

Use of Sequential Intramolecular Heck Cyclizations for Preparing Bicyclo[3.2.1]octane Fragments of Tetracyclic Stemodane and Stemarane Diterpenes

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We dedicate this publication to Professor Ryoji Noyori in recognition of his seminal contributions to the field of organic synthesis and the insightful leadership he has provided to the worldwide organic chemistry community.

Abstract: Use of an intramolecular bis-Heck cyclization to furnish the BCD ring systems of tetracyclic diterpenes of the stemodane and stemarane families is disclosed.

Key words: Heck reaction, terpenoids

Stemodinone (**1**) and stearin (**2**) are members of a group of tetracyclic diterpenes that have been isolated from the leaves of the West Indies plant *Stemodia maritima* L. (Scrophulariaceae) (Figure 1).² These stemodia extracts are structurally similar to the fungal metabolite aphidicolin (**3**), another tetracyclic diterpene that exhibits a variety of pharmacological activities including antiviral and antitumor properties.³

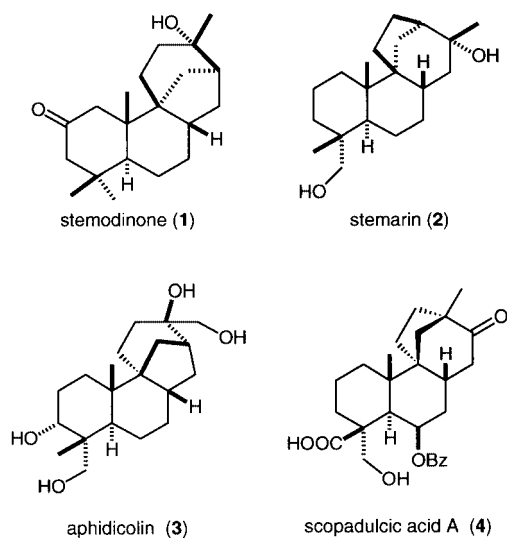


Figure 1 Structures of Representative Tetracyclic Diterpenes.

As a result of their challenging structures and significant biological activities, the stemodia family of natural products has attracted considerable attention from synthetic chemists, with imaginative total syntheses being described from several laboratories.^{4,5} We recently reported the first total syntheses of (-)- (**4**) and (+)-scopadulcic acid A, a member of the structurally related tetracyclic scopadulane diterpene family.⁶ The defining reaction of

our approach to **4** was a cascade intramolecular bis-Heck cyclization of trienyl iodide **5A**, a transformation that assembles the B, C and D rings as well as the C9 and C12 quaternary stereocenters of the scopadulane ring system (Figure 2).⁷ Herein we describe our evaluation of the use of a related strategy for assembling the bridged tricyclic BCD rings of the stemodia natural products.

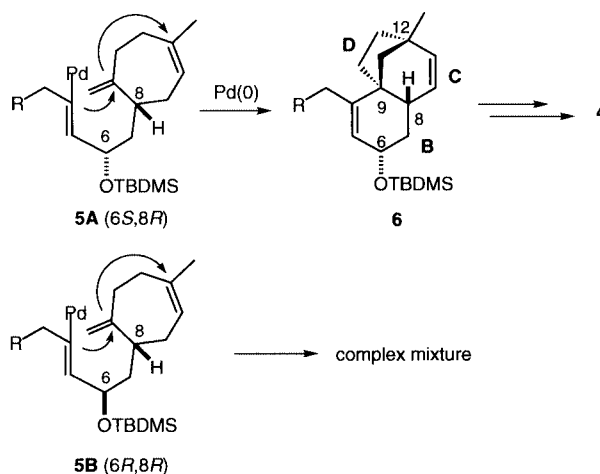
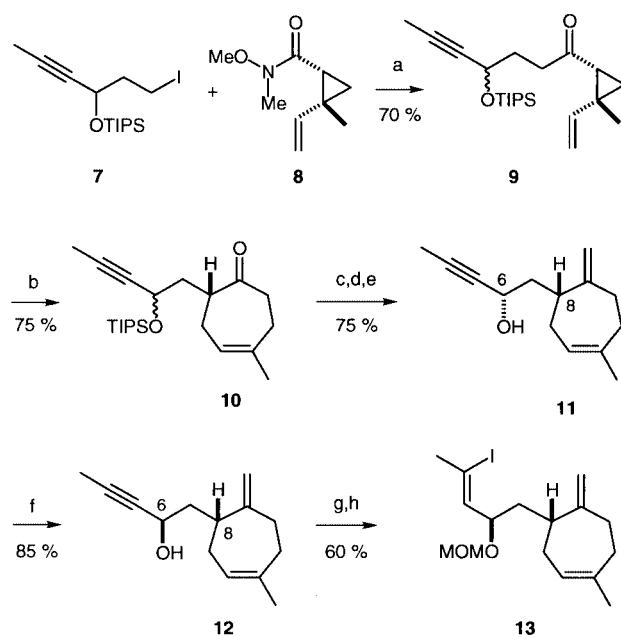


