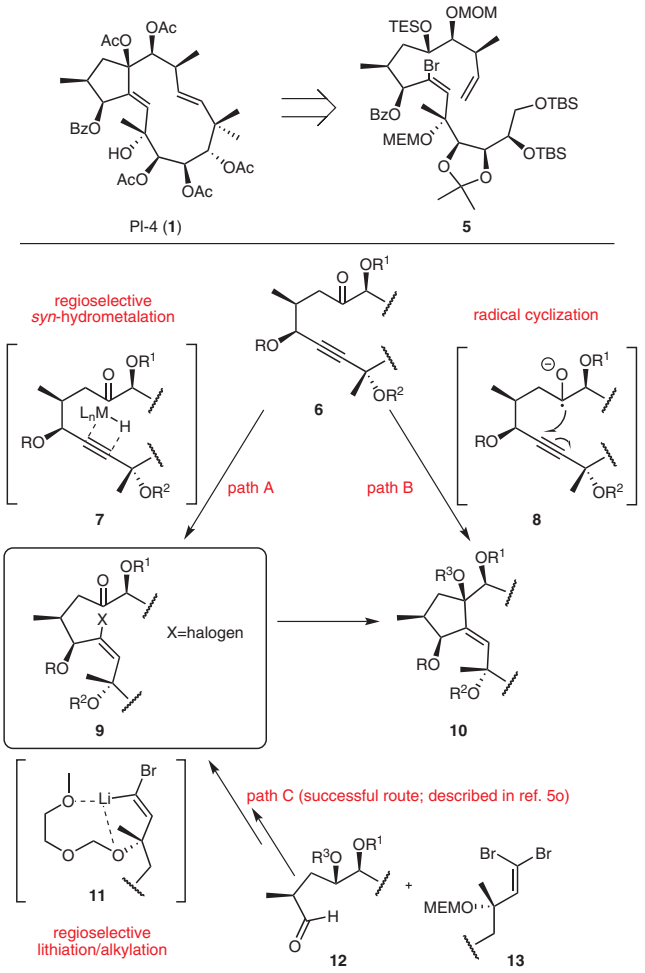
cess **5** via different strategies, such as hydrometalation reactions and radical protocols.



Scheme 1 General considerations

The initial retrosynthetic considerations towards the jatrophane diterpene Pl-4 are outlined in Scheme 1. We envisaged a late stage closure of the cyclopentane ring and intended the preparation of vinyl halide **5** as a precursor for the key cyclization reaction. The initial strategy (path A) relied on a regioselective *syn*-hydrometalation of ynone **6**. Alternatively, in a more concise manner, the alkyne in intermediate **6** could also be directly employed in a 5-*exo*-*dig* ring closure reaction via an initially formed ketyl radical (path B). Attempts towards the preparation of the highly advanced intermediate **5** via paths A and B are described in detail. The eventually successful regioselective lithiation/alkylation sequence (path C) has already been described.[5o]

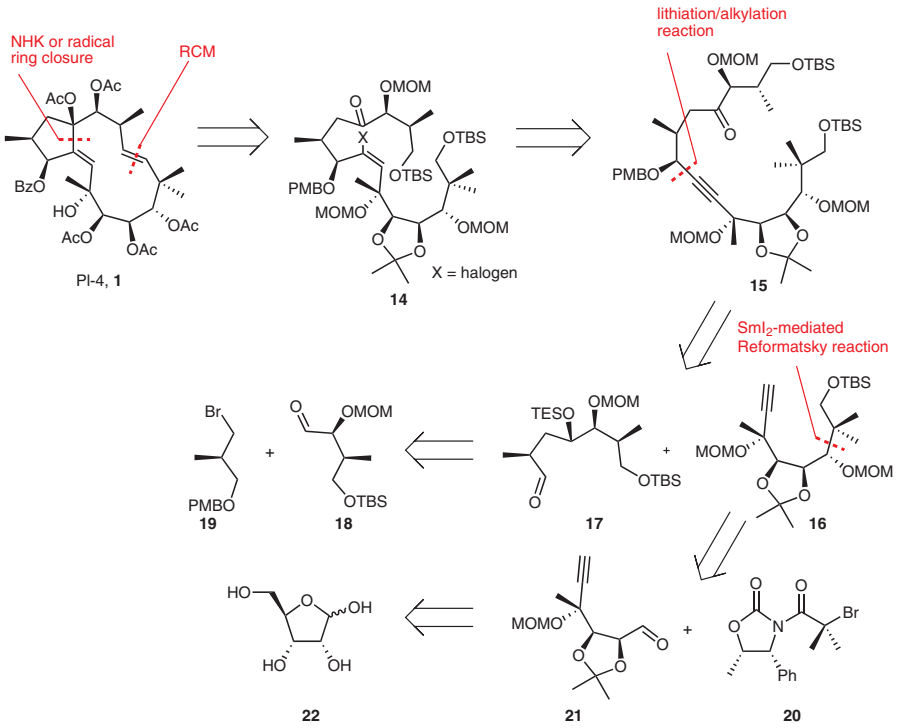
Hydrometalation Approach: The initial retrosynthetic analysis towards Pl-4 (**1**) is outlined in Scheme 2. As mentioned above, we intended to close the twelve-membered macrocycle as well as the cyclopentane ring at a very late stage of the synthesis via a ring-closing-metathesis (RCM), and a Nozaki–Hiyama–Kishi (NHK) or a radical reaction, respectively. The precursor for the ring-closing reaction, intermediate **14**, should become accessible from alkyne **15** through a *syn*-selective hydrometalation reaction. The sterical influence of the quaternary center adjacent to the alkyne should govern the metal to the more accessible, desired position. Alkyne **15** was envisaged to be elaborated from aldehyde **17** and terminal alkyne **16** by a lithiation/alkylation sequence. While **17** can be prepared from aldehyde **18** and known bromide **19**, alkyne **16** is accessible via a route featuring a diastereoselective samarium diiodide mediated Reformatsky reaction as a key step.[5k,8] D-Ribose was chosen as an inexpensive and readily available starting material for aldehyde **21**.

