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Synthesis of a New Versatile Dienophile and its Use in a Highly Diastereoselective Diels-Alder Reaction

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Abstract : By using respectively one equivalent of the propargyl zinc alcoholate and silylated propargyl bromide, the preparation of 2-methylene-5-trimethylsilyl-pent-4-yn-1-ol was improved. This latter is the precursor of the corresponding aldehyde which was used for the first time as a dienophile in [4+2] reactions. The cycloadducts were obtained in very high yields and in a totally diastereoselective manner.

Keywords : Gibberelins ; cyclisation ; Diels-Alder reactions ; Zinc.

Diterpenes belonging to the Gibbane family are widespread in nature.[1] The gibberellins are constituents of both fungi and higher plant, in which gibberellic acids particularly GA_9 and GA_{12} (Figure 1), are normal growth factors. The remarkable effect of the gibberellins on plant growth and the unique tetracyclic structure have stimulated many interesting approaches to these compounds.[2]

GA_9 GA_{12}

Figure 1

In connection with our interest in the synthetic development of transition-metal-catalyzed cycloisomerizations or cycloadditions,[3] we investigated stereoselective routes to the basic skeletons **1** of these tetracyclic diterpenes (Scheme 1). The discovery that cyclopentadienyldicarbonyl cobalt (I) catalyzes the Conia-ene type reaction of ε-acetylenic β-ketoesters to form highly functionalized methylenecyclopentanes in a regio-, chemo- and stereoselective manner[4] allowed us to propose an easy access to the basic skeleton of the gibbane family *via* a cascade of a double Conia-ene and a Diels-Alder reactions (Scheme 1).

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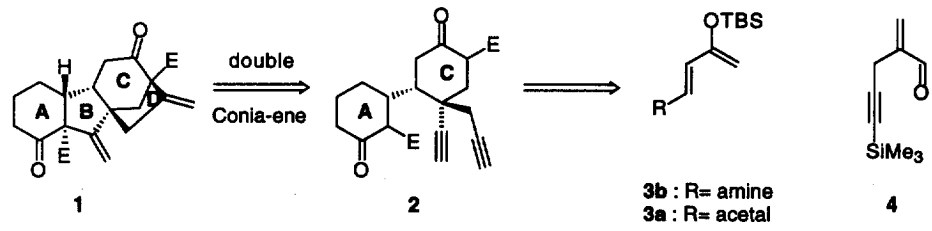
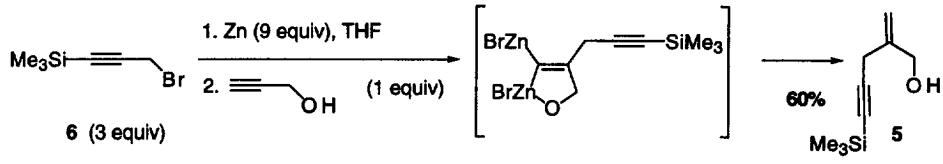


Scheme 1

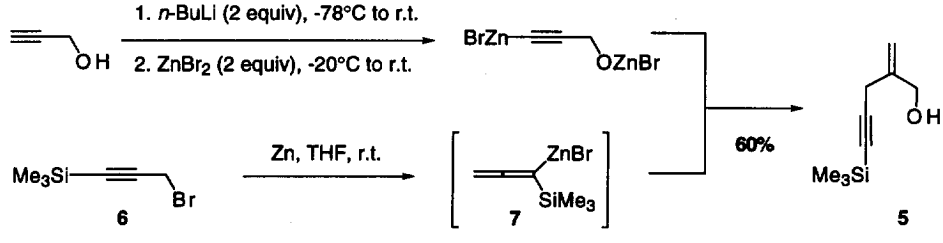
In this communication, we report the synthesis of the new dienophile **4** and its first use in Diels-Alder reactions.

The precursor of the aldehyde **4** was the enynol **5** which was prepared, as outlined in scheme 2, following the procedure of Miginiac.[5] The organozinc reagent derived from the trimethylsilylpropargyl bromide[6] adds in a totally regio- and chemoselective manner to the propargyl alcohol to provide the enynol **5** in 60% yield.



