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Unexpected Alkene Isomerization during Iterative Cross-Coupling To Form Hindered, Electron-Deficient Trienes

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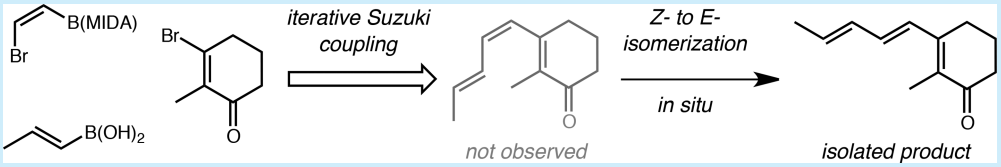
Supporting Information



ABSTRACT: An iterative cross-coupling approach to conjugated trienes was explored as part of a planned stereoselective synthesis of bicyclic terpenes. Using a bifunctional bromoboronate building block, sequential Suzuki coupling reactions were employed to provide a conjugated trienone target containing a tetrasubstituted alkene. During the final cross-coupling step, an unexpected alkene isomerization was observed to give less hindered *trans* products. Examination of different substrates determined that conjugation to a ketone withdrawing group was responsible for isomerization, rather than steric hindrance of the tetrasubstituted alkene.

A wide variety of terpene natural products contain a decalin substructure, often adorned with methyl or isopropyl substituents, additional rings, and various patterns of oxidation.[1] In particular, many natural products share the vicinal dimethyldecalin core structure **1** (>15000 natural products), including a significant number of sesquiterpenes (Figure 1).[2] This class includes the eremophilane skeleton

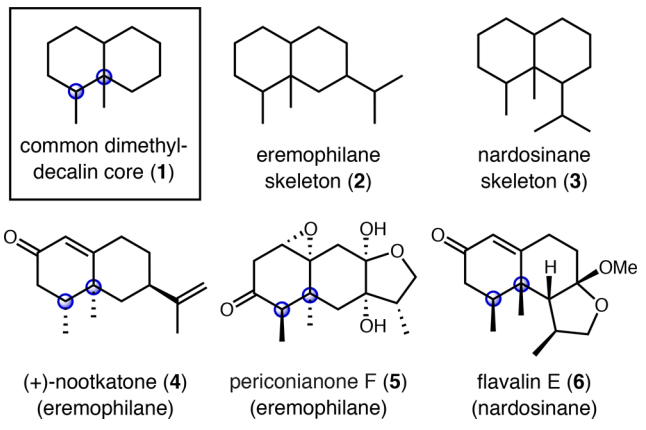


Figure 1. Dimethyldecalin core is found in many terpenes, including the eremophilane and nardosinane sesquiterpenes.

(>1300 natural products, approximately) and nardosinane skeleton (>160 natural products), represented by nootkatone (**4**), periconianone F (**5**), and flavalin E (**6**).[3] While the syntheses of individual members of this family have been reported and creative synthetic strategies beyond the often-used Robinson annulation have been advanced, the construction of the dimethyl decalin core **1** *stereoselectively* still poses a challenge, and new synthetic approaches would be of significant value.[4−6]

We were attracted to the possibility of generating the dimethyldecalin substructure using a 6π-electrocyclization reaction to forge the left-hand six-membered ring (**7** → **8**, Figure 2), substantially simplifying the target.[7,8] The proposed

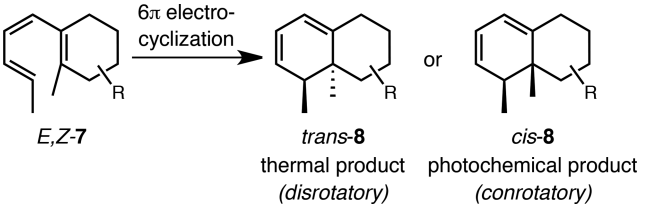


Figure 2. Proposed 6π-electrocyclization strategy to either *trans*- or *cis*-dimethyldecalin products using thermal or photochemical conditions, respectively.