The preparation of the northern fragment of the natural product commenced with TBS-protected aldehyde **23** (Scheme 3), readily available from ethylene glycol via a known two-step procedure.[9] While Brown crotylation[10] delivered the chiral homoallylic alcohol **26** in low and irreproducible yield, the compound was obtained in satisfying yield and enantiomeric excess under Roush crotylation conditions.[11] Next, MOM-protection of the secondary alcohol and a desilylation/oxidation sequence allowed the isolation of aldehyde **27**.

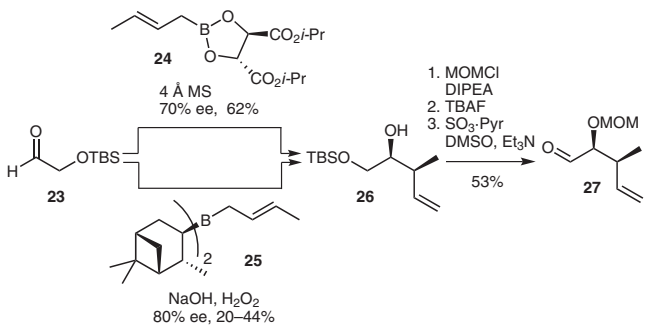
The synthesis of the coupling partners for aldehyde **27**, bromides **31** and **32**, is outlined in Scheme 4. Protection of the hydroxyl moiety in commercially available (–)-(*R*)-Roche ester **28** as its TES or TBS ether was followed by diisobutylaluminum hydride reduction of the methyl ester. Then, the bromide was introduced either by mesylation of the primary alcohol, followed by nucleophilic displacement with tetrabutylammonium bromide,[12] or alternatively under Appel conditions.

All attempts to accomplish the coupling of bromides **31** or **32** with aldehyde **27** failed (Scheme 4). Lithiation of **31** with *n*- or *tert*-butyllithium in different solvents resulted in decomposition of the lithiated species. The instability of silyl ethers towards organolithium species is well documented[13] and we hoped to solve the problem by exchanging the labile TES ether for a more stable TBS group in **32**. Unfortunately, lithiation of halide **32** using *n*-butyl- or *tert*-butyllithium also failed to deliver the desired product. Addition of magnesium bromide–diethyl etherate and lithium bromide to the lithiated species for the in situ formation of the transmetalated Grignard species[14] resulted in decomposition of the starting material. Direct formation of the Grignard species, reaction with indium (activated under sonication), or NHK coupling conditions only allowed the re-isolation of **32**.

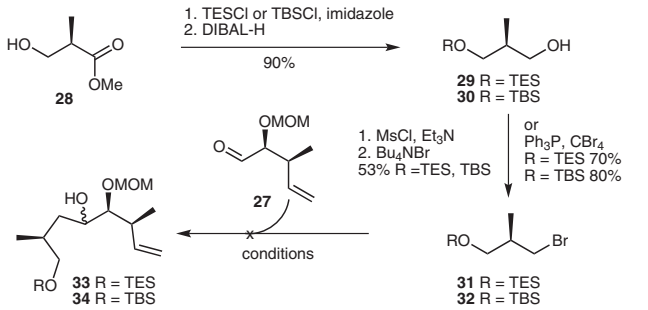
Because of the instability of the silyl ethers, we decided to introduce a PMB protecting group. Reaction of Roche ester **28** with PMB-trichloroacetimidate followed by lithium



