Palladium-catalysed Polycyclization of Dienynes to give Carbocyclic angularly Bisanellated Cyclohexadiene Derivatives[1]

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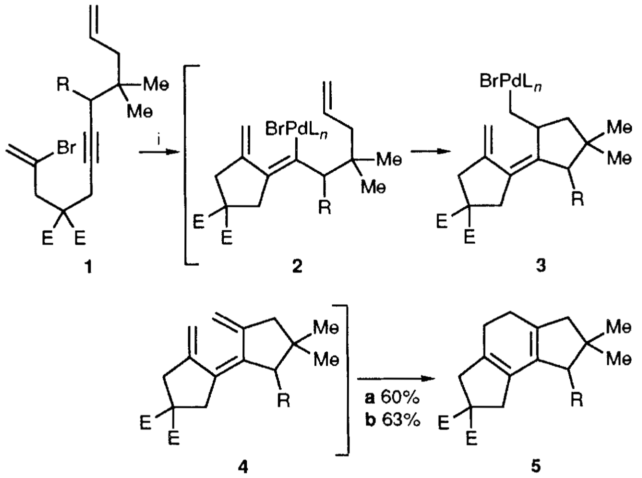
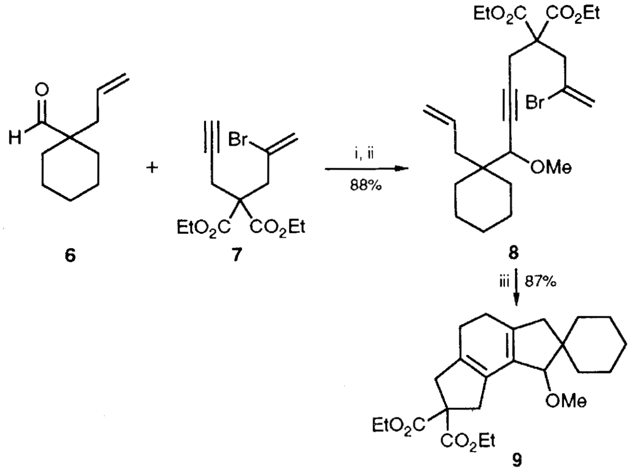
Various 2-bromododeca-1,11-dien-6-ynes **1a,b**, **8** and *trans*- or *cis*-**10a,b** when subjected to Heck reaction conditions, cleanly undergo palladium-catalysed biscyclizations followed by an electrocyclic rearrangement to form tricyclic cyclohexadienes **5a,b**, **9** and *cis*- or *trans*-**11a,b** as sole products (7 examples).

Modern synthetic approaches to complex natural products increasingly utilize appropriate combinations of several different reaction types in one experimental operation.[2] Although palladium-catalysed zipper-mode cyclizations using Heck reaction conditions[3] have recently attracted widespread attention for the construction of bi-, tri- and tetra-cyclic systems,[4] little has yet been reported about developing domino-type processes, which are based on this cyclization methodology.[5] During our studies directed towards the simple construction of tricyclic systems, we recently observed the unexpected formation of an angularly bisanellated cyclohexadiene upon exposing 2-bromo-4-oxatrideca-1,12-dien-7-yne to a palladium catalyst.[6] We now report that this process is of general use, especially for the construction of carbocyclic systems.



E = CO_2Me
a; R = OMe
b; R = OH

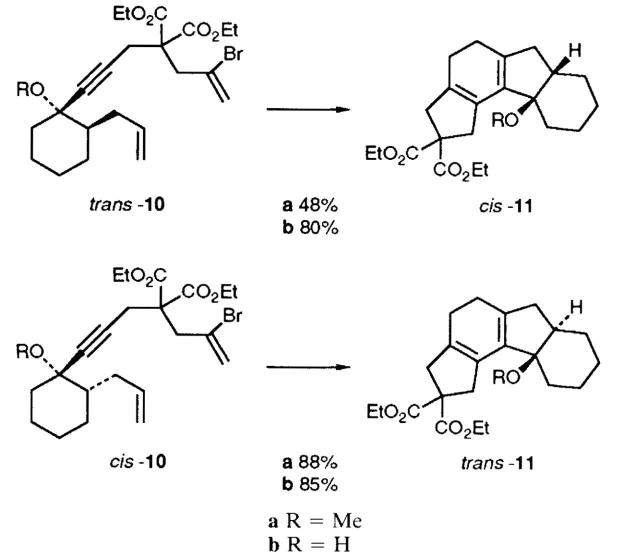
Scheme 1 *Reagents and conditions*: i, $Pd(OAc)_2$ (3–5 mol%), PPh_3 (12–20 mol%), Ag_2CO_3 (2 equiv.), MeCN, 80 °C, 2–3 h