6π-electrocyclization reaction would allow the introduction of both the tertiary and quaternary stereocenters in a single step, where the relative stereochemical outcome would be predictable based on the choice of reaction conditions (thermal or photochemical) using the Woodward−Hoffmann rules.[9] This strategy would potentially facilitate the synthesis of a variety of eremophilane, nardosinane, and related sesquiterpenes through a unified approach.

With this idea in mind, we required an efficient synthesis of a conjugated triene precursor incorporating functionality that would allow for further elaboration to different targets. Ketotriene **9** has been previously synthesized by Ramage and

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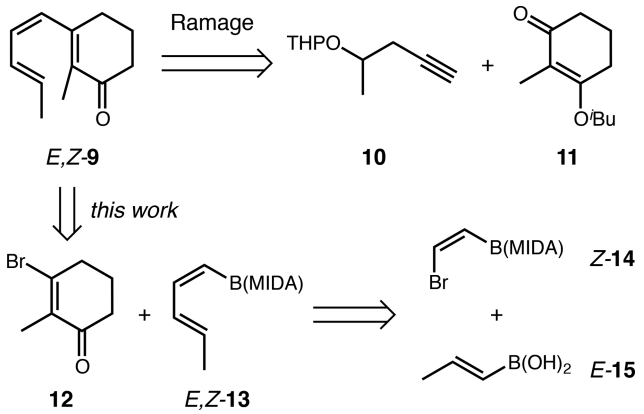
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Comparison of Reported Synthesis of Trienone 9 by Ramage and Proposed Iterative Cross-Coupling Approach