Scheme 2 Retrosynthetic analysis: hydrometalation approach

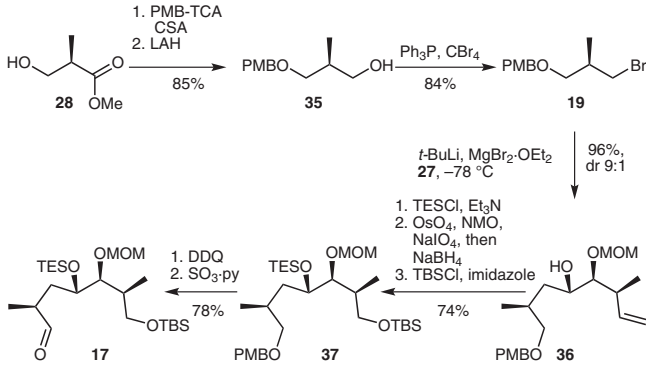


Scheme 3 Synthesis of aldehyde **27**

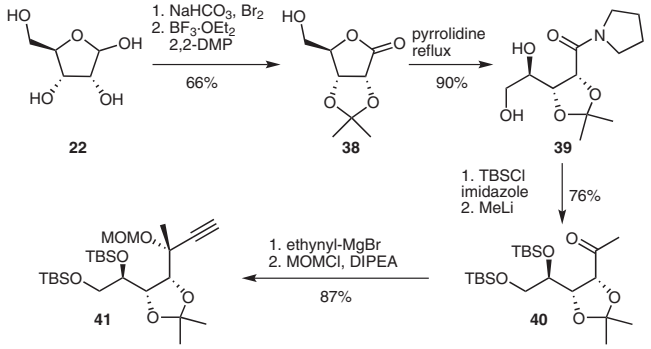


Scheme 4 First attempt at the synthesis of the northern fragment of Pl-4

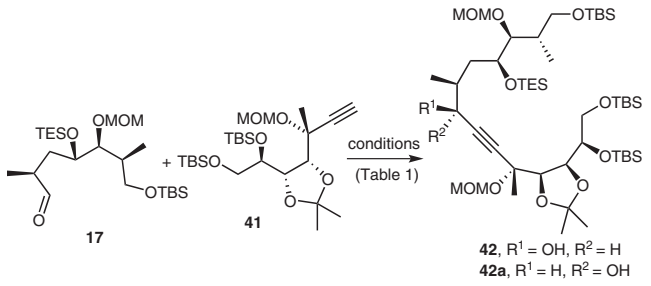
aluminum hydride reduction allowed the isolation of alcohol **35** (Scheme 5). The bromide was installed applying the Appel protocol and **19** could be obtained in good overall yield. With bromide **19** in hand, the crucial coupling reaction could be approached. Lithiation of **19** with *tert*-butyllithium at –78 °C and subsequent addition of magnesium bromide–diethyl etherate afforded the intermediate Grignard species, which readily reacted with aldehyde **27** to deliver the desired adduct **36** in excellent 96% yield, as a 9:1 diastereomeric mixture. The expected, predominant formation of the *S*-configured alcohol through this chelation-controlled addition reaction[14c] could be confirmed by NMR studies.[5o] However, as the hydroxyl moiety is oxidized at a later stage of the synthesis, the stereochemical outcome of the reaction is inconsequential to the overall efficiency and both diastereomers could be employed for all successive steps.[15] Next, the corresponding secondary hydroxyl group was protected as its TES ether. The following steps were devoted to masking the terminal alkene as a primary TBS ether to prevent potential side reactions in the hydrometalation reaction later in the synthesis. Dihydroxylation of the terminal alkene with catalytic amounts of osmium tetroxide and *N*-methylmorpholine *N*-oxide, was followed by addition of sodium periodate to deliver the desired aldehyde in a one-pot procedure and it was instantly reduced with sodium borohydride to give the corresponding alcohol. Next, the primary hydroxyl group was TBS protected to afford fully protected intermediate **37**, which was then converted into aldehyde **17** via a 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) mediated debenzylation and oxidation of the primary alcohol under Parikh–Doehring conditions.[16]



Scheme 5 Completion of the northern fragment of Pl-4



Scheme 6 Preparation of the southern fragment of Pl-4



Scheme 7 Alkyne/aldehyde coupling

For the preparation of the southern part of the natural product D-ribose (**22**) was selected as an inexpensive and readily available starting material (Scheme 6).[5k] Oxidation of the lactol with bromine and sodium hydrogen carbonate delivered D-ribonolactone, which was converted into acetonide **38**.[17] Exposure of the lactone to pyrrolidine at elevated temperature afforded amide **39** in excellent yield. Both hydroxyl functionalities in **39** were silylated before addition of methyllithium at –78 °C allowed the isolation of methyl ketone **40**. The synthesis of alkyne **41** was accomplished after Grignard reaction with ethynylmagnesium bromide,[18] which afforded the terminal alkyne as single isomer,[19] and MOM protection of the newly generated tertiary alcohol. Alkyne **41** was used in the further course of the synthesis as a simplified model system for the southern fragment of Pl-4.

As summarized in Table 1, various conditions for the coupling of alkyne **41** and aldehyde **17** (Scheme 7) were evaluated. Unfortunately, a chiral alkylation reaction, following the Carreira protocol,[20] with (–)-*N*-methylephedrine, zinc triflate, and triethylamine only resulted in re-isolation of the starting materials (entries 1 and 8). When butyllithium was used for the lithiation of alkyne **41**, the desired coupling products **42** and **42a** could be obtained, however, the yield of the reaction was non-reproducible on a larger scale (entry 2). Unfortunately, further addition of hexamethylphosphoramide or cerium(III) chloride resulted in a decreased yield (entries 3 and 4).[21] Non-nucleophilic bases proved to be advantageous for the coupling reaction and the desired products **42** and **42a** could be isolated in 71% yield when lithium hexamethyldisilazide was employed in tetrahydrofuran at –78 °C (entry 5). In this case, transmetalation using cerium(III) chloride helped to further improve the overall yield of the coupling reaction to excellent 84% (entry 7). The only drawback was the stereochemical outcome of the alkyne/aldehyde coupling reaction as under all reaction conditions, the desired intermediates **42** and **42a** were isolated as a 1:2 mixture of diastereomers, favoring the undesired isomer.[22] However, at this point we decided to proceed with the synthesis before improving the diaste-

Table 1 Alkyne/Aldehyde Coupling Conditions

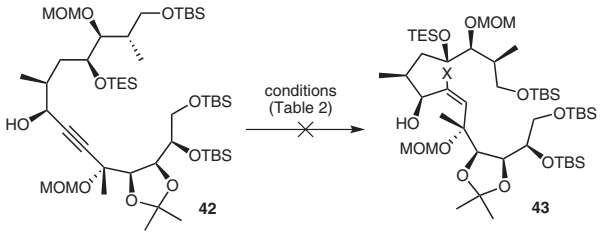
Entry	Reagents	Temp (°C)	Solvent	Yield (%)
1	(–)-*N*-methylephedrine, $Zn(OTf)_2$, Et_3N	r.t.	toluene	0[a]
2	BuLi	–78 to r.t.	THF	26–47[b]
3	BuLi, $CeCl_3$	–78 to r.t.	THF	5[b]
4	BuLi, HMPA	–78 to r.t.	THF	10[b]
5	LHMDS	–78 to r.t.	THF	71[b]
6	KHMDS	–78	THF	53[b]
7	LHMDS, $CeCl_3$	–78	THF	84[b]
8	(–)-*N*-methylephedrine, $Zn(OTf)_2$, Et_3N	r.t.	THF	0[a]

[a] No reaction was observed, re-isolation of the starting materials.
[b] dr (**42**/**42a**) 1:2.

reoselectivity or developing methods for the inversion of the stereocenter in the undesired isomer.

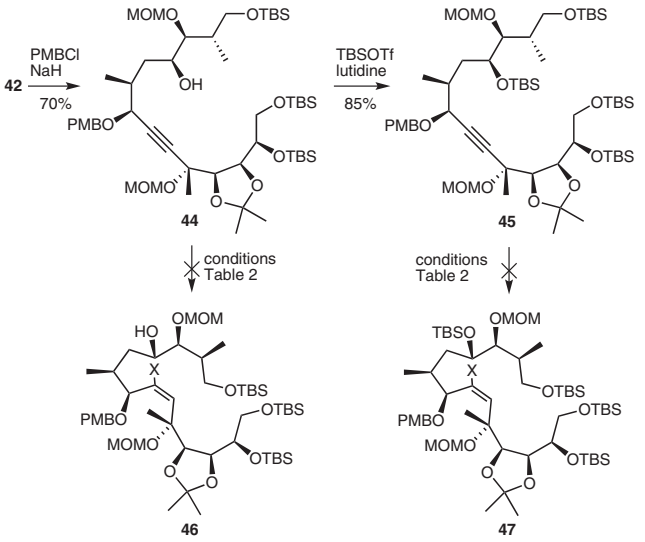
With internal alkyne **42** in hand, the stage was set to explore the key hydrometalation reaction. We expected that reaction of alkyne **42** with an organometallic species should result in an attack of the metal at the less-hindered position with concomitant *syn*-hydrogenation, which should establish the desired double bond geometry. Subsequent metal–halogen exchange would further provide a synthetic anchor for the closure of the cyclopentane ring, either via a radical process, or a NHK coupling reaction.