Figure 2 Sequential Heck Cyclizations of Epimers **5A** and **5B**.

An intriguing finding during our earlier synthesis of scopadulcic acid A (**4**) was the profound effect that stereochemistry of the allylic C6 siloxy group played in the pivotal bis-Heck cyclization: the 6*S*,8*R* epimer **5A** cleanly cyclized, as depicted in Figure 2, to scopadulane precursor **6** [R = (OCH₂CH₂O)CH₂CH₂CH₂], whereas the corresponding 6*R*,8*R* epimer **5B** furnished a complex mixture of products under identical conditions.^{6a,d} Although structures of these latter materials were not firmly established, there were indications that the major products arose by a process in which initial Heck insertion of the exo methylene group occurred from the β-face (the opposite sense to that observed with epimer **5A**). If this conjecture was correct and the efficiency of the process could be optimized, bis-Heck cyclizations of stereoisomer **5B** could provide a route to tricyclic products having the stemodane or stemarane skeleton. To further evaluate this possibility, we

chose to explore related cyclizations of a simpler substrate having $R = H$ with the anticipation that elucidation of the structure of products would be more straightforward in this series.

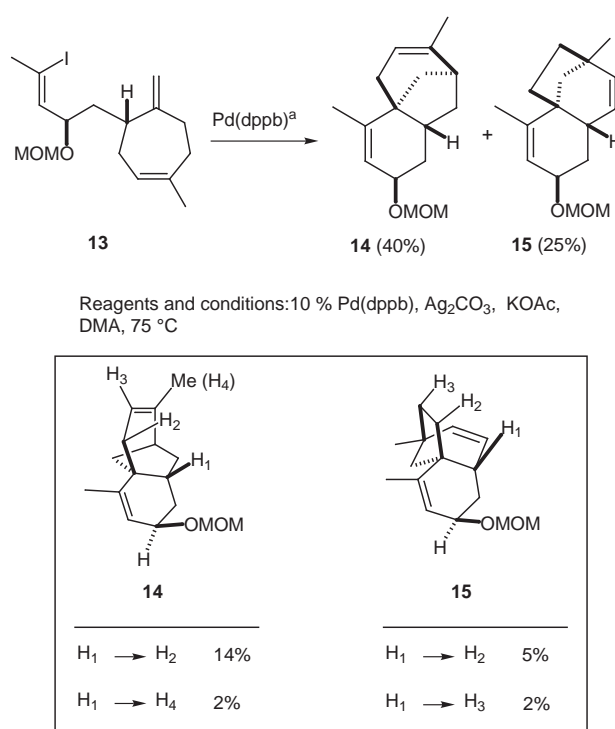
Using a strategy identical to the one employed in our synthesis of **4**, racemic $6R^*,8R^*$ trienyl iodide **13** was assembled as summarized in Scheme 1. Coupling the organolithium derivative of **7**^{8,9} with racemic cyclopropyl carboxamide **8**^{6d} provided a mixture of epimeric ketones **9** in 70% yield (Scheme 1). Silylation of **9** under thermodynamic conditions yielded the corresponding enoxysilanes,¹⁰ which underwent Cope rearrangement at 100 °C in toluene to give cycloheptenones **10** as a ~1:1 mixture of epimers. Installation of the exocyclic methylene group and subsequent deprotection of the TIPS ether delivered a separable mixture of **11** and $6R^*,8R^*$ epimer **12**; the undesired $6S^*,8R^*$ epimer **11** could be converted to **12** by Mitsunobu inversion. This two stage sequence provided **12** in 69% overall yield from **10**.¹¹ Reduction of **12** with sodium bis-(2-methoxyethoxy)aluminum hydride (Red-Al[®]), followed by quenching the vinylalane intermediate with NIS furnished an iodo alcohol that was protected to give **13**. The choice of the MOM protecting group was made after initial survey experiments indicated that silicon protecting groups were labile under some Heck reaction conditions.



