Pergamon

Tetrahedron Letters, Vol. 38, No. 47, pp. 8193-8196, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10253-2

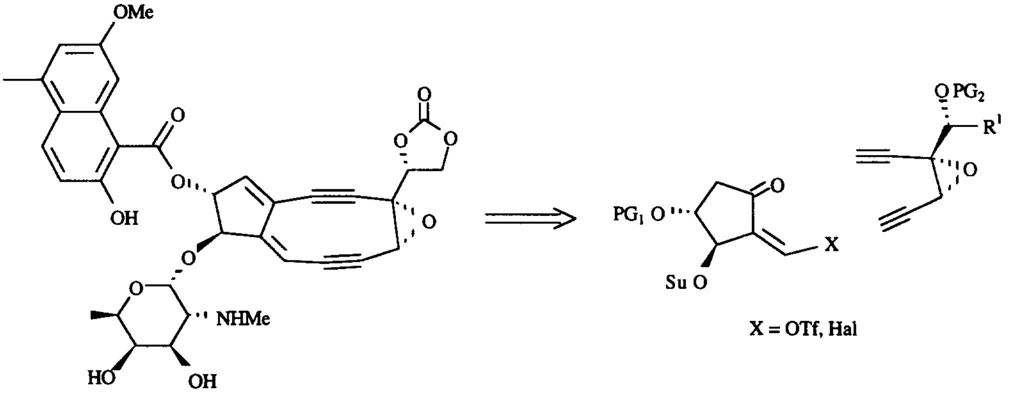
Synthesis of Enynes Related to Neocarzinostatine Using the New Pd / Ag Catalyzed Coupling Reaction

P. Bertus,° P. Pale#[1]

° Laboratoire des réactions sélectives et applications, associé au CNRS, Université de Reims-Champagne-Ardenne,
BP 1039, 51687 Reims, France.
Laboratoire de synthèse et réactivité organique, Institut Le Bel, Université L. Pasteur,
4 rue B. Pascal, 67000 Strasbourg, France.

Abstract: Both E and Z isomers of 2-triflyloxymethylene cyclopentanone, 1 and 2 respectively, have been coupled with various functionalized acetylenes in the presence of the Pd/Ag set of catalysts. This method provides a rapid and stereoselective access to various E or Z 2-(alkynyl)methylene cyclopentanone derivatives, which are promising and versatile intermediates toward NCS-Chrom and analogs. © 1997 Elsevier Science Ltd.

Neocarzinostatin Chromophore (NCS-Chrom; Scheme 1) was the first isolated[1,2] member of a small class of antitumor antibiotics.[3,4] The peculiarity of these natural products originates from their unprecedented mode of action. Indeed, their biological activity is due to a triggered cyclization of a highly conjugated system to a 1,4-benzenoid diradical, which is believed to occur after binding to DNA. The resulting diradical then abstracts a hydrogen from the deoxyribosyl moiety of DNA, eventually leading to DNA cleavage.[3,5] In NCS-Chrom, unlike the other members of this family, the reactive part is an epoxydienediyne rather than an enediyne.[6-7]



Scheme 1: NCS Chromophore and a retrosynthetic analysis

The potent biological activity of NCS-Chrom and its unique challenging structure have stimulated an ever increasing effort on the part of synthetic chemists. Although no total synthesis of NCS-Chrom has so far been described,[8] several approaches have been experimented,[3-4,9] in wich Pd-catalyzed coupling reactions are widely used.

---

[1] Fax: +388 416 042; e-mail: ppale@chimie.u-strasbg.fr

Indeed, coupling 1,2-diethynyl oxiranes with a cyclopentanone derivative bearing a suitably functionalized methylene group might provide a rapid access to NCS-Chrom and analogs (Scheme 1). Although rather " simple ", such disconnection seems to be impeded by the fact that direct coupling of halogenated alkenes or triflyloxyalkenes with epoxyacetylenes was unprecedented.[10] To overcome this problem, we have investigated the coupling reaction of a model epoxyacetylene with the 4-*tert*butyl cyclohex-1-enyl triflate. This led us to recently demonstrate that ethynyloxiranes can in fact be directly coupled if a new set of catalysts, based on silver and palladium complexes, is used.[11] In a closer approach toward our goal, we have now investigated the coupling of vinyl triflates related to the five-membered ring included in the NCS-Chrom structure. Our preliminary results are presented in this communication. We show here that the Pd/Ag catalyst mixture can indeed be employed for the coupling of 2-triflyloxymethylene cyclopentanones.