As outlined in Scheme 8 and Table 2, reaction of alkyne **42** with tributyltin hydride and a catalytic amount of dichlorobis(triphenylphosphine)palladium(II) (entry 1)[23] or palladium(II) acetate and tricyclohexylphosphine (entry 2)[24] only resulted in isolation of the starting material, even when the reaction was carried out at elevated temperatures. Next, we decided to apply hydrozirconation conditions.[25] However, no product formation was observed when the Schwartz reagent[26] was added to a solution of alkyne **42** in toluene (entry 3);[5m] the same outcome was observed after addition of methyllithium and zinc chloride (entry 4).[27] Our final attempt was a nickel-mediated hydrometalation reaction,[28] which resulted in decomposition of the starting material (entry 5).



Scheme 8 Hydrometalation reaction I

Either sterical hindrance, or the free hydroxyl moiety in alkyne **42** might be responsible for the unsatisfying outcome of the hydrometalation reaction. Thus, secondary alcohol **42** was allowed to react with sodium hydroxide and 4-methoxybenzyl chloride, which resulted in PMB protection of the secondary hydroxyl moiety adjacent to the alkyne, with concomitant cleavage of the TES group. The fully protected substrate was obtained after exposure of PMB ether **44** to TBS triflate and 2,6-lutidine (Scheme 9). With alkyne **45** in hand, the hydrometalation conditions, outlined in Table 2, were re-evaluated. Also, since PMB ether **44** was available, this compound was included in this study. Unfortunately, all experiments carried out with either **44** or **45**, confirmed our previous results and the desired vinyl halide was not obtained.



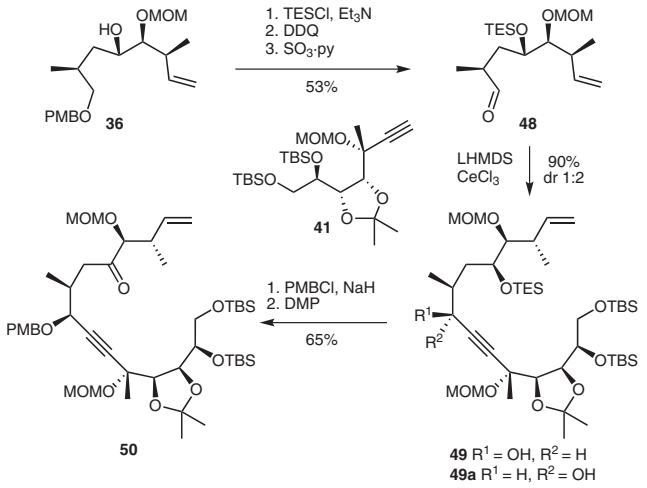
Scheme 9 Hydrometalation reaction II

We could rule out that the free hydroxyl moiety in **42** was responsible for the unfavorable outcome of the intended hydrometalation reaction and we concluded that the sterical hindrance of the internal alkyne might be the limiting factor. These results are in agreement with literature examples, as in most cases, hydrometalation reactions are carried out on unsubstituted or sterically less demanding substrates.[29] As the only remaining option, the cleavage of the MOM group on the quaternary center next to the internal alkyne, seemed unfeasible with respect to the protecting group strategy and overall efficiency of the synthesis, the hydrometalation route was abandoned.

Alkyne cyclization approach: Several methods describing the direct intramolecular cyclization reaction of aldehydes or ketones with internal or terminal alkynes have been published: Nickel-mediated intramolecular ring-closing reactions between internal alkynes and ketones[30] as well as cyclization reactions via low-valent titanium complexes[31] can be used for the preparation of five-membered cycloalkanols. Samarium diiodide is a useful reagent for the formation of ketyl radicals, which triggers

Table 2 Hydrometalation Reaction Conditions

Entry	Alkynes	Reagents	Temp (°C)	Result
1	**42**, **44**, **45**	$PdCl_2(PPh_3)_2$, Bu_3SnH, H_2O quench	r.t. to 60	re-isolation of substrate
2	**42**, **44**, **45**	$Pd(OAc)_2$, Cy_3P, Bu_3SnH, H_2O quench	r.t. to 60	re-isolation of substrate
3	**42**, **44**, **45**	$Cp_2Zr(HCl)$, I_2 quench	60	re-isolation of substrate
4	**42**	$Cp_2Zr(HCl)$, MeLi, $ZnCl_2$, I_2 quench	–78 to r.t.	re-isolation of substrate
5	**42**, **45**	$NiCl_2(PPh_3)_2$, DIBAL-H, NBS quench	0 to r.t.	decomposition



Scheme 10 Preparation of the cyclization precursor

cyclization reactions of alkynes.[32] According to these promising literature precedents, an alternative approach was launched, based on the direct utilization of internal alkynes without the foregoing installation of a vinyl halide, as pursued in the hydrometalation approach. Additionally, this idea seemed even more appealing, as the protection of the terminal double bond within the northern fragment, originating from the enantioselective crotylation reaction, is not required, and can be directly employed in the final RCM reaction later.