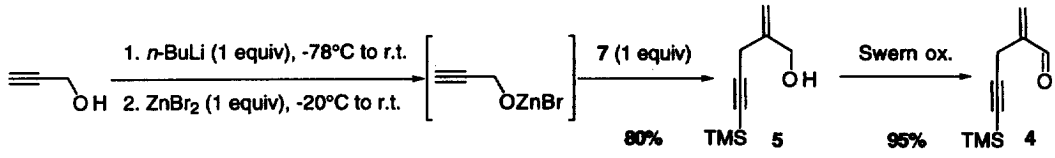
Scheme 2

However, the use of this method in synthesis displays some drawbacks especially because it requires a large amount (three equivalents) of the organozinc reagent. Therefore, we turned our attention, aiming at decreasing the number of equivalents of the bromide compound. Thus, a lithiated dianion was prepared by deprotonation of the propargyl alcohol with *n*-butyllithium followed by a transmetalation with $ZnBr_2$ (Scheme 3). The resulting mixture was subsequently added to one equivalent of the allenylzinc reagent **7**, generated from **6** to afford the enynol **5** in the same yield as above.



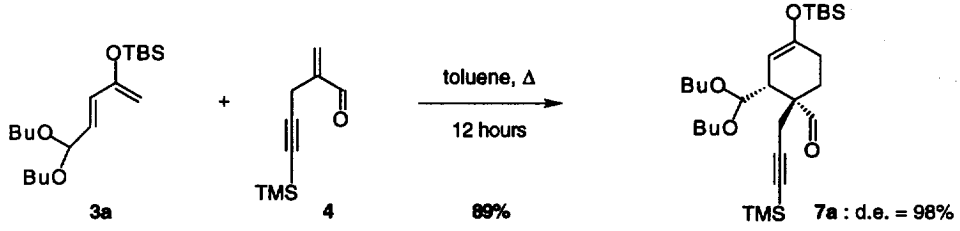
Scheme 3

Even though, this result was satisfactory for its potential use in the synthesis of more complex molecules, we checked other conditions. Indeed, as reported in the literature,[7] it is unlikely that an organozinc reagent can be considered as a strong enough base to deprotonate an alkyne. Thus, one equivalent of the zinc alcoholate of the propargyl alcohol (generated from an equivalent amount of *n*-BuLi and $ZnBr_2$) (Scheme 4) was subjected to a stoichiometric amount of the derivative **7** and led to the enynol **5** in 80% yield. Finally, Swern oxidation[8] of the latter provided enynal **4** in 95% yield.



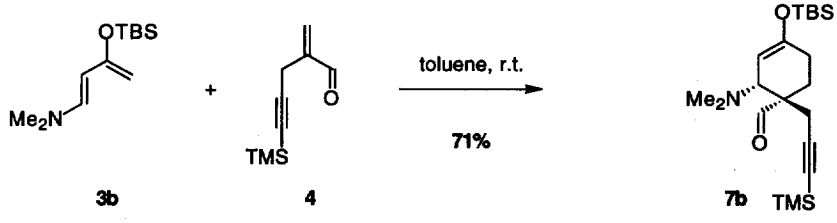
Scheme 4

To the best of our knowledge, the enynal **4** had never been engaged in a [4+2] cycloaddition. Following the procedure of Danishefsky,[9] refluxing of the diene **3a**[10] and **4** in toluene overnight provided the cycloadduct **7a** in a high yield (89%) and in a totally diastereoselective manner according to the preferential *endo* orientation (Scheme 5).[12]



Scheme 5

Moreover, the dienophile **4** was exposed to the diene **3b** in toluene at room temperature in the conditions described by Rawal.[12] The cycloadduct **7b** was obtained as a single isomer in a 71% yield and with a total *endo* selectivity (Scheme 6). The assignment of the *cis* configuration in **7a** and **7b** proved to be nontrivial and was based by analogy with literature.[12, 13]



Scheme 6

In summary, we have disclosed a very efficient and wasteless method of preparation of the enynol **5** by using only one equivalent of propargyl bromide and of the zinc propargylalcoholate. The oxidation of **5** led to the corresponding aldehyde **4** which is a new versatile dienophile.[14] The [4+2] cyclizations between **4** and the diene **3a** or **3b** provided the cycloadduct **7a** or **7b** as a single isomer and in a high yield. The studies are currently under active progress to generalize this method to other propargyl alcohols and to synthesize the basic skeleton of the gibbane familly.

