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Letter

Total Synthesis of Jerangolid B via sp^3–sp^2 Stille Coupling

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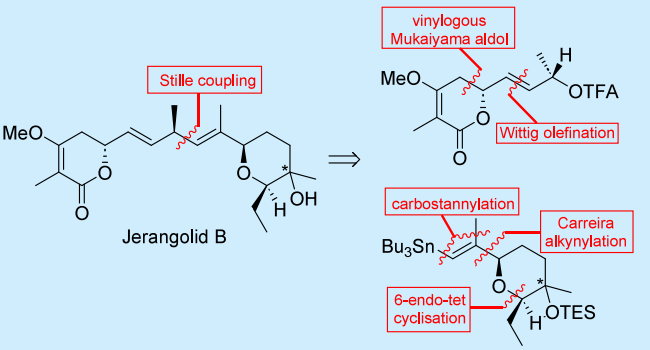
ABSTRACT: First isolated from *Sorangium cellulosum* So ce 307, jerangolids are a class of natural products with high antifungal activity and minimal toxicity toward mammals. Comprised of a skipped diene substructure with a chiral center in between a δ-lactone and a pyran substituent, they present an intriguing synthetic challenge. We herein report the first synthesis of jerangolid B through a modular approach that incorporates sp^3–sp^2 Stille coupling as the key step to generate the skipped diene structure. By comparing our synthetic jerangolid B to the data published in the literature, we could show that the configuration at C14 is R.



Jerangolids are a class of polyketides that were first isolated by Höfle et al. in 1995 from the myxobacterium *Sorangium cellulosum* So ce 307.[1] They consist of a skipped 1,4-pentadiene core motif, which is connected to an δ-lactone and a pyran substituent (Figure 1).

Structurally, they are closely related to ambruticins, which were isolated from *Polyangium cellulosum* var. *fulvum* and *Sorangium cellulosum* So ce 10 by Strandtmann et al.[2] Their highly potent antifungal activity paired with minimal toxicity toward mammals make the jerangolids an interesting target for total synthesis.[1a,2e] Both classes target the high osmolarity glycerol (HOG) signaling pathway in histidine kinase 1 (Hik1) expressing cells, leading to an intracellular accumulation of free fatty acids and glycerol resulting in cell death.[3] Because both have the skipped diene and the pyran motif (C6–C17) in common, it has been proposed that this structure constitutes the pharmacophore responsible for biological activity.[4] Their unique mode of action and challenging structural motif make the jerangolids an interesting synthetic target.

To date, several syntheses of natural occurring jerangolids are known.[5] Jerangolid D (**4**, 22 steps, 6.1% yield) was the first to be synthesized by Markó et al.,[5a] followed by jerangolid A (**5**, 23 steps, 1.9% yield) by Hanessian et al.[5b] and recently the synthesis of jerangolid E (**2**, 23 steps, 4.0% yield) by Hahn et al. in 2018.[5c] Their key strategy relies on using olefination reactions to generate the skipped diene structure from three respective building blocks. Several syntheses of truncated non-natural analogues of jerangolids and ambruticins have been described as well, though jerangolids B (**1**) and H (**3**) remain elusive.[4a,6] Although vast efforts have been made, there still exists no general method that allows all natural jerangolids and their potential derivatives to be accessed.

In our quest to find a common synthetic strategy, we turned our attention to the synthesis of jerangolid B (**1**) (Scheme 1).

We envisioned building the skipped diene at C8 through sp^3–sp^2 Stille coupling of chiral allylic trifluoroacetate **6** with vinylstannane **7**. The idea behind this is that, in palladium-catalyzed allylic substitution reactions, hard nucleophiles, such as vinylstannane **7**, attack the generated π-allylpalladium complex directly via an inner sphere mechanism, leading to overall inversion of configuration.[7] The required stereocenter at C8 can be traced back to methyl L-(−)-lactate (**9**). Stannane **7** could be synthesized by Carreira alkynylation of aldehyde **10**, followed by 6-*endo*-tet cyclization and carbostannylation of the generated terminal alkyne. Using only two building blocks, which can be coupled late in the synthesis, should allow us to easily generate derivatives through modification of either building block.