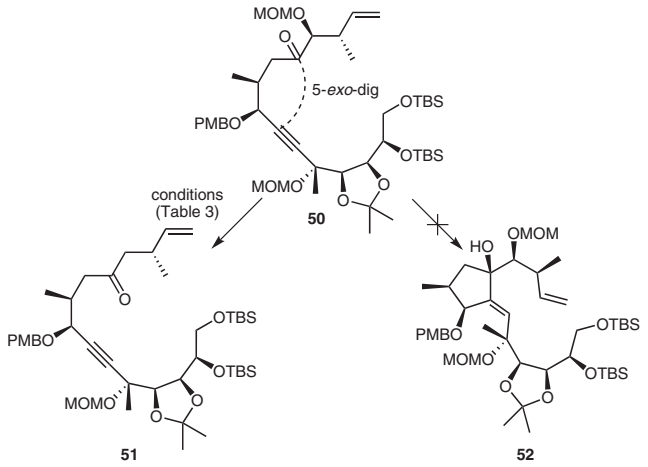
As outlined in Scheme 10, we started our endeavors from previously prepared alkene **36**. Silylation of the secondary alcohol was followed by cleavage of the benzyl ether and Parikh–Doehring oxidation of the primary hydroxyl group to give **48**.[5o] Next, the lithiation/alkylation reaction of aldehyde **48** and alkyne **41** was pursued. We were pleased to find that the previously established cerium-mediated coupling reaction delivered the desired diastereomeric adducts **49** and **49a** in excellent 90% overall yield. Again, the stereochemical outcome of the coupling reaction was not perfectly satisfying, as a 1:2 mixture of diastereomers, favoring the undesired isomer, was obtained.[33] We again decided to proceed with the synthesis using the desired diastereomer **49** without any optimization or correction of the stereocenter in **49a**. PMB protection of the secondary alcohol resulted in simultaneous cleavage of the TES group. Exposure of the resulting alcohol to Dess–Martin periodinane allowed the isolation of the substrate **50** for the crucial radical ring-closure reaction.

With alkynone **50** in hand, conditions for the cyclopentane formation were investigated. As pointed out above, addition of samarium diiodide to the cyclization precursor **50** should initiate the formation of a ketyl radical that should further attack the internal alkyne and establish the five-membered ring via a 5-*exo*-*dig* ring-closing reaction (Scheme 11, Table 3). Unfortunately, the samarium diiodide mediated reaction only resulted in the re-isolation of the starting material when carried out at –78 °C (entry 1), and partial formation of the reduced intermediate **51** at elevated temperature (entry 2). The isolation of the reduced species **51** gives evidence that a ketyl radical is formed during the course of the reaction. However, the second step, the formation of the cyclopentane ring system, did not occur. We hoped that the addition of *tert*-butyl alcohol, methanol, hexamethylphosphoramide, lithium chloride, or nickel(II) iodide (entries 3–9) would facilitate the ring closure, but the desired cyclized product could not be isolated.

Table 3 Cyclization Reaction Conditions[a]

Entry	Reagents	Temp (°C)	Result
1	SmI_2	–78	re-isolation of substrate
2	SmI_2	r.t.	**51** + substrate
3	SmI_2, *t*-BuOH	–78	**51** + substrate
4	SmI_2, *t*-BuOH, HMPA	–78	**51** + substrate
5	SmI_2, *t*-BuOH, HMPA	0	**51**[b]
6	SmI_2, HMPA	r.t.	**51**[b]
7	SmI_2, MeOH	0 to r.t.	**51**[b]
8	SmI_2, NiI_2	r.t.	**51**[b]
9	SmI_2, LiCl	r.t.	**51**[b]
10	$Ni(cod)_2$, IPr·HCl, Et_3SiH, *t*-BuOK	0 to r.t.	re-isolation of substrate
11	$Ni(cod)_2$, Bu_3P, Et_3SiH	0 to r.t.	re-isolation of substrate
12	$Ni(cod)_2$, Bu_3P, BEt_3	r.t.	re-isolation of substrate

[a] **51** was isolated in less than 10% yield under all given reaction conditions.
[b] Slow decomposition of the starting material.

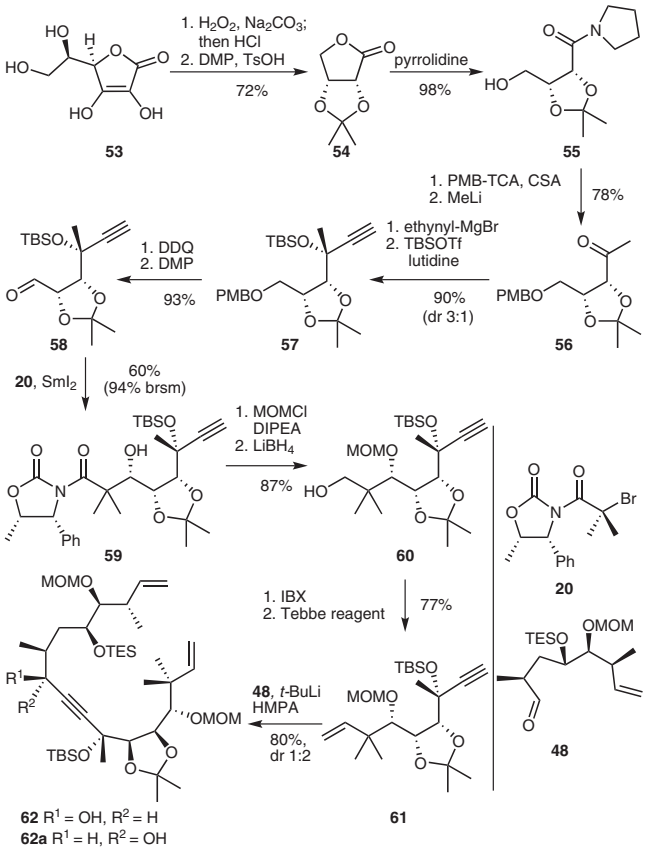


Scheme 11 Cyclization reaction

Next, we explored an intramolecular nickel-catalyzed coupling reaction in the presence of triethylsilane and various types of ligands, including tributylphosphosphine and IPr [1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene] as an N-heterocyclic carbene ligand (NHC), to form the five-membered ring (entries 10–12).[30a] Unfortunately, all experiments resulted in isolation of the starting material. The results and conditions applied for the intended cyclization reaction are summarized in Table 3.

At this point we reasoned that again the sterical hindrance of the internal alkyne might be responsible for the lack of reactivity, as the ketyl formation was observed under the samarium diiodide mediated cyclization conditions. We expected that a closer spatial arrangement of the two reacting functionalities would enhance the reactivity and trigger the formation of the cyclopentane ring. Thus, we decided to slightly modify the route towards the natural product and intended to close the macrocycle via a RCM reaction prior to establishing the five-membered ring.