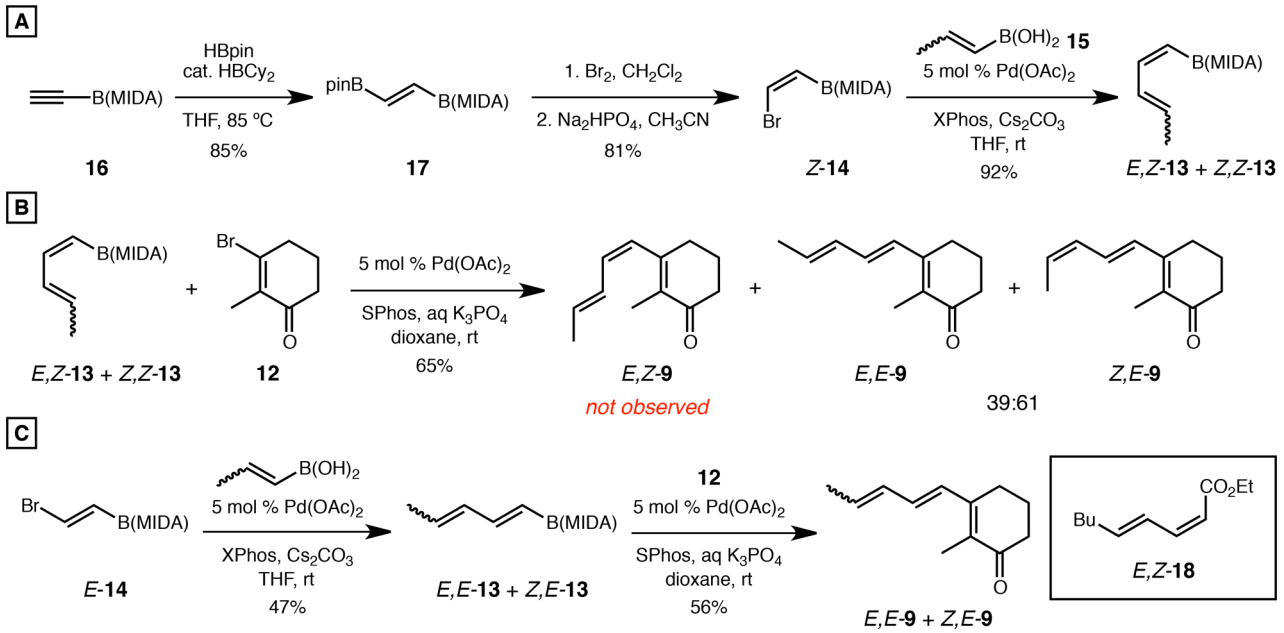


Sattar using the Stork−Danheiser protocol with alkyne **10** and vinylogous ester **11** as building blocks (Scheme 1).[8] This classical synthesis relies on a partial reduction of the alkyne to produce the *Z*-alkene but produces a mixture with starting material and over-reduced alkane product that are not readily separable. We wondered if we might take advantage of recent developments in cross-coupling to stereospecifically synthesize the desired triene through the Suzuki coupling of stereodefined alkene building blocks.[10] In particular, the iterative cross-coupling strategy using bifunctional MIDA-boronates (*N*-methyliminodiacetic acid boronate esters) recently described by Burke and co-workers appeared to be an ideal method to efficiently construct this triene with complete control of alkene geometry.[11] Stereospecificity would be critical to ensure the *Z*-geometry about the central alkene that is necessary for electrocyclization. This polyene cross-coupling/electrocyclization strategy has been pioneered by Trauner and Beaudry using a Stille coupling/8π/6π electrocyclization cascade toward the SNF4435 polyketides and recently employed independently by Parker and Vosburg in modern approaches to kingianin A and the endiandric acid scaffold, respectively.[12,13] Here we report our early efforts to apply MIDA-boronate cross-coupling to stereospecifically synthesize the highly hindered *E,Z*-triene **9** and the observation of an unexpected *Z* to *E* alkene isomerization process during a Suzuki coupling reaction. This isomerization led to the loss of stereoselectivity and defines a current challenge for the synthesis of conjugated polyenes that are highly electron-deficient and sterically hindered using the iterative cross-coupling strategy.

Our route began with a slight modification of the known synthesis of *Z*-2-bromovinylboronic acid MIDA ester (*Z*-**14**, Scheme 2A).[14] Hydroboration of commercially available ethynyl MIDA boronate **16** gave *E*-diboronate **17**. A two step bromination/elimination sequence using Na_2HPO_4 as the base gives the required *Z*-bromoboronate **14** with high stereoselectivity. A Suzuki coupling with propenylboronic acid **15** with $Pd(OAc)_2$ and XPhos in THF led to dienyl MIDA boronate **13** with retention of *Z*-configuration as expected.[14,15] Two isomers are formed (in a 1:1 ratio) resulting from the mixture of *E*- and *Z*-propenyl Grignard reagent used to generate the *E*/*Z*-propenylboronic acid **15**. Attempts to separate the *E,Z*- and *Z,Z*-isomers of dienyl MIDA boronate **13** by crystallization and chromatography were unsuccessful. This sequence proceeds in 63% overall yield over four steps, providing efficient access to this useful building block.

We next investigated the Suzuki coupling of dienyl MIDA boronate **13** with β-bromoenone **12** (Scheme 2B). We first employed optimized conditions reported by Burke and co-workers for *in situ* hydrolysis/coupling with catalytic $Pd(OAc)_2$, SPhos, and aqueous K_3PO_4 in THF or dioxane at room temperature. Under these conditions, we observed the conversion to a mixture of two triene products. The two isomers differed at the double bond distal to the carbonyl group, as was expected starting from the mixture of *E*- and *Z*-MIDA boronates **13**. However, close inspection of the ^{1}H NMR spectra suggested that both isomers have a central *E*-alkene (*E,E*-**9** and *Z,E*-**9**), with $^3J_{HH}$ values of 15.4 Hz in both

Scheme 2. Synthesis of Trienone Isomers Using Iterative Suzuki Cross-Coupling Reactions of MIDA-boronates



