S7-1 *[2000 Oct. 20 (Fri) 13:30~14:05/Hall C]*

The Stereoselective Palladium-catalyzed Cyclizatioin and Its Application to the Syntheses of the Bioactive Natural Products

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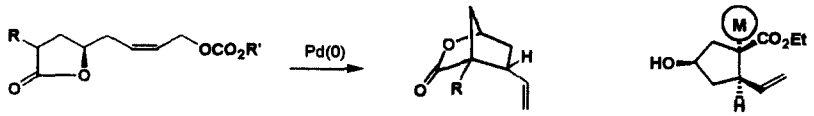
Palladium catalyzed cyclization has proven to be one of the most powerful synthetic tools for carbocycle construction in terms of high chemo-, regio- and diastereoselectivities.1 The recent interests of organic chemists have also included palladium-catalyzed asymmetric cyclization of allylic precursors. However, stereocontrol of the nucleophilic carbon possessing two anion stabilizing groups has been less explored2 due to the difficult stereocontrol at this center as well as the ultimate loss of the stereochemistry upon removal of the anion stabilizing auxiliary. Accordingly, 1,2-diastereocontrol of the new two stereogenic centers in palladium-catalyzed cyclizations of allylic precursors and retention of the established stereochemistries remain as formidable tasks in spite of their significant synthetic utilities especially for the preparation of thermodynamically less favorable *cis*-disubstituted carbocyclic products.

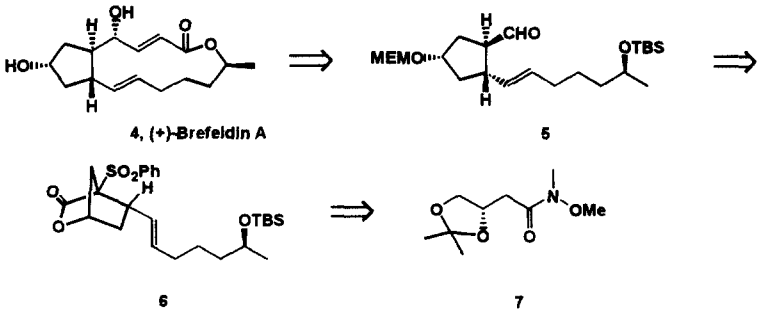
Recently, we have developed new variants of the palladium-catalyzed diastereoselective cyclization involving 1,3-asymmetric induction as well as 1,2-diastereocontrol of two new stereogenic centers.3,4 Furthermore, an excellent desulfonylation of the cyclization product with retention of stereochemistry of the initial cyclization product provides the additional 1,3'-asymmetric induction (scheme 1).



1 2 R = SO_2Ph, CN, CO_2Et 3

Figure 1

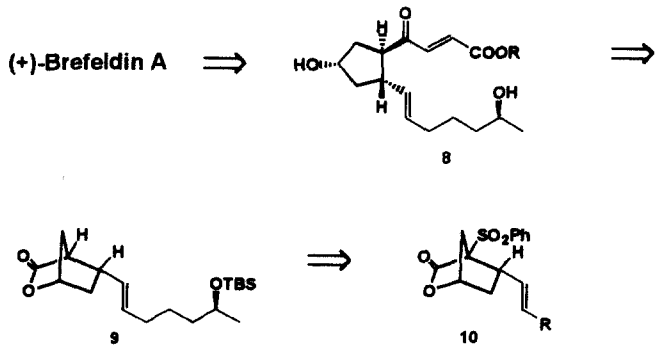
The bicyclic lactone **2** (R = SO2Ph) serves as an excellent equivalent of the optically active anion **3** by virtue of geometric advantage for the preparation of thermodynamically disfavorable *cis*-trisubstituted carbocyclic products. The synthetic utility of the optically active *cis*-trisubstituted hydroxycyclopentane **3** (M = H) has been demonstrated by the efficient conversion to the key intermediates for a variety of bioactive carbocycles including carbaprostacyclin and its analogues.



Scheme 1

Particularly, the advanced synthetic intermediate **5** for (+)-brefeldin A has been efficiently synthesized from the known Weinreb amide **7** by an application of this sequence5 as outlined in scheme 1. The key feature of this versatile synthetic route involves a highly stereoselective construction of hydroxycyclopentane skeleton of (+)-brefeldin A. The requisite hydroxyheptenyl side chain possessing correct stereochemistries and olefin geometry are also established during this process.

Very recently, we have completed a concise total synthesis of brefeldin A by an advanced synthetic route employing direct introduction of acrylate moiety to the key bicyclic lactone intermediate **9** (scheme 2). Moreover, a versatile method for the efficient introduction of an acrylate moiety to the lactone systems utilizing *trans*-vinylogous acyl anion equivalent has also been developed.



Scheme 2

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