As mentionned above, 2-(ethynyl)methylene cyclopentanone derivatives might be versatile intermediates toward NCS-Chrom and analogs.[12] Thus, we have investigated the coupling of both *E* and *Z* isomers of 2-triflyloxymethylene cyclopentanone,[13] **1** and **2** respectively, with some functionalized acetylenes in the presence of the Pd/Ag catalysts (Table 1).

In the conditions we developped for the synthesis of epoxyenynes,[11] the TPS derivative of the commercially available *Z* 3-methyl pent-2-en-4-yn-1-ol readily coupled with **1** in a very clean reaction. The yield was excellent and only the *Z* isomer was observed (Table 1, entry 1). With the corresponding epoxide, the coupling was still effective leading in a clean reaction to the conjugated epoxyenynone **5** as a single stereoisomer. The yield was lower but still correct owing to the complexity and the sensitivity of the product formed (entry 2). Coupling of the same acetylenes with the *E* triflate isomer **2** proved to be as efficient, although the corresponding enynones were obtained in slightly lower yields (entries 5, 6 vs 1, 2). Such differences might be accounted for the differences in stabilisation of the vinyl palladium cationic complexes formed by oxidative addition,[14] an increased stability of the Z complex might be expected due to further coordination of the electrophilic palladium center by the keto oxygen neighbor. These results show that, as far as we can judge, the method is highly stereoselective since only one stereoisomer can be detected in each case, with retention of the stereochemistry of either the *E* or the *Z* starting vinyl triflates.

1,5-Diynes could also be cleanly coupled in these conditions with comparable yields (Table 1, entries 3-4). 1,5-Hexadiynes are obvious precursors for the synthesis of the nine-membered cyclic core of NCS-Chrom., but in order to avoid bis-coupling, one of the acetylenic functions must be protected. Thus, 1-trimethylsilyl-3-*tert*butyldiphenylsilyloxy hexa-1,5-diyne[15] was submitted together with **1** to our standard conditions and the expected enediynone **6** was obtained in an acceptable yield (entry 3). In order to obtain a more realistic intermediate toward NCS-Chrom for further studies, the 1-*tert*butyldimethylsilyl-3,4-epoxy-4-methyl hexa-1,5-diyne,[16] an epoxy analog, was coupled with the *Z* isomer of the 1-triflyloxymethylene cyclopentanone **1** and the expected product **7** was obtained in reasonnable yields. It is noteworthy that compound **7** already included all the proper functional groups, especially the epoxy ring, ready for ring closure.

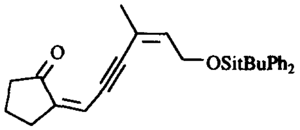
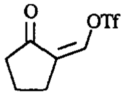
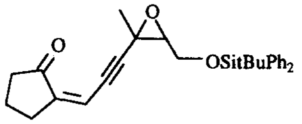
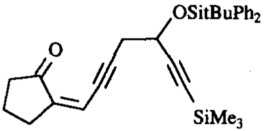
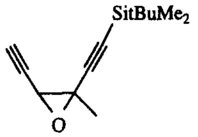
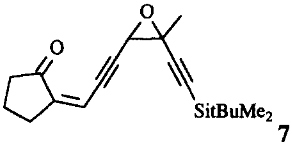
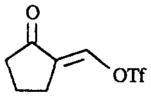
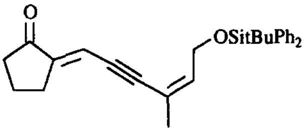
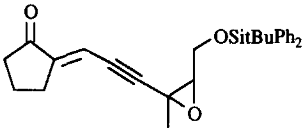
Entry	Activated Alkene[a]	Alkyne	Time	Yield[b]	Product
1			4 d	96 %	 4
2	 1		2 d	52 %	 5
3			24 h	46 %	 6
4			18 h	56 %	 7
5	 2		2 d	92 %	 8
6			2 d	40 %	 9

Table 1: a) our standard coupling conditions (see ref 11) were used: $Pd(PPh_3)_4$ 10 %, AgI 20 %, DIPEA 1.25 equiv. in DMF; b) yields of isolated products.