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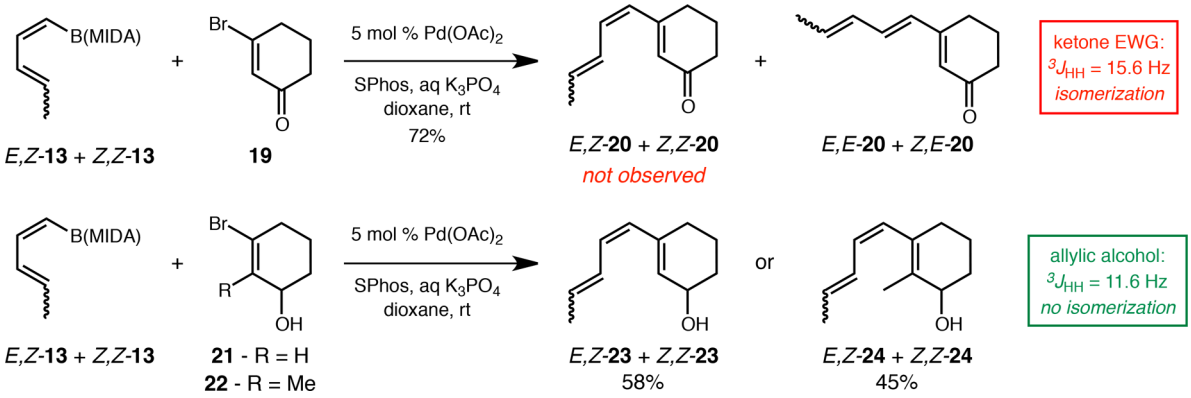
Scheme 3. Suzuki Coupling of Less Hindered and More Electron-Rich Vinyl Bromides To Probe the Cause of Alkene Isomerization



cases. This outcome was quite surprising, as it indicated that the central *Z*-alkene had isomerized to the corresponding *E*-alkene under the conditions of the Suzuki coupling. Carrying out the reaction in the strict absence of light had no effect on this process, suggesting that it is not a photochemical isomerization.[16] To verify this unexpected outcome, we synthesized the corresponding *E*-dienyl MIDA boronate **13** and performed a Suzuki coupling reaction with bromide **12** (Scheme 2C). We obtained the same two triene products, again isomeric at the alkene distal to the ketone, confirming their structure. While the success of using a Suzuki coupling to produce the tetrasubstituted alkene in trienone **9** is remarkable, the accompanying isomerization reaction was problematic for the planned electrocyclization that requires a *Z*-geometry of the central double bond.

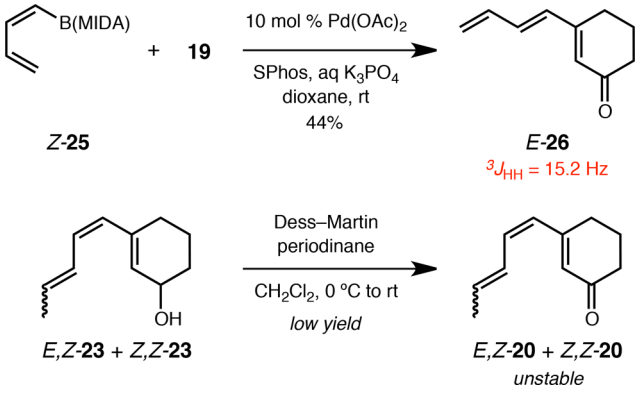
This type of isomerization, while fairly uncommon under the mild conditions of a typical Suzuki coupling, has been observed in some circumstances and particularly with certain electron-deficient conjugated π-systems.[17,18] An early report by Mavrov outlined the synthesis of dienoate *E,Z*-**18** (Scheme 2C) by a Suzuki coupling of the corresponding *E*-vinylboron precursor and *Z*-β-bromoacrylate.[18] The stereochemical outcome of the reaction depended on the reaction temperature and phosphine ligand used, with dppe favoring isomerization, PPh_3 giving a mixture (at high temperature) and dppf giving the expected product *E,Z*-**18** with 95% stereochemical fidelity (at room temperature). Given the similarity to our system, we therefore tested dppf as an alternative ligand in our reaction at room temperature, but the outcome was the same: the two major products in the ^{1}H NMR of the crude reaction mixture had undergone isomerization (*E,E*-**9** and *Z,E*-**9**, 48% combined yield) and we could not identify the expected *Z*-products. It seems that isomerization was too facile to be avoided with this substrate under the conditions examined.

