Tetrahedron Letters, Vol. 33, No. 52, pp. 8039-8042, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Palladium-Catalyzed Polycyclizations of Substituted Dienynes: Stereoselective Routes to Highly Complex Polycycles[1]

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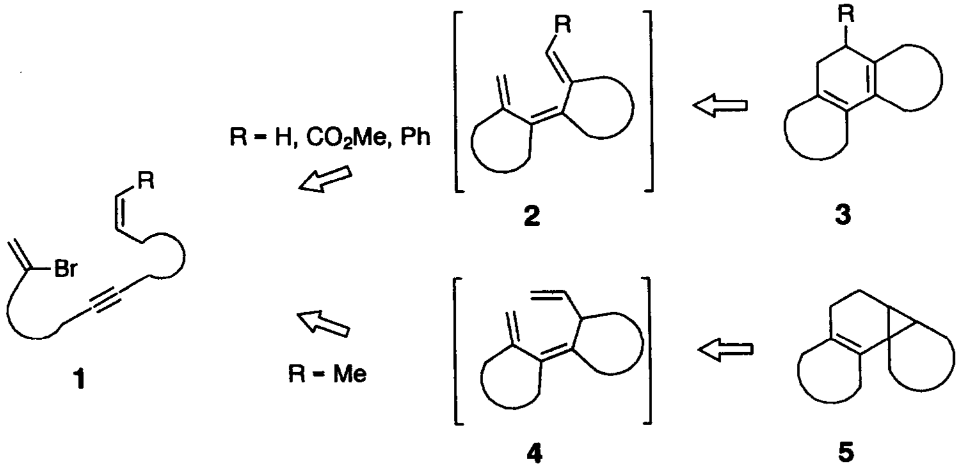
Key words: palladium-catalysis; polycyclization; 6π-electrocyclization; domino process; rotaselectivity; Diels-Alder reactions, intramolecular

Abstract: 12-Substituted 2-bromo-1,11-dien-6-ynes were found to undergo a palladium-catalyzed biscyclization followed by a diastereospecific 6π-electrocyclic rearrangement or a Diels-Alder reaction to give substituted angularly bisanellated cyclohexadienes or polycyclic bicyclo[4.1.0]hept-2-ene derivatives containing a three-membered ring, depending on the type and pattern of substituents.

Although originally only designed to couple unsaturated substituents onto alkenes, the Heck reaction[2] nowadays also serves as a versatile method for the construction of polycycles[3] including compounds in which stereogenic centres of the precursors are preserved.[4] But only little has yet been reported about a strategy combining a palladium-mediated polycyclization with the creation of new stereogenic centres.[5] Recently, we reported a new methodology for the construction of carbocyclic angularly bisanellated cyclohexadiene derivatives by a domino type process.[6,7] When 2-bromo-dodeca-1,11-dien-6-ynes are subjected to Heck reaction conditions, they cleanly undergo palladium-catalyzed biscyclizations followed by an electrocyclic rearrangement to form tricyclic cyclohexadienes. Our approach to utilize this sequence with concomitant diastereoselective creation of new stereogenic centres relies on two possibilities, the 6π-electrocyclic rearrangement of triene **2** to give bisanellated cyclohexadiene **3** or an intramolecular Diels-Alder reaction of the isomeric triene **4** to form the strained tetracycle **5** (Scheme 1).

