Cascade Cyclization: Carbopalladative Cyclization Followed by Electrocyclic Closure as a Route to Complex Polycycles

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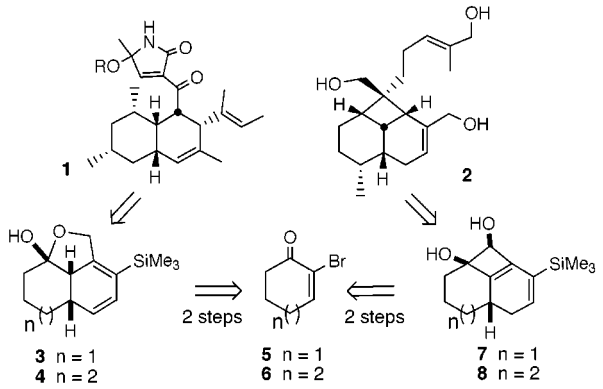
Received September 11, 2001

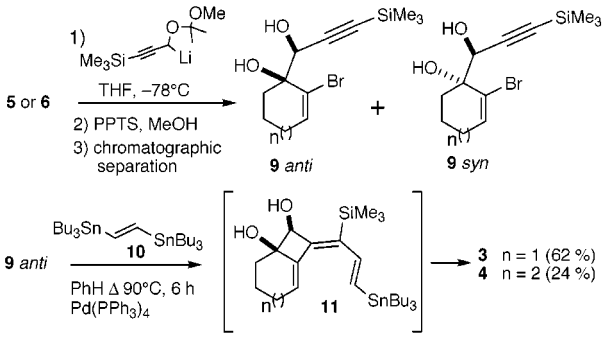
The rapid and efficient synthesis of new complex molecules requires the development of new methodologies shortening the number of steps. In this context, the chemist is looking for processes which involve several reactions in a one-pot operation. Along these lines, several elegant cascade reactions have been recently described in the literature showing their very high potential.[1] Particularly efficient in this field is the use of the transition metal-catalyzed coupling reaction for the formation of new carbon−carbon bonds.[2] We recently found that polycyclic ring systems could be easily produced for the synthesis of biologically active natural products using a carbopalladation cross-coupling reaction of vinyl halides with vinylstannanes. This methodology could potentially be applied to the synthesis of ascosalipyrrolidinone **1**,[3] which displays an unprecedented and structurally unusual tetramic acid containing a cis-fused Decalin, as well as to the tricyclic structure of trihydroxydecipiadiene **2**.[4] In a retrosynthetic analysis of **1**, the central Decalin system could be prepared from the highly functionalized hemiketal **3** and the skeleton of **2** from the unusual strained tricyclic diol **7** containing a cyclobutene moiety (Scheme 1).

We report herein a short synthesis (2 steps) of [4.4.0] and [5.4.0] cis-fused bicyclic systems of type **3** and **4** and the first synthesis of two new tricyclic structures, the tricyclo[5.3.1.$0^{5,11}$]-undecadiene **7** and tricyclo[6.3.1.$0^{5,11}$] dodecadiene **8**, including a cyclobutenic bridgehead double bond respectively prepared from bromocycloalkenones **5** and **6**. The reaction pathway involves a cascade of three different reactions including an unusual and quite rare 4-exo-dig cyclization[5] eventually leading stereospecifically to a masked bicyclic ketone **3** and **4** (Scheme 2). The starting material, diol **9***anti*, was prepared in large scale by addition of a properly protected metalated propargylic alcohol[6] on bromocycloalkenones **5**/**6** followed by deprotection and chromatographic separation of the two **9***anti* and **9***syn* diastereomers. The anti relative stereochemistry of the diol was established by ^{1}H-NOESY experiments on a derivative of **9**.[7]

Scheme 1



Scheme 2



When the diol **9***anti* was heated with *trans*-bis(tributylstannyl)-ethylene[8] (**10**) and Pd(PPh$_3$)$_4$ for 2 h, a single product was formed in 62% yield (Scheme 2). This compound was found to lack the tributylstannyl group and the triple bond and to possess a cis-fused Decalin system. The product was finally identified as hemiketal **3**, the structure of which was unambiguously confirmed by X-ray diffraction analysis (Figure 1) as a single diastereomer.