Synthesis of the lactone building block (Scheme 2) started with the preparation of aldehyde **14** according to the procedure described by Könning et al.[8] Methyl L-(−)-lactate (**9**) was protected as TBS ether **11** followed by DIBALH reduction to aldehyde, and subsequent Wittig olefination yielded the unsaturated ester **12** quantitatively as a 1.5:1 *Z*/*E* mixture. After a second DIBALH reduction, allylic alcohol **13** was then subjected to the one-pot oxidation/isomerization protocol, which afforded aldehyde **14** in quantitative yields.[8]

Next we subjected aldehyde **14** to a vinylogous Mukaiyama aldol reaction (VMAR)[9] with freshly prepared silyl ketene acetal **15**.[10] We were initially delighted to find that using (*S*)-

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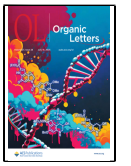


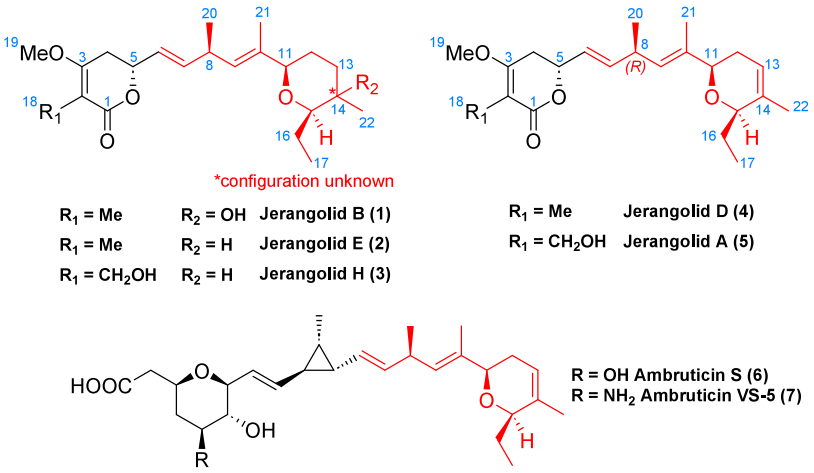
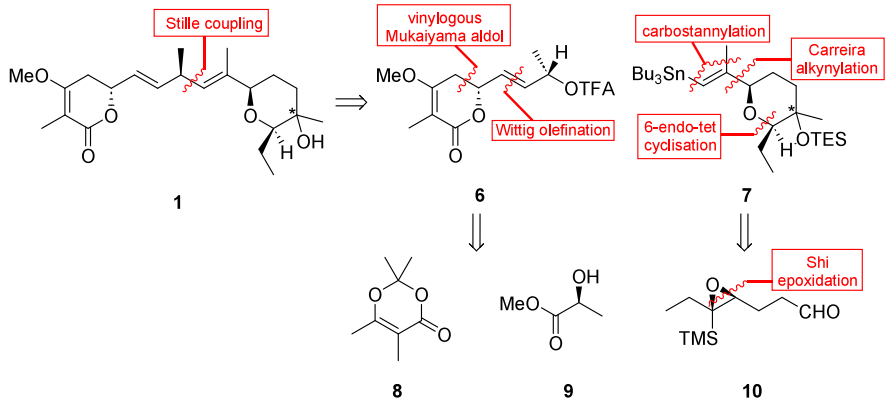
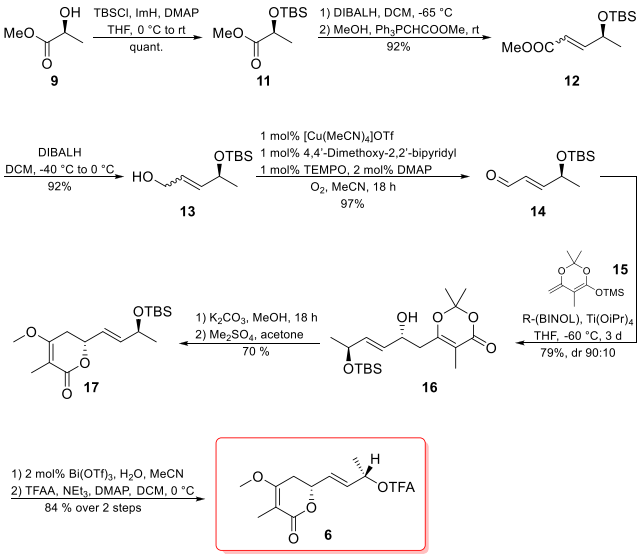


Figure 1. Structures of known jerangolids and selected ambruticins.