Scheme 1 Reagents and conditions: a) **7**, Et₂O, -78 °C; *t*-BuLi; **8**; b) TMSOTf, Et₃N; toluene, 100 °C. c) KHMDS, MePh₃PBr, 0 °C. d) TBAF (1.0 M THF solution), 25 °C. e) HPLC, 1:25 EtOAc-hexanes, 60 Å SiO₂. f) DEAD, Ph₃P, PhCO₂H; K₂CO₃, MeOH. g) Red-Al[®], 25 °C; NIS, -78 °C; h) CH₃OCH₂Cl, *i*-Pr₂EtN, CH₂Cl₂.

With sufficient quantities of the $6R^*,8R^*$ stereoisomer **13** available, a variety of Heck cyclization conditions were screened (Scheme 2). Attempted cyclization of **13** using

the catalyst system employed in our scopadulcic acid A synthesis [Pd(OAc)₂, Ag₂CO₃, THF]^{6a} gave a complex mixture of products, as did reactions employing (Ph₃P)₄Pd. Use of Pd-bis(tri-*o*-tolylphosphine) with a variety of acid scavengers [Ag₂CO₃, Et₃N, *i*-Pr₂EtN or KOAc] surprisingly led to the elimination of HI to regenerate the propargylic alcohol unit. Fortunately, we found that **13** cyclized reasonably cleanly under cationic Heck conditions.⁷ For example, cyclization of **13** at 75 °C in *N,N*-dimethylacetamide (DMA) using 10 mol% of Pd(dppb) and excess Ag₂CO₃ and KOAc provided two readily separable tricyclic products **14** and **15** in 40% and 25% yields, respectively.¹² Structures for **14** and **15** followed unambiguously from extensive 2D NMR and nOe experiments. The diagnostic ¹H-¹H nOe enhancements depicted in Scheme 2 firmly established that the larger bridge is *cis* to the angular hydrogen in both products.^{13,14}



Scheme 2

A possible rationale for the outcome of the Heck cyclization of $6R^*,8R^*$ trienyl iodide **13** is provided in Figure 3. As we have discussed earlier, insertion of the vinylpalladium intermediate initially generated from **13** could take place by two conformations (**16** and **16'**) that have a favored (nearly coplanar) arrangement of the Pd-C σ and the C-C π bonds.^{6a} As suggested in Figure 3, a destabilizing interaction between the palladium fragment and the allylic alkoxy group in conformer **16'** should result in the initial insertion taking place by way of **16** to form *trans*-bicyclo[5.4.0]undecadienyl palladium alkyl intermediate **17**. A surprising outcome of the present investigation is