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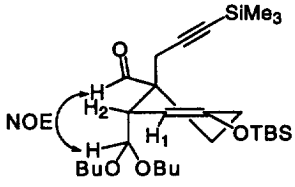
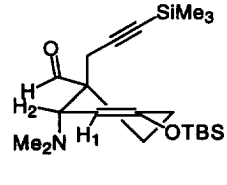
References and Notes

1. (a) Fujita, E.; Node, N. *Progress in the Chemistry of Organic Natural Products* **1984**, *46*, 78. (b) Phinney, B. O.; Spray, C. In *Plant Growth Substances*, Waring, P. F. Ed., Academic Press : London, **1982**, 683.
2. Mander, L. N. *Chem. Rev.* **1992**, *92*, 573-612 and references cited therein.
3. (a) Cruciani, P.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1995**, *60*, 2664-2665. (b) Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699-2708. (c) Cruciani, P.; Aubert, C.; Malacria, M. *Synlett* **1996**, 105-107.
4. (a) Stammler, R.; Malacria, M. *Synlett* **1994**, 92. (b) Cruciani, P.; Aubert, C.; Malacria, M *Tetrahedron Lett.* **1994**, *35*, 6677-6680. (c) Renaud, J. L.; Petit, M.; Aubert, C.; Malacria, M *Synlett* **1997**, 931-932.
5. Mesnard, D.; Miginiac, L. *J. Organomet. Chem.* **1991**, *420*, 163-170.
6. Gaudemar, M. In *Organometallic Syntheses*, King, R. B; Eisch, J. J. Eds., Elsevier: Amsterdam, **1986**, Vol. 3, 409.
7. Knoess, H. P.; Furlong, M. T.; Rozema, M. J.; Knochel, P. *J. Org. Chem.* **1991**, *56*, 5974-5978.
8. Mancuso, A. J.; Huang, S. L.; Swern, D. J. *J. Org. Chem.* **1978**, *43*, 2480-2482.
9. Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996-7000.
10. The diene **3a** was prepared in two steps in a 50% overall yield : i) a modified Horner-Wadsworth-Emmons reaction,[11] between the monoketal of glyoxal and the diethyl(acetyl)methylphosphonate. ii) a trapping of the enolate of the enone by *tert*-butyldimethylsilyl chloride.
11. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183-2186.
12. (a) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165-7166. (b) Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 5252-5253. (c) Kozmin, S. A.; Janey, J. M.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 3039-3052.
13. If we assume that the *endo* adducts generally exist in the conformation in which the amino group is pseudoaxial and the electron-withdrawing group is equatorial, the observed coupling constant $J_{1,2}$ = 4.6 Hz between H_1 and H_2 in **7b**, (value in good agreement with those reported by Rawal : see ref.13c) confirmed the *cis* relationship between the amino group and the aldehyde. By extension in the case of **7a**, the coupling $J_{1,2}$ is 4.3 Hz means that the acetal and the propargyl group are in an unusual *trans* diaxial arrangement. In that favored conformation, we observed a NOE between the protons of the aldehyde and the acetal.



7a ($J_{1,2}$ = 4.3 Hz)



7b ($J_{1,2}$ = 4.6 Hz)

14. A sample of the enynal **4** was given to the group of Dr. J. Rodriguez, University of Aix-Marseille III and it was also shown as a good Michael acceptor. See : Filipini, M. H. ; Rodriguez, J. *J. Org. Chem.* **1997**, *62*, 3034-3035.