The synthesis of the RCM precursor is outlined in Scheme 12. The modified sequence started with readily available D-isoascorbic acid (**53**) which was converted into acetonide-protected lactone **54** via a known two-step procedure.[34] Alcohol **55** became available after reaction of lactone **54** with pyrrolidine. The resulting primary hydroxyl group was protected as its PMB ether before treatment with methyllithium allowed the isolation of methyl ketone **56** in excellent yield. Next, C2 elongation with ethynylmagnesium bromide delivered the corresponding tertiary alcohols in a 3:1 diastereomeric ratio, favoring the desired *R*-configured isomer, which was protected as its TBS ether to give **57**.[35] Then, the PMB group was removed with DDQ and the primary alcohol was oxidized with Dess–Martin periodinane to give aldehyde **58**. The installation of the geminal dimethyl group was accomplished via a diastereoselective samarium diiodide mediated Reformatsky reaction of aldehyde **58** and chiral bromide **20**, and advanced alcohol **59** was obtained as single isomer.[5k,8] MOM protection of the secondary alcohol was followed by reductive cleavage of the chiral auxiliary with lithium borohydride and primary alcohol **60** was isolated in good yield. Alkene **61** was obtained after 2-iodoxybenzoic acid (IBX) oxidation of the primary alcohol functionality, followed by installation of the terminal alkene with Tebbe's reagent. Lithiation of the terminal alkyne moiety in **61** with *tert*-butyllithium, and subsequent reaction with aldehyde **48** afforded the RCM precursor in 80% yield, again as a 1:2 (**62**/**62a**) mixture of diastereomers.

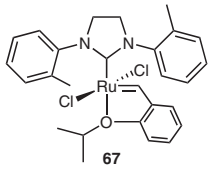
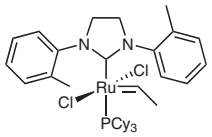


Scheme 12 Preparation of the RCM precursor

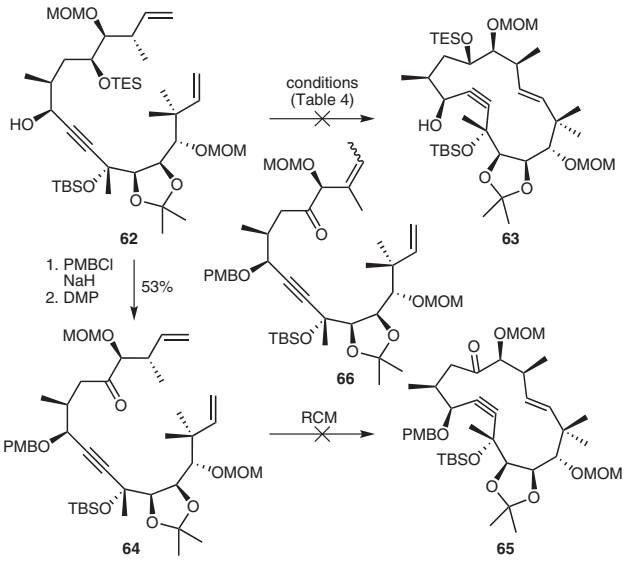
With diene **62** in hand, the closure of the 15-membered ring was attempted. As outlined in Table 4 (entries 1–6), different reaction conditions and RCM catalysts were evaluated.[36] Unfortunately, we were not able to achieve the desired macrocyclization using either diene **62** or fully protected substrate **64**, available after PBM protection of the hydroxyl group with concomitant cleavage of the TES ether and subsequent oxidation of the secondary alcohol, were met with failure (Scheme 13). All attempts resulted in re-isolation of the starting material, along with minor amounts (up to 10%) of the thermodynamically more stable double bond isomer **66** (exemplarily shown for the reaction starting from diene **64**).

As the outcome of RCM reactions strongly depends on the steric environment of the double bonds, we reasoned that the geminal dimethyl moiety in **62** and **64** prevents the formation of the 15-membered macrocycle. The influence of the sterical effects might even be more pronounced as

Table 4 RCM Conditions

Entry	Catalyst	Solvent	Temp (°C)
1	Grubbs 2nd generation[36a]	CH_2Cl_2	40
2	Grubbs 2nd generation	toluene[a]	80 to 110
3	Grubbs 2nd generation	DCE	80
4	Hoveyda–Grubbs 2nd generation[36b]	toluene[a]	80 to 110
5[36c]	 **67**	toluene[a]	80 to 110
6[36c]	 **68**	toluene[a]	80 to 110

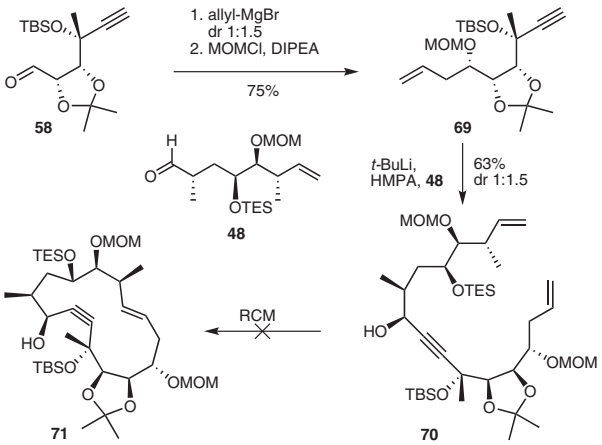
[a] Double-bond isomerization was observed with **62** and **64**.



Scheme 13 Ring-closing metathesis reaction

the alkyne functionality adds additional rigidity to the system. We decided to prepare a structurally simplified model compound lacking the geminal dimethyl group. As only little information on the structural requirements for MDR-reversal activity of jatrophanes is available, the synthesis and biological evaluation of derivatives is of essential importance.