Scheme 1. Retrosynthetic Analysis of Jerangolid B (1)



Scheme 2. Construction of the Lactone 6 Building Block



BINOL as the chiral ligand (Table 1, entry 1) produced allylic alcohol **16** in good yields with a 5:95 dr.[11] However, through Mosher ester analysis, we discovered that the product was the undesired diastereomer. Simply changing to (*R*)-BINOL provided the desired isomer, albeit in lower yields and dr (Table 1, entry 2). To explain the lower selectivity and yield,

Table 1. Optimization of the VMAR for the Synthesis of Compound 16

	conditions[a]	yield (%)	dr (*anti*/*syn*)
1[b]	0.5 equiv of (*S*)-BINOL, 20 °C, and 4 h	80	5:95
2	0.5 equiv of (*R*)-BINOL, −20 °C, and 4 h	60	83:17
3	0.5 equiv of (*R*)-BINOL, −60 °C, and 3 days	79	90:10
4	0.5 equiv of (*R*)-BINOL, −78 °C, and 3 days	55	87:13
5	$Cu(OTf)_2$, *S*-(Tol-BINAP), $PH_3SiF_2(Bu_4N)$, −78 °C, and 24 h	59	51:49

[a]All reactions were conducted in THF(abs) using 1.5 equiv of compound **15**. [b]A total of 0.5 equiv of $Ti(OiPr)_4$ was used in entries 1−4.

we assume that (*S*)-**14** and (*R*)-BINOL form a mismatched pair, whereas (*S*)-**14** and (*S*)-BINOL form a matched pair. To increase the selectivity in the mismatched pair, we lowered the reaction temperature to −60 °C (Table 1, entry 3) and obtained 79% compound **16** with an acceptable dr of 90:10. Further decreases in the temperature proved to be detrimental (Table 1, entry 4). Additionally, other conditions described by Carreira et al. were tested (Table 1, entry 5) but were unsuccessful.[12]

Lactone **17** was obtained by cyclization under mildly basic conditions with subsequent O-methylation using Me_2SO_4 in a good yield.[10b,13] The use of $TMSCHN_2$ also worked as a methylating reagent, albeit in only a 45% yield.[14] It is noteworthy that the lactone subunit, in general, is quite

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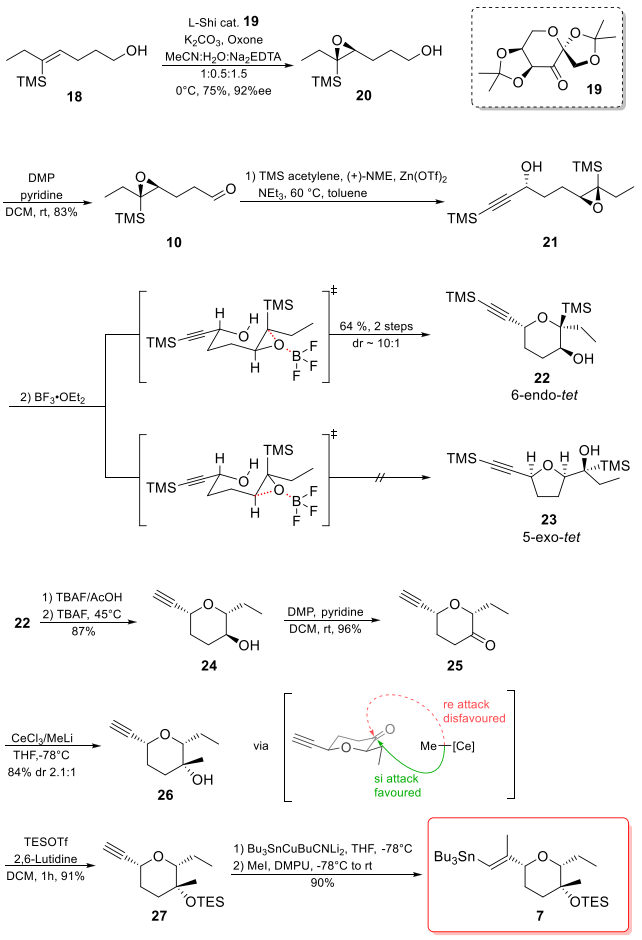
vulnerable. Catalytic amounts of Lewis acid in the presence of water led to enol ether cleavage after extended periods of time, while basic conditions caused deprotonation at C4, resulting in the formation of trienic acid.[15] Considering this, it is generally advantageous to introduce this subunit at a later stage in the synthesis. Careful deprotection (*vide supra*) of compound **17** using catalytical amounts of $Bi(OTf)_3$ in water/acetonitrile,[16] followed by trifluoroacylation, finally led to the desired lactone **6** in 84% yield over two steps (Scheme 2).