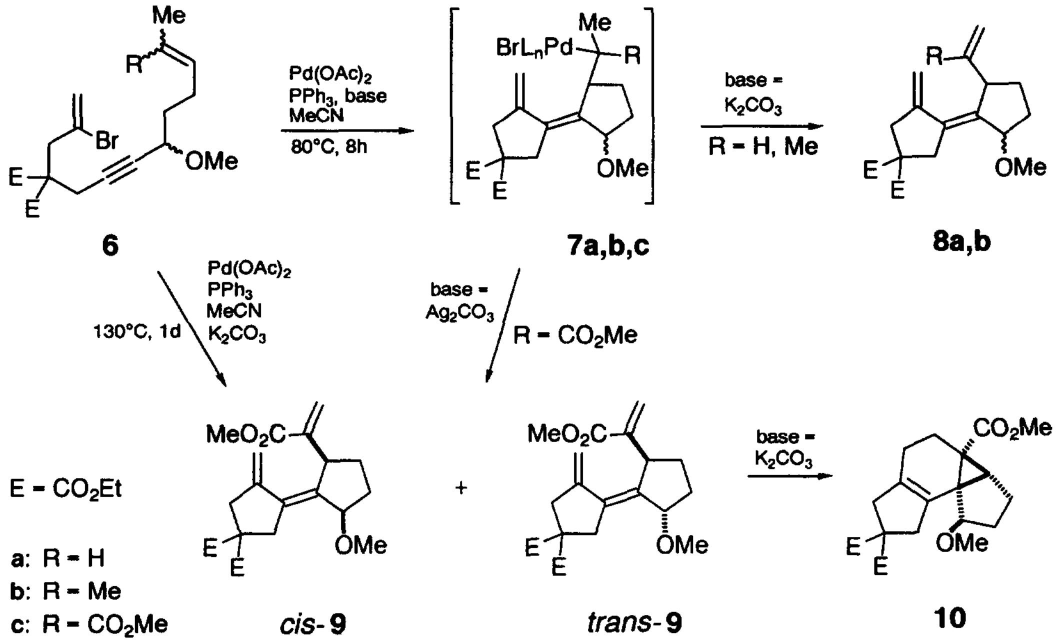
Scheme 1



To begin with, the cyclization of dienynes **6a,b** with one and two methyl substituents at C-12, respectively, was studied. When **6a,b** were treated with 3-5 mol% $Pd(OAc)_2$, 12-20 mol% PPh_3 and 2 equiv. of potassium carbonate in acetonitrile for 8 h at 80°C, mixtures of the diastereomeric trienes **8a,b**[8] were obtained in 70 and 65% isolated yields. In these model systems, apparently β-hydride elimination in the alkylpalladium bromide intermediate **7** preferably takes place from the methyl groups, and 6π-electrocyclization cannot occur. All attempts to force trienes **8a,b** to undergo an intramolecular Diels-Alder reaction failed so far (Scheme 2).

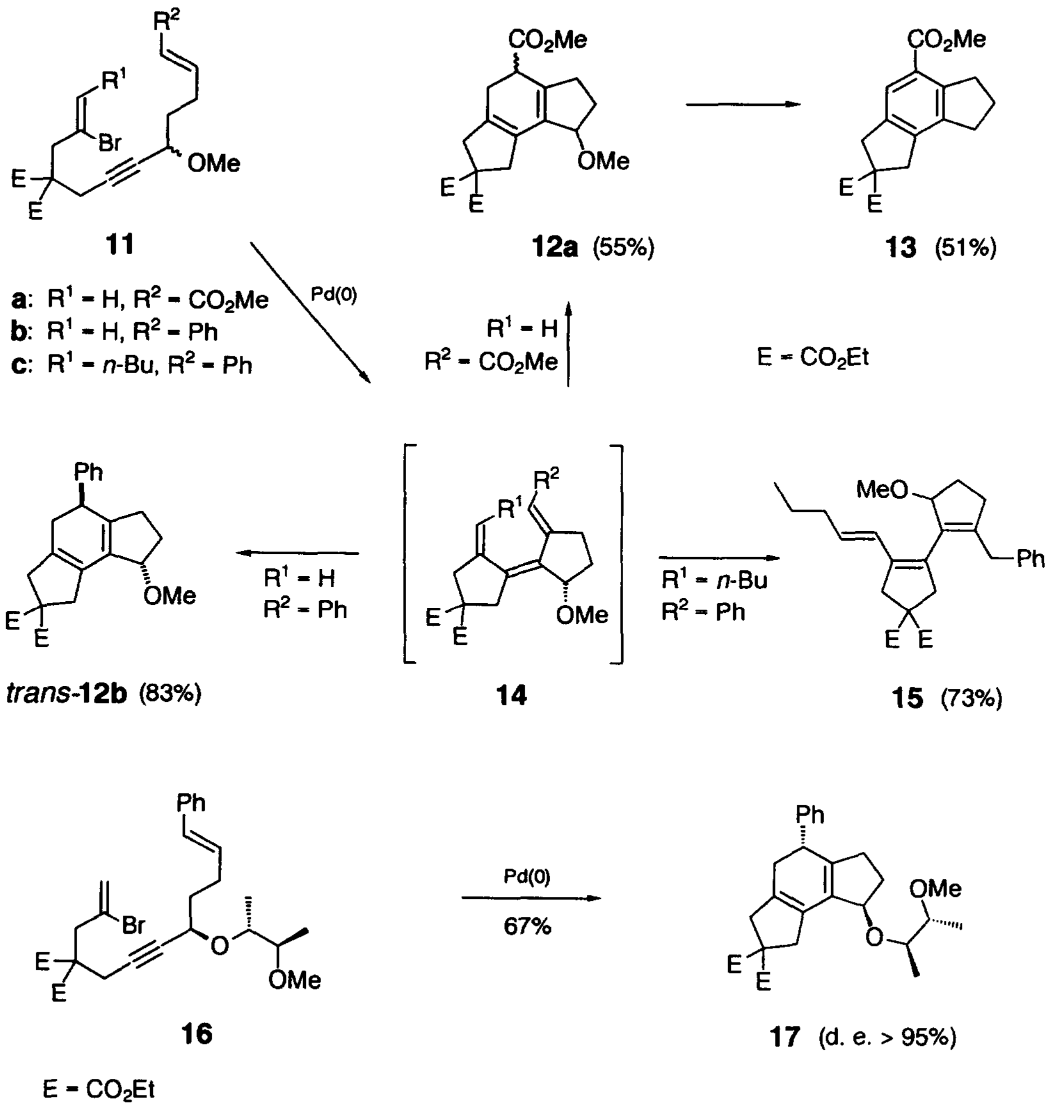
When one methyl group in **6** is replaced by a methoxycarbonyl as in **6c**, treatment with 3 mol% $Pd(OAc)_2$, 12 mol% PPh_3 and 2 equiv. of silver carbonate at 80°C for 8 h also resulted in the formation of a diastereomeric mixture of trienes *cis/trans*-**9**. But at elevated temperature (130°C) and with potassium carbonate as a base, *trans*-**9** underwent the anticipated intramolecular Diels-Alder reaction to give the tetracycle **10** in 47% isolated yield, *cis*-**9** was left unchanged (31% reisolated).

