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Cascade Cyclization: An Easy Access to Highly Unsaturated Polycyclic Ring Systems through a Tandem Stille/[4 + 2] Reaction under Mild Conditions

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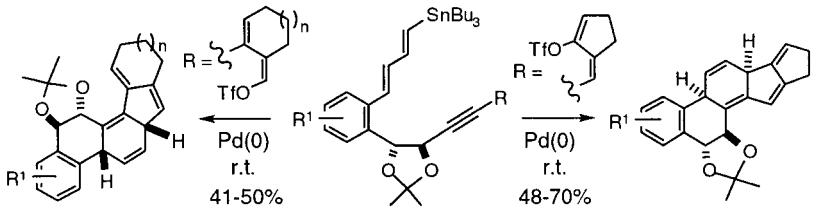
ABSTRACT



The synthesis of several polycyclic compounds 1a–c, 2, and 3 has been performed through a tandem Stille/[4 + 2] cascade reaction from cyclic bis(enoltrifluomethanesulfonate) 4a–c, 5, and 6, respectively. The reaction proceeds very efficiently in a one-pot operation at *room temperature* in DMF in the presence of a catalytic amount of $Pd(CH_3CN)_2Cl_2$ and LiCl.

The generation of molecular complexity through the sequencing of multiple novel bond-forming processes in a single synthetic operation is an important direction for the realization of practical syntheses.[1] In this context, several examples of intramolecular cross-coupling reactions have been reported in the literature. Particular to this field are the Heck reaction in the oligocyclization of dienynes,[2] the carbopalladation−termination cascade processes,[3] or more recently, the intramolecular version of the Stille coupling/Diels−Alder cycloaddition reported by Deslongchamps.[4]

As part of our studies on the discovery and development of new cascade reactions,[5] we report herein a strategy, based on an intramolecular Stille cyclization/[4 + 2] cycloaddition (Scheme 1), but conducted on a 13-membered dienyne at room temperature that simultaneously assembles three rings in a one-pot operation affording the pentacyclic skeletons **1a**−**c**, **2**, and **3** present in several natural products.[6] The starting materials are the conjugated tetraeneynes **4a**−**c**, **5**, and **6** prepared in six steps from the propargylic syn diol **10**[7] (or its 6-methoxy or 5,6-dimethoxy derivatives).

Protection as a dioxolane followed by its Stille coupling with *trans*-bis(tributylstannyl)ethylene[8] **11** furnished the

(1) (a) Tietze, l. F.; Beifuss, U. *Angew. Chem.* **1993**, *32*, 131. (b) Ho, T.-L. *Tandem Reactions in Organic Synthesis*; Wiley: New York, **1992**. (c) Wender, P. A.; Miller, B. L. *Org. Synth. Theory Appl*. **1993**, *2*, 27. (d) Bertz, S. H.; Sommer, T. J. *Org. Synth. Theory Appl*. **1993**, *2*, 67.

(2) (a) Ang, K. H.; Bräse, S.; Steinig, A. G.; Meyer, F. E.; Llebaria, A.; Voigt, K.; de Meijere, A. *Tetrahedron* **1996**, *52*, 11503−11528. (b) Henniges, H.; Meyer, F. E.; Schick, U.; Funke, F.; Parsons, P. J.; de Meijere, A. *Tetrahedron* **1996**, *52*, 11545−11578.

(3) (a) Grigg, R.; Major, J. P.; Martin, F. M.; Whittake M. *Tetrahedron Lett.* **1999**, *40*, 7709−7712. (b) Casaschi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron* **2001**, *57*, 607−615.

(4) (a) Duncton, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, *10*, 1235−1246. (b) Marsault, E.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 3317−3320.

(5) Suffert, J.; Salem, B.; Klotz, P. *J. Am. Chem. Soc.* **2001**, *123*, 12107−12108.