Next, we turned our attention to the synthesis of vinylstannane **7** (Scheme 3). Our synthesis started with alkene

Scheme 3. Synthesis of Pyran Fragment 7



18, which was prepared in two steps from commercially available 5-trimethylsilyl-pent-4-yn-1-ol as described previously.[6a] Alkene **18** was then cleanly transformed into epoxide **20** through Shi epoxidation, using catalyst **19** derived from L-sorbose, with 75% yield and 92% ee.[17] Subsequent DMP oxidation delivered aldehyde **10** in 83% yield. Because **10** decomposes rather quickly even at −18 °C, it was used immediately after purification in the following step.

We then generated the stereocenter at C11 via Carreira alkynylation of compound **10**.[18] Our initial runs using standard Carreira conditions led to complete decomposition of the starting material. Compound **10** is an aliphatic aldehyde, which can easily react with itself via aldol addition under these conditions.[19] It was therefore crucial to add aldehyde **10** very slowly via a syringe pump. Additionally, TMS acetylene needed to be used in great excess due to its high volatility. Our best results were achieved by using 1.1 equiv of $Zn(OTf)_2$, 1.2 equiv of NEt_3, and 1.2 equiv of (+)-NME at 60 °C and adding aldehyde **10** over 10 h, obtaining propagyl alcohol **21**, which was directly cyclized using $BF_3{\cdot}OEt_2$ without purification. This led to 6-*endo*-tet cyclization, forming compound **22** as a 10:1 mixture of separable diastereomers. Usually, the spiro transition state leading to 5-*exo*-tet product **23** is favored over the fused transition state leading to the preferred 6-*endo*-tet product **22** in epoxide openings.[20] The installation of a TMS group at the axial position was therefore pivotal for the success of this step, as it facilitates the 6-*endo*-tet cyclization by selectively weakening the adjacent C−O bond through a favorable $\sigma_{C-Si}-2p_O$ orbital interaction and stabilizing the developing positive charge in the transition state.[21]

To obtain the right configuration of the tertiary alcohol at C14 in jerangolid B (**1**), the TMS group at C15 first needed to be cleaved for the Si site to become accessible for methylation.[22] Therefore, through protiodesilylation of the TMS groups with TBAF, we obtained compound **24** in an 87% yield. The acetylenic TMS group had to be cleaved first with a mixture of TBAF/AcOH, as just using an excess amount of TBAF sometimes leads to major formation of the Peterson olefination product.[21d,23] Subsequent oxidation afforded ketone **25** in near-quantitative yields.

Both terminal acetylene and the α positions in ketone **25** are CH-acidic, which prompted us to investigate methods for clean stereoselective methylation without inducing deprotonation and subsequent side reactions.[24] We first explored the $ZnCl_2$-catalyzed addition of Grignard reagents to ketones developed by Hatano et al. (Table 2, entries 1−3).[25] Using MeMgBr and

Table 2. Optimization of the C14 Methylation of Compound 25[a]

	Me[M]	$[M]X_n$	yield (%)	dr (*R*/*S*)
1	1.1 equiv of MeMgBr	0.1 equiv of $ZnCl_2$	70	39:61
2	1.1 equiv of MeMgBr and 0.2 equiv of $TMSCH_2MgCl$	0.1 equiv of $ZnCl_2$ and 1.1 equiv of LiCl	74	45:55
3	1.5 equiv of MeLi and 3.0 equiv of $TMSCH_2MgCl$	1.5 equiv of $ZnCl_2$ and 1.1 equiv of LiCl	72	37:63
4	1.0 equiv of MeMgBr	1.0 equiv of $CeCl_3$	76	40:60
5	1.0 equiv of MeLi	1.0 equiv of $CeCl_3$	52	83:17
6	2.0 equiv of MeLi	1.0 equiv of $CeCl_3$	69	61:39
7	3.0 equiv of MeLi	1.0 equiv of $CeCl_3$	75	75:25
8	4.5 equiv of MeLi	1.5 equiv of $CeCl_3$	84	68:32
9[b]	4.5 equiv of MeLi	1.5 equiv of $CeCl_3$	30	86:14