Scheme 2



In order to establish a 6π-electrocyclization as the second step in the domino sequence, the substituent at C-12 may not possess any accessible β-hydrogens. For instance, when dienyne **11a** with a methoxycarbonyl group at C-12 was treated with 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and 2 equiv. of silver carbonate, cyclohexadiene **12a** was obtained in 55% isolated yield.[9] Unfortunately though, under the basic conditions employed, epimerisation at the newly formed stereogenic centre took place, and no stereoselectivity was observed. Changes in reaction conditions like rising the temperature from 60 to 120°C and substituting silver by potassium carbonate led to the formation of benzene derivative **13** in 51% yield besides 24% of the isomerized cyclohexadiene. Apparently, compound **12a** undergoes 1,4-elimination of methanol probably initiated by deprotonation α to the methoxycarbonyl group with excess base, and the resulting methylenecyclohexadiene subsequently isomerizes to the aromatic product **13** (Scheme 3).

Scheme 3



With a phenyl substituent at C-12 as in dienyne **11b**, cyclization under standard conditions (10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 3 equiv. K_2CO_3, MeCN, 60°C, 3 d) gave only a single diastereomer, namely the *trans*-disubstituted tricycle *trans*-**12b** without epimerisation, in 83% yield. This apparent rotaselectivity in the electrocyclization step is caused by the methoxy substituent, which favours one of the two possible disrotatory movements,[10] bringing the phenyl and the methoxy substituent into the *trans*-configuration. Isomerisation of the diene unit was only observed at elevated reaction temperature (130°C) in the presence of 3 equiv. of potassium carbonate. The enantiomerically pure dienyne **16**,[11] accordingly yielded enantiopure bisanellated cyclohexadiene **17** (67% isolated) with high diastereoselectivity (d. e. >95%).[12] With an alkyl substituent (*Z*)-at C-1 oriented as in dienyne **11c**, disrotatory 6π-electrocyclization of the intermediate 1,3,5-hexatriene **14c** does not take place. Rather than a cyclohexadiene, an isomeric hexatriene **15** is formed upon treatment of **11c** with $Pd(OAc)_2$ (10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 2 equiv. K_2CO_3, MeCN, 80°C, 2 d) in 73% yield (based on 50% converted starting material), apparently by an antarafacial 1,7-hydrogen shift in the intermediate **14c**.

Further studies are presently under way to apply this methodology to the synthesis of complex natural products.

Acknowledgements: Financial support of this work by the Volkswagen-Stiftung and the Fonds der Chemischen Industrie is gratefully acknowledged. We are indebted to BASF, BAYER, HOECHST and DEGUSSA AG for generous gifts of chemicals. F. E. M. and H. H. are grateful to the Studienstiftung des deutschen Volkes and the Fonds der Chemischen Industrie for graduate fellowships.

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12. The diastereomeric excess (d. e.) was determined by ^1H NMR spectroscopy using a chiral shift reagent $(Eu(hfc)_3)$. The absolute configuration of cyclohexadiene **17** will be determined by an X-ray crystal structure analysis in due course.

(Received in Germany 27 August 1992)