(6) (a) Hirota, A.; Ando, Y.; Monna, S.; Hirota, H. *Biosci. Biotechnol. Biochem.* **1994**, *58*, 1931−1932. (b) Gunasekera, S. P.; Gunasekera, M.; McCarthy, P. *J. Org. Chem.* **1991**, *56*, 4830−4833. (c) Hohmann, J.; Guenther, G.; Vasas, A.; Kalman, A.; Argay, G. *J. Nat. Prod.* **1999**, *62*, 107−109. (d) Shoji, N.; Umeyam, A.; Shin, K.; Takeda, K.; Arihara, S.; Kobayashi, J.; Takei, M. *J. Org. Chem.* **1992**, *57*, 2996−2997.

(7) Suffert, J.; Toussaint, D. *Tetrahedron Lett.* **1997**, *38*, 5507−5510.

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

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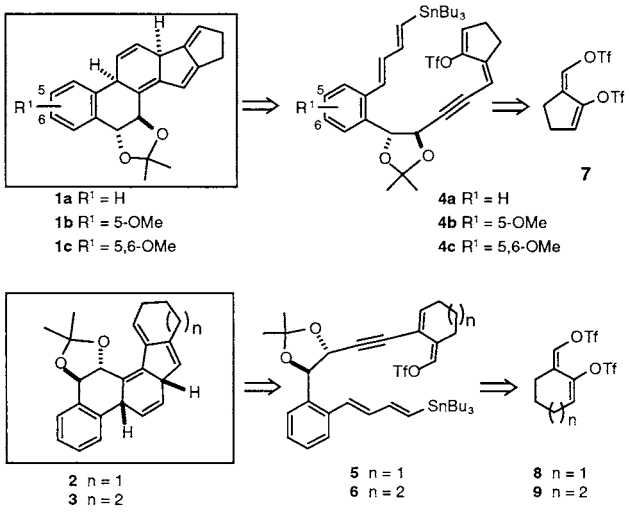
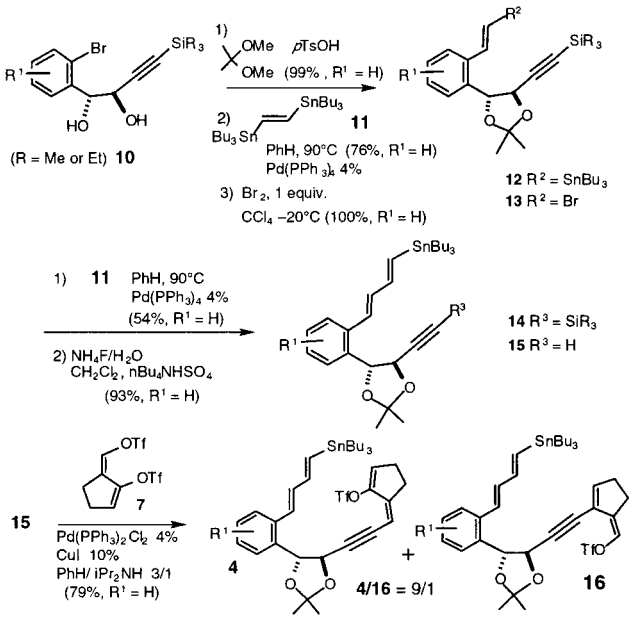
Scheme 1



β-tributylstannylstyrene **12** (75%, R = H, two steps). After metal−halogen exchange with Br_2, the bromide **13** was converted into the tributylstannyldiene **14** in 54% yield by a second Stille cross coupling with **11**. Compound **14** was treated with NH_4F under phase transfer catalysis[9] to give **15** and then coupled under Cacchi-like Pd(0) catalysis[10] with **7** to give **4** and **16** (Scheme 2). The desired sensitive mono-