By careful monitoring of the reaction, we observed after 30 min the formation of an intermediate that slowly reacts to give **3**. After isolation of this compound by chromatography and intensive 2D ^{1}H NMR and NOESY experiments, its structure was assigned to the bicyclo[4.2.0]octendiol (**11**). To our knowledge, such a cyclobutane derivative has never been prepared previously via a tandem 4-exo-dig carbopalladation/Stille cross-coupling reaction. No trace of the corresponding direct Stille product was observed in this case. However, related bicyclic [4.2.0]octadienes or [3.2.0]heptene have been recently obtained from the intramolecular Heck reaction,[9] from copper(I) chloride-mediated internal conjugate addition of alkenyltrimethylstannane to the α,β-alkenic ester unit[10] or by intramolecular carbometalation of 1,6-eneynes.[11] To have an insight to the mechanistic aspect of the formation of **3**, the starting diol was submitted to the same reaction conditions in the presence of the vinylic deuterated analogue **12**.[12] The two deuteriums were specifically incorporated at positions 4 and 5 in place of the two vinylic protons affording **13** and indicating a clean isomerization of the starting double bond. Furthermore, when pure **11** (n = 1) was heated in benzene for 2 h

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(1) (a) Wender, P. A.; Miller, B. L. *Org. Synth. Theory Appl.* **1993**, *2*, 27. (b) Bertz, S. H.; Sommer, T. J. *Org. Synth. Theory Appl.* **1993**, *2*, 67. (c) Malacria, M. *Chem. Rev.* **1996**, *96*, 289−306. (d) Ang, K. H.; Bräse, S.; Steinig, A. G.; Meyer, F. E.; Llebaria, A.; Voigt, K.; de Meijere A. *Tetrahedron* **1996**, *52*, 11503−11528. (e) Henniges, H.; Meyer, F. E.; Schick, U.; Funke, F.; Parsons, P. J.; de Meijere, A. *Tetrahedron* **1996**, *52*, 11545−11578.

(2) For reviews on palladium cascade reactions see: (a) de Meijere A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379−2411. (b) Bräse, S.; de Meijere, A. In *Metal-Catalysed Cross Coupling Reaction*; Stang, P. J., Diederich, F., Eds.; Wiley-VCH: Weiheim, Germany, 1997. For examples of palladium cascade reactions, see: (c) Grigg, R.; Major, J. P.; Martin, F. M.; Whittake M. *Tetrahedron Lett.* **1999**, *40*, 7709−7712.

(3) Osterhage, C.; Kaminsky, R.; Kônig, G. M.; Wright, A. D. *J. Org. Chem.* **2000**, *65*, 6412−6417.

(4) Ghisalberti, E. L.; Jefferies, P. R.; Sheppard, P. *Tetrahedron Lett.* **1975**, 1775−1778.

(5) Bailey, W. F.; Ovaska, T. V. *Tetrahedron Lett.* **1990**, *31*, 627−630. Breuil-Desvergnes, V.; Goré, J. *Tetrahedron* **2001**, *57*, 1951−1960. Bogen, S.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **1997**, *119*, 5037−5038.

(6) (a) Ushida, K.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1976**, *32*, 2941−2942. (b) Suffert, J.; Toussaint, D. *Tetrahedron Lett.* **1997**, *38*, 5507−5510.

(7) See Supporting Information

(8) Bottaro, J. C.; Hanson, R. N.; Seitz, D. E. *J. Org. Chem.* **1981**, *46*, 5221−5222.

(9) Bräse, S. *Synlett* **1999**, *10*, 1654−1656.

(10) Piers, E.; Boehringer, E. M.; Yee, J. G. K. *J. Org. Chem.* **1998**, *63*, 8642−8643.

(11) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636−1638.

(12) **12** was prepared by deuteriostannylation of tributylstannylacetylene in the presence of AIBN.

10.1021/ja0170495 CCC: $20.00
Published on Web 11/08/2001

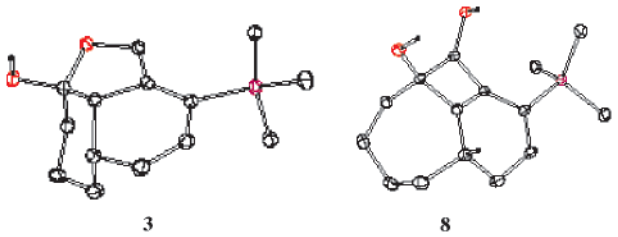
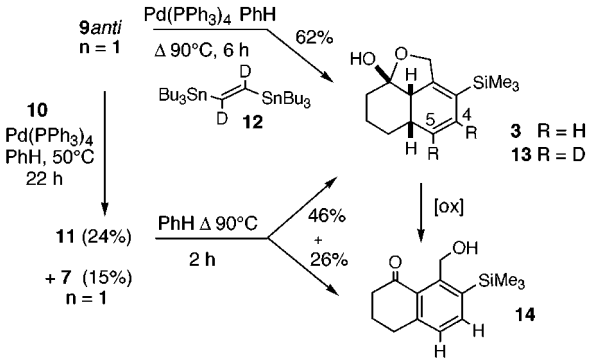
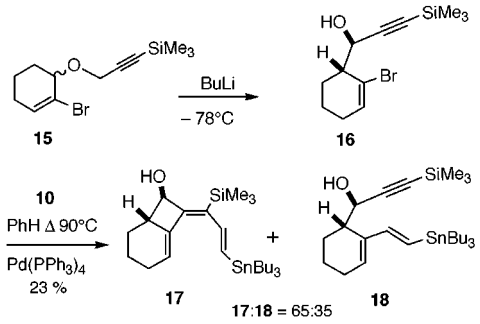


Figure 1. X-ray crystal structures showing the two ORTEP views of compounds **3** and **8**.