Scheme 2 *Reagents and conditions*: i, Bu^nLi, tetrahydrofuran, −78 to 0 °C; ii, Me_2SO, MeI, 10 °C; iii, $Pd(OAc)_2$ (3 mol%); PPh_3 (6 mol%); Ag_2CO_3 (2 equiv.), MeCN, 80 °C, 4 h

Indeed, when 2-bromo-10,10-dimethyl-9-methoxy-4-oxatrideca-1,12-dien-7-yne is treated with 3–5 mol% of $Pd(OAc)_2$, 12–20 mol% of PPh_3 and 2 equiv. of silver carbonate in acetonitrile for 10 h at 80 °C, 3-methoxy-4,4-dimethyl-11-oxatricyclo[7.4.0.$0^{2,6}$]trideca-1(9),2(6)-diene is obtained in 43% isolated yield. As in the previously reported case, this moderate yield must be due to the presence of an oxygen atom in the precursor and the product,[6] because as we have found now, acyclic dienynes without a heteroatom in the chain, react very cleanly without formation of any side products.

For instance, dienyne **1a**, when treated with 3–5 mol% of $Pd(OAc)_2$, 12–20 mol% of PPh_3 and 2 equiv. of silver carbonate in acetonitrile for 3 h at 80 °C, gives the tricyclic cyclohexadiene **5a** in 60% isolated yield.† Even the unprotected propynylic alcohol **1b** cleanly cyclizes to form the tricyclic alcohol **5b** (63%) under identical reaction conditions in 2 h.‡



Scheme 3 Reagents as for step iii, Scheme 2, for 3 h. *cis* and *trans* refer to the relative positions of the allyl and alkoxy substituents.

We envisage this transformation to proceed by biscyclization of dienyne **1** *via* the intermediate **2** and **3**, catalysed by palladium(0). β-Hydride elimination from **3** can lead to triene **4** which then undergoes an electrocyclic rearrangement to give cyclohexadiene **5** (Scheme 1). To prohibit palladium-catalysed isomerizations of trienes **4** to cross-conjugated trienes,[6] silver(I) or thallium(I) salts have to be added to the reaction mixture.[7]

This domino transformation can also be performed with the dienyne unit attached to a preexisting ring. Thus, the spirocyclohexane tricycle **9** can conveniently be prepared in only two steps from the easily accessible 1-allyl-1-formylcyclohexane **6**[8] and diethyl 6-bromohept-6-en-1-yne-4,4-dicarboxylate **7**.§ Reaction of **6** with the lithium salt of **7** and quenching of the resulting lithium alkoxide with methyl iodide[9] gives the monocyclic precursor **8** (88% isolated yield), which, upon treatment with $Pd(OAc)_2$, PPh_3 and silver carbonate in acetonitrile at 80 °C, cyclizes to form the spirotricycle **9** in 87% isolated yield.

Even with a cyclohexane moiety attached to two adjacent carbons in the acyclic carbon backbone, as in *trans*-**10a**,¶ as well as its diastereoisomer *cis*-**10a**, the domino cyclization sequence is achieved smoothly to give the corresponding *cis*- and *trans*-fused tetracycles *cis*-**11a** and *trans*-**11a** in 48 and 88% yield, respectively (relative configuration determined by NOESY experiments). Even in this rather sensitive system protection of the tertiary propynylic alcohol functionality proved not to be necessary. Domino cyclization of the unprotected propynylic alcohols *trans*-**10b** and *cis*-**10b** leads to *cis*-**11b** and *trans*-**11b** in impressive yields of 80 and 85%, respectively.

In conclusion, this new methodology offers a simple and rapid entry into tricyclic ring systems with the advantage of creating a useful conjugated diene unit for further elaboration in the cyclized product. The simple assembly of the acyclic precursors, good yields and the catalytic process make this

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† NMR investigations of the crude product showed total consumption of starting material and no byproducts. The isolated yield of 60% is due to a substantial loss of products during purification *via* column chromatography.

‡ All new compounds were fully characterized by IR, ^1H NMR, ^{13}C NMR, MS, HRMS or microanalysis. All cyclohexadiene derivatives reported here are air-sensitive.

§ Diethyl 6-bromohept-6-en-1-yne-4,4-dicarboxylate **11** can be prepared in two steps from diethyl malonate, 2,3-dibromopropene and 3-bromopropyne in 86% overall yield.

¶ Dienynes *cis*- and *trans*-**10a** can be prepared in two steps from 2-allylcyclohexanone and diethyl 6-bromohept-6-en-1-yne-4,4-dicarboxylate in 30 and 32% overall yield, respectively.

domino process an interesting alternative to previously documented intramolecular sequences, which lead to angularly bisanellated cyclohexadiene derivatives.[10]

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