Scheme 2

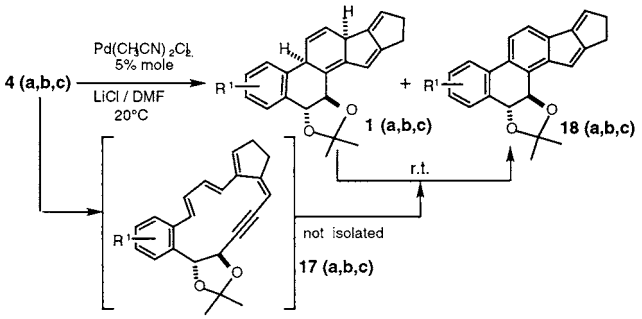


triflate **4a** was separated from **16** and isolated in 79% yield (R = H) applying our previously described procedure.[11]

Compounds **5** and **6** were also conveniently prepared in 72 and 66% yields, respectively, by a coupling between **8** and **9** and the dieneyne **15** following our recent results.[12] In these cases, the triflate substitution proceeded regioselectively on the endocyclic position. No trace of the exocyclic substitution of the triflate was observed.

With monocoupling product **4** in hand, the stage was set for the intramolecular coupling with the (*E*,*E*)-(tributylstannyl)dienyne moiety. The expected reaction product, when **4a** (R^1 = H) was treated under the Stille cross-coupling conditions, should have been the macrocyclic tetraenyne **17a** (Scheme 3). None of this compound was observed in the

Scheme 3



crude reaction mixture, but surprisingly two new products were formed at room temperature. Careful ^{1}H NMR analysis showed that these two compounds corresponded to the structures **1a** and **18a**.

When this mixture was stored for 24 h without solvent, compound **1a** was completely transformed into **18a** through an oxidative aromatization that already started before and continued during the isolation of the cyclohexadiene derivative. The total yield after purification from **4a** to **18a** was 48%. The substitution of the aromatic moiety with one or two methoxy groups provided higher yields of the cyclized products **1b** (61%) and **1c** (70%). As expected, the starting monotriflates **5** and **6** also cyclized smoothly under the same conditions to give polycycles **2** and **3** in 51 and 50% yields, respectively. All isolated cyclohexadiene derivatives gave finally the biphenyl products through the oxidative process.[13] Despite working in a carefully deoxygenated solvent, eventually **1a** was slowly oxidized into the biphenyl **18a** at room temperature during the reaction process. The relative stereochemistry in compound **1a** was established by NOE analysis. The structures of **1a**−**c**, **2**, **3**, **5**, **6**, and **18a**−**c** were totally assigned.[13]

In a first analysis, compound **4a** could undergo a Stille macrocyclization and a subsequent transannular Diels−Alder (TADA) tandem reaction as described by Deslongchamps.[4] To the best of our knowledge, all these kinds of reactions were carried out in a temperature range between 70 and 280

(9) Herold, P. *Helv. Chem. Acta* **1988**, *71*, 354−362.
(10) Cacchi, S.; Morera, G.; Ortar, G. *Synthesis* **1986**, 320−322.
(11) Scheuplein, S.; Harms, K.; Brückner, R.; Suffert, J. *Chem. Ber.* **1992**, *125*, 271−278.
(12) Brückner, R.; Suffert, J. *Synlett* **1999**, 657−679.
(13) See Supporting Information.

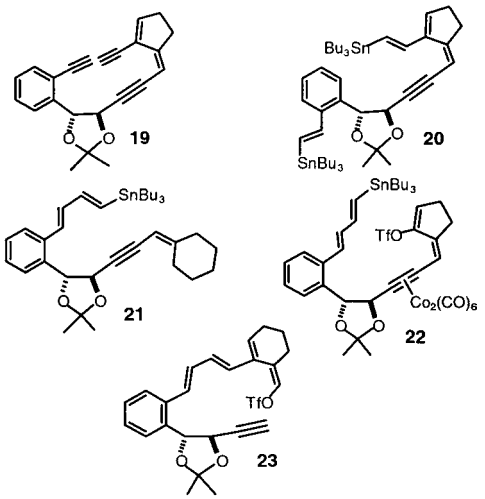


Figure 1. Candidates for the cyclization experiments.