Scheme 3



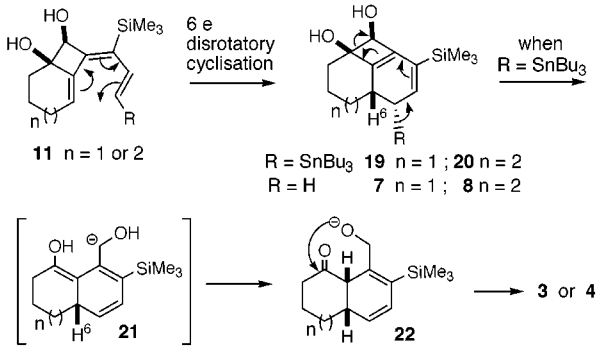
Scheme 4



in the absence of the catalyst, compounds **3** and **14** were obtained in 46% and 26% yield, respectively (Scheme 3). This fact strongly supports a thermal rearrangement of the strained molecule **11** leading to **3** via a cascade reaction. The formation of **14** can be explained by an opening of the hemiketal **3** followed by a spontaneous oxidative aromatization of the cyclohexadiene although the reaction occurred under rigorously inert conditions.

This is further supported by the reactivities of other structurally related analogues. When a similar procedure was employed for diol **9***syn* ($n = 1$), no trace of the related product **3** or Stille cross-coupling product was isolated. After 6 h, the reaction gave mainly decomposition of the starting diol and traces of a new unidentified compound. If the propargylic alcohol **16**, easily prepared from **15** by a [2,3]-Wittig rearrangement in 98% yield with complete control of the stereoselectivity, was submitted to the same conditions, a mixture of two products (assigned as **17** and **18**) was isolated in 23% yield with a ratio of 65:35, respectively (Scheme 4). The different reactivity of compound **16** vs **9***anti* could be explained by the presence of the diol function and the formation of an intramolecular hydrogen bond in **9***anti* which

Scheme 5



properly positions the triple bond in proximity to the vinyl palladium intermediate. The carbopalladation of the triple bond is then kinetically favored. This is not the case in **16**. No further rearrangement of **17** was observed and again only decomposition occurred.

The proposed mechanism for the formation of **3** is shown in Scheme 5. A six-electron disrotatory electrocyclization results in the strained tricyclic diol **19**. The anti stereochemistry between the proton 6 and the tributylstannyl group is fixed by the electrocyclization process. Intermediate **19** undergoes a concerted elimination of $SnBu_3$ and ring opening of the cyclobutenediol leading to the enol **21**.

The formation of the conjugated diene **22** is then followed after prototropy by an intramolecular attack of the alcoholate on the ketone from the concave face to form the last stereocenter, resulting in the hemiketal **3**. Strong evidence for this mechanism is supported by the isolation and characterization of the strained tricyclic compounds **7** and **8** obtained respectively in 32% and 62% yield when **9***anti* ($n = 1$ and 2) is treated with tributylstannylethylene. The unusual structure of **8** was unambiguously confirmed by an X-ray diffraction analysis (Figure 1).[7] The reaction was also applied to the synthesis of [5.4.0] cis-fused bicyclic hemiketal **4** isolated with 24% yield as a pure diastereomer.

We have described a new process that converts simple propargylic anti diols to functionalized polycyclic products via an unprecedented cascade reaction summarized as follows: (1) 4-exo-dig carbopalladation of an alkyne, (2) disrotatory electrocyclization, (3) concerted $SnBu_3$ elimination/cyclobutene ring opening, and (4) face selective cyclic hemiketal formation. The syntheses of the cyclobutanediol **11**, cyclobutanol **17**, and the two tricyclic compounds **7** and **8** through an intramolecular carbopalladation are presented for the first time. Efforts are currently underway to probe the scope and limitations of this new protocol cascade reaction and to its application to the synthesis of ascosalipyrrolidinone **1**, trihydroxydecipiadiene **2**, and analogues. These results will be disclosed in the future.

Acknowledgment. We thank Professors P. A. Wender and M. L. Snapper for fruitful discussions, the CNRS for financial support, and the MNERT (B.S.) for fellowship.

Supporting Information Available: Experimental procedures, physical data and NMR spectra for **3**−**18** and synthetic intermediates, and X-ray data for **3** and **8** ($n = 2$) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org. The structures of **3** and **8** have been deposited at the Cambridge Crystallographic Data Centre under the numbers CCDC 172736 and 172737 respectively.

JA0170495