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 stemarin (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

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 scopadulan 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 scopadulan 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.

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 6S,8R epimer 5A cleanly cyclized, as depicted in Figure 2, to scopadulan precursor 6 [R = (OCH2CH2O)CH2CH2CH2], whereas the corresponding 6R,8R 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 8,10 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 ~1:1 mixture of epimers. Coupling the propargylic alcohol unit. Fortunately, we found that 12 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

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)2Pd. Use of Pd-bis(tri-o-tolyphilphosphine) 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 1. Reagents and conditions: a) 7, Et, Li. –78 °C; t-BuLi; 8, b) TMSOTf, Et3N, toluene, 100 °C; c) KHMD, Me3PBr, 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-Al6, 25 °C; NIS, –78 °C; h) CH3OCH2Cl, i-Pr2EtN, CH2Cl2.

Scheme 2. Reagents and conditions: 10% Pd(dppb), Ag2CO3, KOAc, DMA, 75 °C.

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...
that subsequent insertion of the trisubstituted cycloheptenyl 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 → 20 → 15 pathway to be favored, because it avoids formation of intermediate 19 having a relatively unstable tertiary Pd–C σ bond. 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) 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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(11) Epimers 11 (δ 2.68–2.73, m) and 12 (δ 2.60–2.63, m) showed
particularly diagnostic 1H NMR signals for their C8 methane
dihydrogens. Comparison of these resonances with those of the
related more complex epimer pair studied earlier, whose
structures were rigorously secured by single-crystal X-ray
analysis of a derivative,10 allowed for unambiguous definition
of the stereosturctures of 11 and 12.
(12) The catalyst was generated by reaction of Pd2(dba)3•CHCl3,
and 1,4-diphenylphosphino)butane (dpbb) 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 rt,
and concentrated.
(13) 1H NMR spin systems were established using 1H COSY
and 1H decoupling techniques. The 1H-1H nOe experiments were
conducted at 500 MHz using the DPFGSE (double pulsed
gradient spin echo) method: Stott, K.; Keeler, J.; Van, Q.
(14) Data for 14: 1H NMR (500 MHz, CDCl3) δ 5.70 (d, J = 5.5
Hz, 1H), 5.14 (br s, 1H); 4.68 (d, J = 6.6 Hz, 1H), 4.64 (d,
J = 6.6 Hz, 1H), 3.96–3.94 (m, 1H), 3.36 (s, 3H), 2.62–2.57
(br d, J = 15.0 Hz, 1H), 2.18–2.08 (m, 3H), 1.99–1.93 (m,
1H), 1.75–1.70 (m, 1H), 1.75 (d, J = 1.5 Hz, 3H), 1.67 (d,
J = 2.0 Hz, 3H), 1.64–1.55 (m, 1H) 1.44 (dd, J = 8.0 Hz, 3.0
Hz, 1H), 1.36–1.32 (m, 1H), 1.26–1.20 (m, 1H); 13C NMR
(125 MHz, CDCl3) δ 146.0, 141.7, 122.3, 117.4, 94.7, 68.8,
55.2, 45.5, 43.4, 41.2, 40.1, 37.5, 37.2, 35.5, 22.3, 20.0; IR
(film) 2912, 1457, 2867, 1653, 1450, 1377, 1149, 1099, 1039, 988, 918 cm
1; HRMS (EI) m/z 248.1750, (248.1776 calcd for C16H24O2,
M).
(15) A Monte Carlo conformational search was conducted on an
analogue of 17 in which the palladium unit was replaced by H
using the MacroModel V6.5X implementation of the MM2*
force field.14 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
conformer of the C6 epimer of cis-bicyclo[5.4.0]undecadienyl
palladium alkyl intermediate 18 that would arise from
cyclization of the 65°,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.16
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