To probe the molecular features that lead to this unexpected isomerization, we tested related substrates with specific substituents removed (Scheme 3). Less hindered bromoenone **19**, which lacks the α-methyl substituent, was coupled to dienyl MIDA boronate **13** in 72% yield and we again observed isomerization of the central double bond to give *E,E*- and *Z,E*-**20** ($^3J_{HH}$ values = 15.6 Hz for both products). This result suggests that the steric hindrance about the tetrasubstituted double bond in trienone **9** is not the cause of isomerization. We therefore tested more electron-rich vinyl bromides **21** and **22** lacking the conjugated ketone group. Suzuki coupling of bromide **21** with dienyl MIDA boronate **13** under the same conditions yielded *E,Z*- and *Z,Z*-**23** in 58% combined yield *with retention of stereochemistry*. The coupling constants of $^3J_{HH}$ = 11.6 Hz for both isomers support the assignment as *cis* double bonds in both cases. Likewise, Suzuki coupling of more hindered bromide **22** proceeded with retention of stereochemistry to provide *E,Z*- and *Z,Z*-**24**. Clearly, while the formation of the tetrasubstituted double bond in product **24** results in a reduced yield compared to triene **23**, the steric hindrance of this moiety does not lead to the isomerization of the central tetrasubstituted alkene in the absence of the conjugated ketone.[19] Rather, the electron-withdrawing effect of the ketone is solely responsible for the unwanted isomerization.[10,18] This behavior is most consistent with isomerization of the product postcoupling after the alkene in question is conjugated to the ketone group. At this stage, however, we cannot exclude the possibility of isomerization prior to reductive elimination.[17b]

One possible mechanism for isomerization is a deprotonation/reprotonation process of the moderately acidic methyl group in conjugated products **9** and **20**, a process that requires the presence of the ketone to acidify this position. To probe this mechanism we synthesized the simpler *Z*-dienyl MIDA boronate **25**[14] lacking the methyl group and subjected it to Suzuki coupling with bromoenone **19** (Scheme 4). We again observed isomerization ($^3J_{HH}$ = 15.2 Hz), suggesting that deprotonation is not required for isomerization.

With access to the *cis*-allylic alcohol products, we sought to reach the target trienones by an alternative route and test their

Scheme 4. Suzuki Coupling of Boronate *Z*-25 and Attempted Oxidation of Allylic Alcohol 23



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Org. Lett. XXXX, XXX, XXX−XXX

stability. As evidenced by the lower yields of alcohols **23** and **24** (Scheme 3), these intermediates were somewhat unstable and decomposed under a variety of oxidation conditions. A Dess−Martin oxidation of the alcohols *E,Z*- and *Z,Z*-**23** appeared to give *E,Z*- and *Z,Z*-**20**, one of the original target trienones, in low yield (Scheme 4). These two isomeric products clearly differed from the previously synthesized *E,E*- and *Z,E*-**20** (Scheme 3), however we were unable to obtain a pure sample and measure coupling constants accurately due to the instability of this compound. While we hesitate to draw firm conclusions, the decomposition of *cis*-trienes supports the hypothesis of post-Suzuki coupling isomerization, facilitated by the electron-withdrawing ketone and driven by the formation of the more stable *trans* products. In the context of previous reports and based on the available data described here, we currently favor isomerization of the electron-deficient product via a palladium hydride species or a Pd(II) species.[20−22] Overall, while the unexpected isomerization of polyenes is not a new phenomenon,[23] the process observed here defines a current challenge for the synthesis of conjugated polyenes that are highly electron-deficient using the iterative cross-coupling strategy. Further catalyst optimization and mechanistic studies will be necessary to overcome these challenges and access the full diversity of natural and synthetic polyenes using this versatile approach.[11]

In conclusion, we have reported the synthesis of a series of trienes and trienones containing tri- and tetrasubstituted alkenes using an iterative Suzuki coupling strategy. An unexpected isomerization process of electron-poor conjugated trienones occurs under the mild conditions of a Suzuki cross-coupling reaction. This isomerization led to the loss of stereoselectivity and complicated the exploration of an electrocyclization strategy to the dimethyldecalin substructure of many terpene natural products. The isomerization reaction was not observed for a substrate lacking the conjugated ketone group, indicating that electronics play the major role in favoring isomerization rather than sterics.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00809.

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

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Notes

The authors declare no competing financial interest.

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