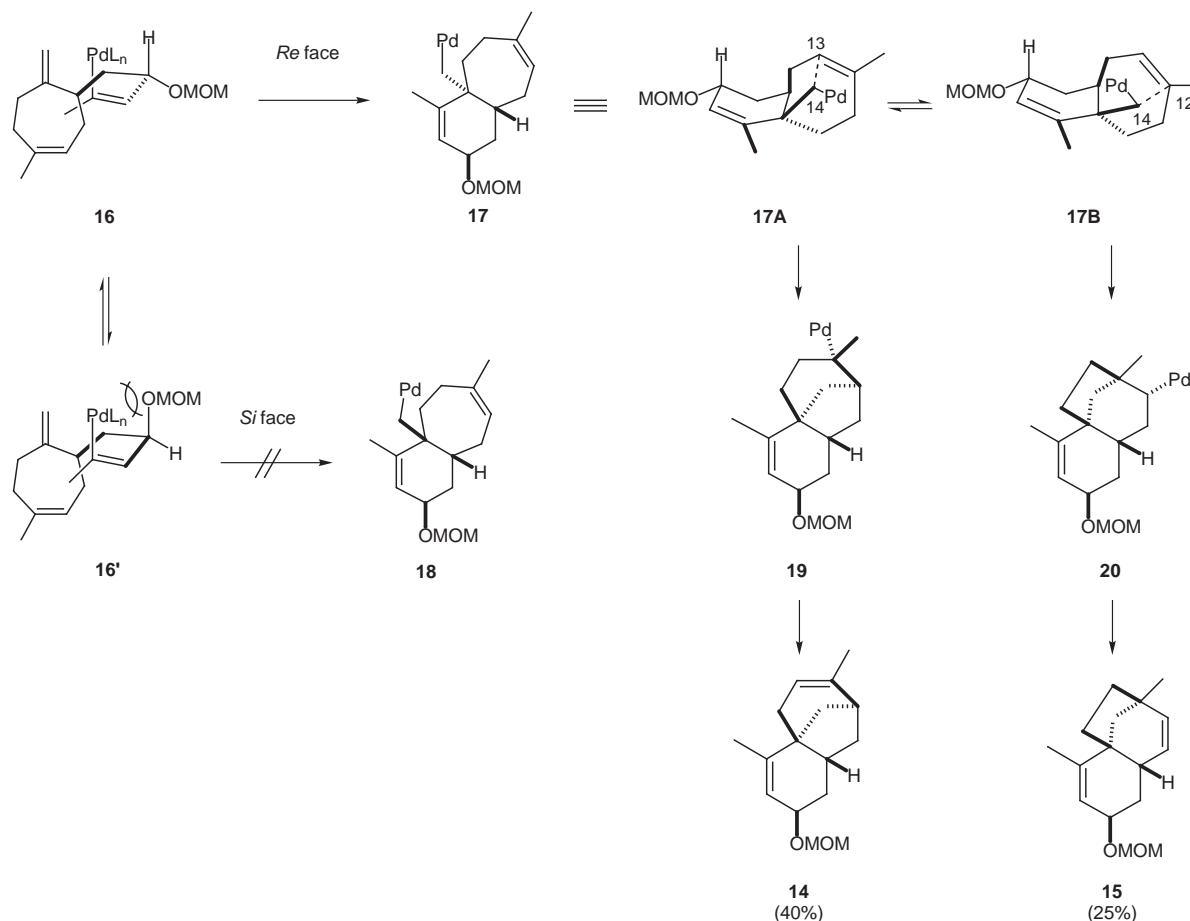


Figure 3 Bis-Heck Cyclizations of the $6R^*,8R^*$ Epimer.

that subsequent insertion of the trisubstituted cycloheptyl double bond of this intermediate occurs to generate both **14**, having the stemodane BCD skeleton, and **15**, having the BCD stemarane ring system. Since the insertion pathways leading to both of these tricyclic products involve 5-exo ring formation, we would have expected the $17B \rightarrow 20 \rightarrow 15$ pathway to be favored, because it avoids formation of intermediate **19** having a relatively unstable tertiary Pd–C σ bond.^{6a} Obviously others factors, at this time only poorly understood, come into play and override the relative instability of intermediate **19**.^{15,16}

In summary, this investigation shows that bis-Heck cyclizations of the $6R^*,8R^*$ epimer of trienyl iodide intermediates employed in our earlier total synthesis of scopadulcic acid A (**4**)^{6a} can generate the synthetically challenging BCD tricyclic moieties of tetracyclic diterpenes of the stemodane and stemarane families. If the factors that are necessary to control regioselection of the second Heck insertion step can be defined, a potentially powerful new approach for total synthesis of *stemodia* natural products should emerge.

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- (12) The catalyst was generated by reaction of Pd₂(dba)₃•CHCl₃ and 1,4-(diphenylphosphino)butane (dppb) at rt in DMA for 15 min (solution changes color from dark red to green-orange). An aliquot of this catalyst solution (10 mol% Pd) was added to a suspension of Ag₂CO₃ (2 equiv), KOAc (2 equiv), and iodide **13**. The resulting suspension was degassed and refilled with Ar, heated at 75 °C for 16 h, allowed to cool to rt, and concentrated.
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- (15) A *Monte Carlo* conformational search was conducted on an analog of **17** in which the palladium unit was replaced by H using the MacroModel V6.5X implementation of the MM2* force field.¹⁶ The five lowest energy conformers found had a universally shorter separation between C13 and C14 than between C12 and C14. An identical search¹⁶ made with this congener of the C6 epimer of *cis*-bicyclo[5.4.0]undecadienyl palladium alkyl intermediate **18** that would arise from cyclization of the *6S**,*8R** epimer of **16** found the separation between C12 and C14 was shortest, which could contribute to the clean generation of the scopadulan ring system from Heck cyclizations of this stereoisomer series.^{6a}
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