Thus, we have demonstrated that highly functionalized enynes, and even epoxy enynes, can be rapidly and stereoselectively elaborated via sp-sp^2 coupling using the palladium-silver couple of catalysts. This reaction could therefore allow for a rapid access to the tricyclic core of NCS-Chrom. and further work is now in progress to achieve this goal.

Acknowledgement: P. B. thanks the "Ministère de l'Education Nationale, de l'Enseignement Supérieur et de la Recherche " for a doctoral fellowship.

Dedication: The authors dedicate this work to Prof. J Chuche, Université de Reims-Champagne-Ardenne, France, on the occasion of his retirement.

References and Notes

1 Ishida, N.; Miyazaki, K.; Kumagai, K.; Rikimaru, M. *J. Antibiot.* **1965**, *18* , 68-76.

2 Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331-334.

3 Nicolaou, K. C.; Smith, A. L. in *Modern Acetylene Chemistry*, Stang, P. J.; Diederich, F. Eds; VCH: Weinheim, 1995, pp 203-283;

4 Lhermitte, H.; Grierson, D. S. Part 1 & 2, *Contemporary Organic Synthesis* **1996**, 41-63 and 93-124.

5 For lead references and a review devoted to NCS, see : Goldberg, I. H. *Acc. Chem. Res.* **1991**, *24*, 191-198.

6 Myers, A. G. *Tetrahedron Lett.* **1987**, *28*, 4493-4496

7 Myers, A. G.; Proteau, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 1146-1147.

8 A synthesis of the NCS-Chrom aglycone has recently been described: Myers, A. G.; Hammond, M.; Wu, Y.; Xiang, J. N.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1996**, *118*, 10006-7.

9 Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453-6518.

10 After the publication of our own solution to this problem,[11] and during the course of this work, another example was described: Reddy, R. S.; Igushi, S.; Kobayashi, S.; Hirama, M. *Tetrahedron Lett.* **1996**, *37*, 9335-9336.

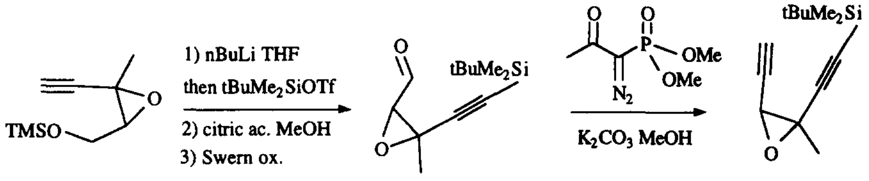
11 Bertus, P.; Pale, P. *Tetrahedron Lett.* **1996**, *37*, 2019-2022.

12 For a related, although distinct, strategy, see:
Nakatani, K.; Arai, K.; Yamada, K.; Terashima, S. *Tetrahedron* **1992**, *48*, 3045-3060.
Nakatani, K.; Arai, K.; Terashima, S. *J. Chem. Soc.; Chem. Comm.* **1992**, 289-291;
Nakatani, K.; Arai, K.; Terashima, S. *Tetrahedron* **1993**, *49*, 1901-1912.

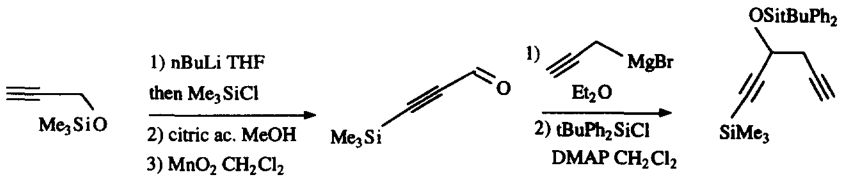
13 Scheuplein, S. W.; Harms, K.; Bruckner, R.; Suffert, J. *Chem. Ber.* **1992**, *125*, 271-278.

14 Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810-1817.

15 This diyne was obtained from the trimethylsilylated *cis* 2,3-epoxy-3-methyl pent-4-ynol[17] through the following sequence (52% overall yield):



16 This diyne was obtained from the 3-trimethylsilyloxy propyne (63% overall yield):



17 J. Cossy, P. Pale *Tetrahedron Lett.* **1987**, *51*, 6039-6040.

(*Received in France* 25 *August* 1997; *accepted* 30 *September* 1997)