[a]Reactions were conducted in THF on a 0.25 mmol scale at −78 °C. [b]A total of 1.5 equiv of (*R*)-BINOL was used.

a catalytic amount of $ZnCl_2$, we attained high yields in overall methylation, but it unfortunately resulted primarily in the unwanted 14-(*S*) epimer in a 39:61 fashion (Table 2, entry 1). We rationalized that increasing the steric demand in the *in situ* generated $R_3ZnMgBr$ ate complex might favor attack from the Si site. However, using catalytic amounts of $TMSCH_2MgCl$ to introduce the $TMSCH_2$ group as a non-transferable dummy ligand to increase steric demand of the ate complex neither increased the yield nor improved the diastereomeric ratio (Table 2, entry 2). Using stochiometric amounts of $(TMSCH_2)_2ZnMeLi$ had no noticeable effect either (Table 2, entry 3).

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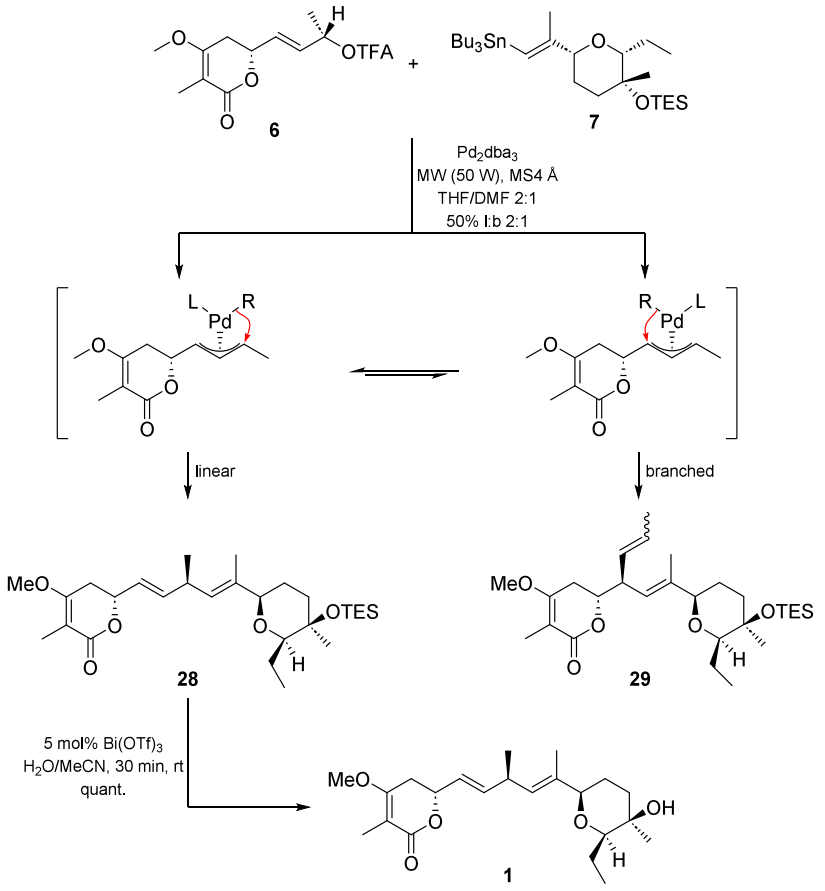
Scheme 4. Final Steps in the Synthesis of Jerangolid B 1