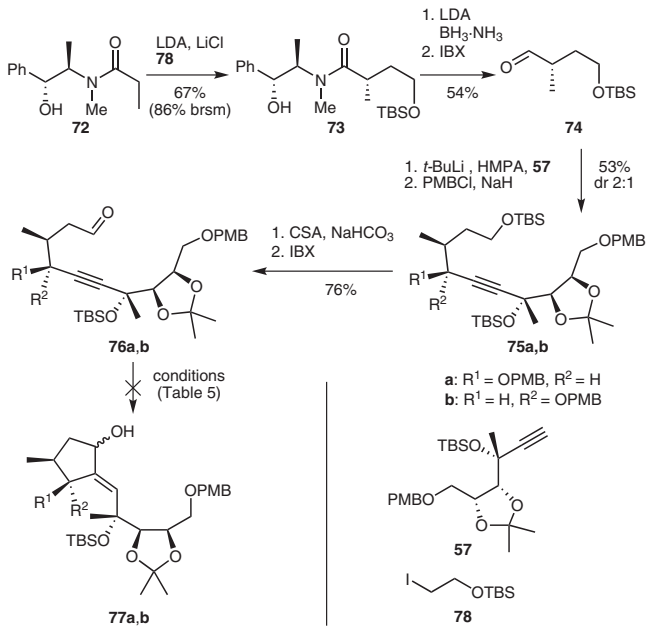
The synthesis of the sterically less demanding RCM precursor is outlined in Scheme 14. The addition of allylmagnesium bromide to aldehyde **58** allowed the isolation of the corresponding allylic alcohols in a 1:1.5 diastereomeric ratio, favoring the undesired isomer.[37] Although we were not concerned with the stereochemical outcome of the Grignard reaction, we decided to alter the reaction conditions only after successful closure of the macrocycle. The diastereomers were separated and the desired compound converted into MOM ether **69** in 82% yield. With **69** in hand, the RCM precursor **70** became accessible after lithiation of the alkyne and subsequent reaction with aldehyde **48**. Unfortunately, all attempts to close the macrocycle via a RCM reaction (conditions as described in Table 4, entries 1–6) remained unsuccessful and the desired product **71** could not be isolated.



Scheme 14 Synthesis of a sterically less demanding RCM precursor

At this point it became obvious that the rigidity provoked by the internal alkyne, was obstructive for the formation of the desired macrocycle. We decided to further investigate our initial idea that envisaged the closure of the cyclopentane ring prior to the macrocyclization. As outlined in Scheme 15, we intended to prepare aldehyde **76** as precursor for a samarium diiodide or nickel-mediated ring-closure reaction. Thus, we could take advantage of the higher reactivity of aldehydes versus ketones. Additionally, the undesired reductive removal of the MOM ether as observed in the samarium diiodide mediated reaction of **62** and **64** would be avoided. The resulting cyclopentanol could later be oxidized to the corresponding ketone and used for further functionalization.

The sequence started with Myer's alkylation using TBS-protected iodide **78** and pseudoephedrine propionamide **72** (Scheme 15).[38] Cleavage of the chiral auxiliary with borane–ammonia complex, and oxidation of the primary alcohol with IBX resulted in the isolation of aldehyde **74**. The following reaction of aldehyde **74** with deprotonated alkyne **57** delivered the corresponding secondary alcohols as an inseparable 1:2 mixture of diastereomers (as previously observed for similar substrates but the stereochemistry was not proven at this point). The alcohol functionality was protected as a PMB ether before the compound was treated with camphorsulfonic acid (CSA) to cleave the primary TBS group in **75a**,**b**. Final oxidation of the primary alcohol with IBX afforded aldehydes **76a**



Scheme 15 Alkyne/aldehyde cyclization: shortened chain length

and **76b** that served as substrates for the intended ring-closing reaction.

Unfortunately, neither reaction of aldehyde **76a** nor **76b,** afforded the desired products. An overview of different reaction conditions applied to aldehydes **76a** and **76b** is presented in Table 5. Because of these disappointing findings the approach was abandoned. The inability to access the desired intermediate led to the development of the ultimately successful dibromide coupling approach (path C in Scheme 1), which has been published elsewhere.[5o]

Herein, we describe two approaches towards a highly advanced intermediate in the synthesis of the jatrophane diterpene Pl-4 (**1**). These routes feature a *syn*-selective hydrometalation reaction, and a radical approach, respectively. Although the desired advanced intermediate **5** could not be accessed, we were able to elaborate efficient protocols for the preparation of structural motifs present in this fascinating class of natural products. Jatrophane diterpenes are synthetically challenging targets, mainly because of the complex stereochemical substitution pattern. Additionally, the high level of oxygenation necessitates sophisticated protecting group strategies and facilitates undesired side reactions and modified reactivity. We are positive that results and strategies discussed within this manuscript, as well as problems and synthetic drawbacks will be of importance for the design of future routes to structurally related jatrophane diterpenes.

All nonaqueous reactions were carried out under a positive pressure of argon using oven-dried (100 °C) or flame-dried glassware. Solvents were purified and dried by standard procedures. The reactions were monitored by TLC (silica gel 60-F254 glass plates). Flash column chromatography was performed with silica gel 60 (0.040–0.063 μm, 240–400 mesh). Optical rotations were measured at the Na D line with a 100-mm path length cell. NMR spectra were recorded either on a 400 or 600 MHz spectrometer. Unless stated otherwise, all NMR spectra were measured in $CDCl_3$ solutions and referenced to the residual $CDCl_3$ signal (^1H, $\delta = 7.26$, ^{13}C, $\delta = 77.16$). IR: all compounds were measured using a single reflection monolithic diamond ATR module. HRMS were performed on a mass spectrometer using ESI-mode and a UHR-TOF (Qq-TOF) mass analyzer.

Details of the synthesis of compounds in Schemes 3–15 are given in the Supporting Information.

(2*S*,5*S*,6*S*)-1-(4-Methoxybenzyloxy)-5-(methoxymethoxy)-2,6-dimethyloct-7-en-4-ol (36)

A solution of bromide **19** (590 mg, 2.16 mmol, 2.0 equiv) in Et_2O (17 mL) was cooled to –78 °C and 1.6 M *t*-BuLi (2.84 mL, 4.54 mmol, 4.2 equiv) was added dropwise over 3 min. The mixture was stirred for 10 min at this temperature and then freshly prepared 1 M $MgBr_2$ (2.48 mL, 2.48 mmol, 2.3 equiv) was added. After 10 min at –78 °C aldehyde **27** (171 mg, 1.08 mmol, 1.0 equiv), dissolved in Et_2O (6.8 mL) was added dropwise via syringe over 3 min. The mixture was allowed to stir at –78 °C for 90 min (TLC monitoring) until total consumption of aldehyde **27**. The reaction was terminated by the addition of sat. aq NH_4Cl (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. The resulting crude mixture of secondary alcohols was purified by flash column chromatography (hexane–EtOAc, 9:1 to 5:1) providing **36** (342 mg) and **36a** (38 mg) as colorless oils, in a 9:1 diastereomeric ratio and 96% overall yield.