°C (or more) on several 14-membered macrocycles[4,14,15] and, even in some cases, on related 13-membered macrocycles.[16] In our case, the TADA tandem reaction took place at room temperature under very mild conditions. Our ultimate goal was to determine if the Pd(0) catalyst was involved in this reaction process. Indeed, several examples of [4 + 2] cycloadditions catalyzed by transition metals such as nickel,[17a] iron,[17b,c] rhodium,[17d,e] or palladium[17f,g] have been described on inactivated systems.To study this mechanistic hypothesis, other approaches using unsaturated molecules **19**−**21** were envisaged. All attempts to prepare the sensitive macrocycle **17a** using several approaches, for example, through a zirconium/copper reductive coupling[18a] of **19**, hydrocupration,[18b] or copper chloride-mediated coupling[18c] of **20**, failed (Figure 1). When **21** was treated with $Pd(CH_3CN)Cl_2$, first at room temperature in DMF and then at 70 °C for several hours or simply heated without any catalyst at 180 °C in mesitylene for 24 h, no reaction took place. The incorporation of a $Co_2(CO)_6$ group for the protection of the triple bond in order to avoid the TADA reaction gave compound **22** in 69% yield. The same catalytic conditions, as used before for the cyclization of **4a**, were applied to **22**. Unfortunately, because of the drastic change in the geometry of the molecule, no cyclization took place under these conditions and the only product, which was isolated after workup, was the unprotected compound **4a**. All other catalytic conditions, using a Pd(0) species, applied to **22** failed. Another approach was tested for the cyclization of **23**: a Sonogashira-type cross-coupling reaction between the exocyclic enoltriflate and the terminal alkyne. The use of $Pd(PPh_3)_3Cl_2$ as a catalyst and CuI as a cocatalyst in the presence of Et_2NH in benzene was unsuccessful. We only observed the polymerization of the starting material **23**. These different negative experiments cannot discard a simple TADA thermal process, which can be due to the constrained cyclic compound **17**.

In conclusion, we emphasize that the reaction **4a** → **1a** proceeded at room temperature on a compound bearing a nonactivated diene and dienophile. We have discovered a cascade reaction under very mild conditions that produces polycyclic substructures present in several natural products. The reaction will now be applied to other polysubstituted acyclic precursors, and the mechanistic aspects of the reaction will be studied in order to elucidate the possible role of the palladium in the [4 + 2] cyclization. The results will be reported in the future.

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Supporting Information Available: Experimental procedures and spectral and analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Xu, Y.-C.; Cantin, M.; Deslongchamps, P. *Can. J. Chem.* **1990**, *68*, 2137−2143.

(15) Ndibwami, A.; Lamoyhe, S.; Soucy, P.; Goldstein, S. Deslongchamps, P. *Can. J. Chem.* **1993**, *71*, 714−725.

(16) Langlois, P.; Soucy, P.; Dory, Y. L.; Deslongchamps, P. *Can. J. Chem.* **1996**, *74*, 129−143.

(17) (a) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc*. **1989**, *111*, 6432−6434. (b) Carbonaro, A.; Greco, A.; Dall'Asta, G. *J. Org. Chem.* **1968**, *33*, 3948. (c) Gilbertson, S. R.; Zhao, X.; Dawson, D. P.; Marshall, K. L. *J. Am. Chem. Soc.* **1993**, *115*, 8517. (d) Wender, P. A.; Jenkins, T. E.; Susuki, S. *J. Am. Chem. Soc*. **1995**, *117*, 1843−1844. (e) Gilbertson, S. R.; Hoge, G. S.; Genov, D. G. *J. Org. Chem.* **1998**, *63*, 10077. (f) Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* **1997**, *119*, 7163−7164. (g) Takacs, J. M.; Clement, F.; Zhu, J.; Chandramouli, S. V.; Gong, X. *J. Am. Chem. Soc.* **1997**, *119*, 5805−5817.

(18) (a) Yoshifuji, M.; Loots, M. J.; Schwartz, J. *Tetrahedron Lett.* **1977**, *15*, 1303−1306. (b) Rao, S. A.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* **1987**, 495−496. (c) Piers, E.; Romero, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 1215−1216.