Changing to Imamoto's procedure using MeMgBr/$CeCl_3$ unsurprisingly led to the same results (Table 2, entry 4).[26] To our delight, using 1.0 equiv of MeLi and 1.0 equiv of $CeCl_3$ resulted in the desired epimer **26** in an 83:17 ratio, albeit in a lower overall yield (Table 2, entry 5). This change in selectivity might in part be explained by the fact that MeLi reacts with $CeCl_3$ to form an organocerium species, whereas with MeMgBr, alkylation is facilitated by the coordination of $CeCl_3$ to the carbonyl group. While classical drying procedures state that $CeCl_3{\cdot}7H_2O$ can be mildly dehydrated by stepwise heating under high vacuum affording anhydrous $CeCl_3$,[26a,27] Evans et al. have shown that the material obtained is the solvated species $[CeCl_3(H_2O)]_n$.[28] Treating this compound in THF with MeLi leads to a complicated organometallic reagent in the form of $[CeCl_aMe_b(OH)_cO_dLi_e]_f$. The formation of this highly complex methylating reagent may also account for the encountered difficulty in reproducing diastereoselectivities (Table 2, entries 4−9). Overall, we found that a mixture of 4.5 equiv of MeLi and 1.5 equiv of $CeCl_3$ maximized overall yields to 84% while still delivering an acceptable diastereomeric ratio of 68:32 (Table 2, entry 8). As both epimers could be separated by flash chromatography, no further optimizations were conducted.

TES protection of tertiary alcohol **26** using TESOTf afforded compound **27** in 91% yield. With stannylcupration of alkyne **27** with subsequent trapping of vinylcuprate with MeI,[29] we obtained the desired vinylstannane **7** in near-quantitative yields after reversed-phase chromatography.

With compounds **6** and **7** synthesized, the stage was set for the sp^3−sp^2 Stille coupling of both building blocks. π-Allyl Stille couplings are staples in organic synthesis and have been extensively used in natural product syntheses to generate skipped 1,4-dienes. However, to our knowledge, no example of a coupling involving a chiral 2° or 3° allylic ester with a vinylstannane has been published in the field of total synthesis to date.[30] This is surprising, given the close mechanistic relationship to the Tsuji−Trost reaction. It is well-established that, in reactions of unsymmetrical 1,3-disubstituted allylic substrates, such as compound **6**, the Tsuji−Trost reaction proceeds stereoselectively with retention of configuration at the stereocenter.[31] This outcome results from a double inversion pathway involving oxidative addition and subsequent nucleophilic attack at the allyl position. Because an epimerization via η^3−η^1−η^3 isomerization is not possible, the catalyst can only influence the regioselectivity, while the configuration is determined by the substrate. In our case, we therefore expect inversion of configuration at C8, as transmetalation of vinylstannane **7** to the Pd(II) center precedes C−C bond formation (Scheme 4).

Through extensive experimentation, we found that the best yields for the coupling of compound **6** with compound **7** were achieved by utilizing Pd_2dba_3 as a catalyst, along with molecular sieves 4Å (to ensure anhydrous conditions) under microwave irradiation in a 2:1 mixture of THF and DMF. After 10 cycles of pulsed microwave irradiation (50 W, 1 min of irradiation, and 1 min of cooldown), we obtained 50% of the coupling product as a 2:1 linear/branched (l/b) mixture, which afforded 33% of pure compound **28** after chromatographic purification. ^{13}C NMR indicated no epimerization at the central carbon center at C8. Removal of the TES group

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under mild conditions using 5 mol % $Bi(OTf)_3$ ultimately afforded jerangolid B (**1**) in quantitative yields. The use of TES was deliberate, as the TBS ether could not be cleaved under standard conditions without major decomposition of the lactone unit in compound **1**. By comparison of the NMR data of 14-*epi*-jerangolid B (**1**)[22] to the data of compound **1** and natural jerangolid B, we could show that C14 has a *R* configuration.

In summary, we achieved the synthesis of jerangolid B (**1**) through a modular synthesis in 20 steps, with the longest linear sequence of 12 steps and 5.7% yield. Key steps included the stereoselective formation of the lactone core **17** through vinylogous Mukaiyama aldol reaction, the formation of the pyran fragment through Carreira alkynylation of aldehyde **10** with subsequent cyclization, and finally stereoselective π-allyl Stille coupling of building blocks **6** and **7** to generate the core jerangolid structure in a single step. Syntheses of other jerangolids and derivates are currently in progress and will be published in due course.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c02569.

Experimental details, characterization data for all new compounds, ^1H and ^{13}C NMR spectra, and crystallographic data (PDF)

Accession Codes

Deposition number 2464216 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This article is dedicated to Prof. Dr. Wolfang Steglich on the occasion of his 92nd birthday and to Prof. Dr. Volker Schurig on the occasion of his 85th birthday.

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