Major Diastereomer 36

$[\alpha]_D^{20}$ +6.3 (*c* 1.0, $CHCl_3$).

Table 5 Cyclization Reaction Conditions

Entry	Reagents	Temp (°C)	Result
1	SmI_2	–78 to –40	re-isolation of starting material
2	SmI_2	0 to 50	decomposition[a]
3	SmI_2, HMPA	–78	mixture of undefined products
4	SmI_2, HMPA, *t*-BuOH	–78	decomposition
5	SmI_2, HMPA, MeOH	–78 to 0	decomposition[a]
6	$Ni(cod)_2$, IPr·HCl, Et_3SiH, *t*-BuOK	r.t. to 50	re-isolation of starting material[a]
7	$Ni(cod)_2$, Bu_3P, BEt_3, Et_3SiH	r.t.	re-isolation of starting material

[a] Partial reduction of the aldehyde to the corresponding alcohol.

IR (ATR): 3460, 2932, 2359, 2341, 1512, 1459, 1363, 1301, 1245, 1172, 1147, 1092, 1031, 914 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.6 Hz, 3 H), 1.07 (d, *J* = 6.8 Hz, 3 H), 1.22–1.31 (m, 1 H), 1.52 (ddd, *J* = 4.3, 10.5, 13.8 Hz, 1 H), 2.08–2.16 (m, 1 H), 2.43–2.56 (m, 1 H), 3.18 (dd, *J* = 3.9, 5.9 Hz, 1 H), 3.23 (d, *J* = 3.9 Hz, 1 H), 3.27–3.31 (m, 2 H), 3.42 (s, 3 H), 3.62–3.69 (m, 1 H), 3.80 (s, 3 H), 4.44 (s, 2 H), 4.67 (d, *J* = 6.8 Hz, 1 H), 4.76 (d, *J* = 6.8 Hz, 1 H), 4.99–5.02 (m, 1 H), 5.02–5.06 (m, 1 H), 5.76–5.88 (m, 1 H), 6.84–6.90 (m, 2 H), 7.22–7.28 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9 (CH_3), 17.7 (CH_3), 30.4 (CH), 37.9 (CH_2), 40.0 (CH), 55.4 (CH_3), 56.2 (CH_3), 69.8 (CH), 72.6 (CH_2), 76.3 (CH_2), 88.7 (CH), 98.9 (CH_2), 113.6 (CH), 115.3 (CH_2), 129.3 (CH), 130.8 (C), 139.9 (CH), 159.2 (C).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{32}O_5$: 375.2148; found: 375.2141.

(4*R*,5*S*)-3-((*S*)-3-{(4*R*,5*R*)-5-[(*R*)-2-(*tert*-Butyldimethylsilyoxy)but-3-yn-2-yl]-2,2-dimethyl-1,3-dioxolan-4-yl}-3-hydroxy-2,2-dimethylpropanoyl)-5-methyl-4-phenyloxazolidin-2-one (59)

A 0.1 M solution of SmI_2 in THF (31.3 mL, 3.13 mmol, 2.5 equiv) was transferred into a 250-mL round bottom Schlenk flask which was precooled to –78 °C. A solution of bromide **20** (449 mg, 1.38 mmol, 1.1 equiv) and aldehyde **58** (390 mg, 1.25 mmol, 1.0 equiv) in degassed THF (20 mL, 3 pump-freeze-thaw cycles) was added to the SmI_2 solution via a cannula over a period of 5 min. The mixture was stirred for 1 h at –78 °C before it was quenched by the addition of aq sat. $Na_2S_2O_3$ (20 mL) and aq sat. $NaHCO_3$ (20 mL) at –78 °C. The biphasic system was allowed to warm to r.t. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the organic solvents were removed under reduced pressure delivering the crude secondary alcohol as a light yellow oil that was purified by flash chromatography (hexane–EtOAc, 9:1) providing **59** (420 mg, 60%, 94% brsm) as single diastereomer.

$[\alpha]_D^{20}$ +34.4 (c 1.0, $CHCl_3$).

IR (ATR): 3511, 3264, 2933, 2858, 2361, 2341, 1773, 1688, 1457, 1338, 1248, 1151, 1086, 1028, 987, 835, 768 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.23 (s, 3 H), 0.30 (s, 3 H), 0.90 (s, 9 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 1.36 (s, 3 H), 1.44 (s, 3 H), 1.48 (s, 3 H), 1.58 (s, 3 H), 1.71 (s, 3 H), 2.58 (s, 1 H), 3.32 (d, *J* = 4.8 Hz, 1 H), 4.08 (d, *J* = 6.3 Hz, 1 H), 4.27 (d, *J* = 6.3 Hz, 1 H), 4.81 (m, 1 H), 4.93 (d, *J* = 4.8 Hz, 1 H), 5.66 (d, *J* = 6.8 Hz, 1 H), 7.27–7.31 (m, 2 H), 7.33–7.44 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –2.9 (CH_3), –2.2 (CH_3), 14.4 (CH_3), 18.5 (C), 20.2 (CH_3), 22.4 (CH_3), 25.7 (CH_3), 26.1 (CH_3), 26.4 (CH_3), 28.2 (CH_3), 50.6 (C), 57.7 (CH_3), 69.1 (CH), 69.5 (C), 74.0 (CH), 75.7 (CH), 79.2 (CH), 84.5 (CH), 86.9 (C), 108.5 (C), 125.8 (CH), 128.8 (CH), 128.9 (CH), 133.8 (C), 152.6 (C), 177.0 (C).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{45}NO_7Si$: 582.2863; found: 582.2859 +/– 5.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. The experimental procedures and analytical data of all intermediates, described within this manuscript, can be found in the supporting information.

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