[S2-3] [4/19/2001(Thur) 16:00-16:30 / Hall B]

Novel Synthetic Approaches to the Bioactive Natural Products via Oxazoline

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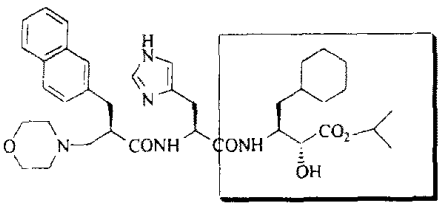
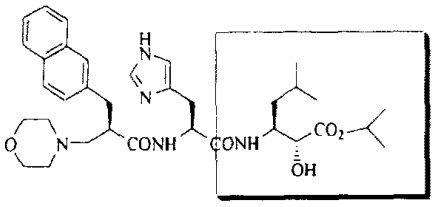
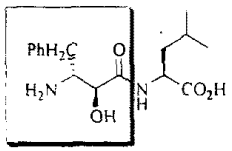
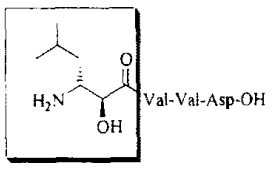
β-Amino α-hydroxy acids are important components in a variety of biologically interesting compounds. For instance, it has recently been found that some inhibitors of angiotensin-converting enzyme (ACE), such as microginin, KRI 1314 (**1**), and KRI 1230 (**2**),[1] contain β-amino α-hydroxy acids in their structure. These molecules are useful agents in hypertension and congestive heart failure therapy. Other biologically active molecules containing this kind of structure are bestatin (**3**) and amastatin (**4**), and Taxol (5).

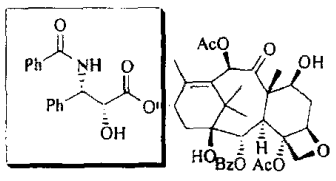
Figure 1. β-Amino α-hydroxy acids







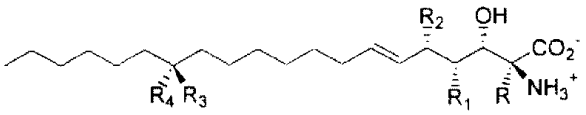




Sphingosines, compounds consisting of polar polyhydroxyl amino head groups and long lipid chains, are membrane constituents involved in a number of cellular events including protein binding (GPI anchor) and transmembrane signaling.[2] A related series of compounds wherein the primary alcohol is oxidized to a carboxylic acid such as sphingofungin B (**6**)[3] or

possesses a quaternary center such as sphingofungin F (7)[4] were found to inhibit the biosynthesis of sphingolipids due to their activity as serinepalmitoyl transferase inhibitors.[5] These compounds are also strikingly similar to myriocin (**8**),[6] a compound shown to be 10-100 times more potent than cyclosporin A.

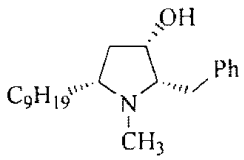
Figure 2. Sphingosine analogues



6 R=H, R^1=R^2=R^3=OH, R^4=H
7 R=CH_3, R^1=R^2=OH, R^3=R^4=O
8 R=CH_2OH, R^1=OH, R^2=H, R^3=R^4=O

Preussin (9), a potent antifungal agent, is a naturally occurring pyrrolidine alkaloid.

Figure 3. Preussin



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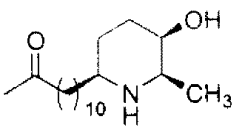
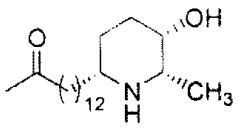
Functionalized piperidines are very important heterocycles because of their presence in numerous alkaloids, pharmaceuticals, and synthetic intermediates.

Figure 4. Functionalized piperidine compounds



Cassine, 10



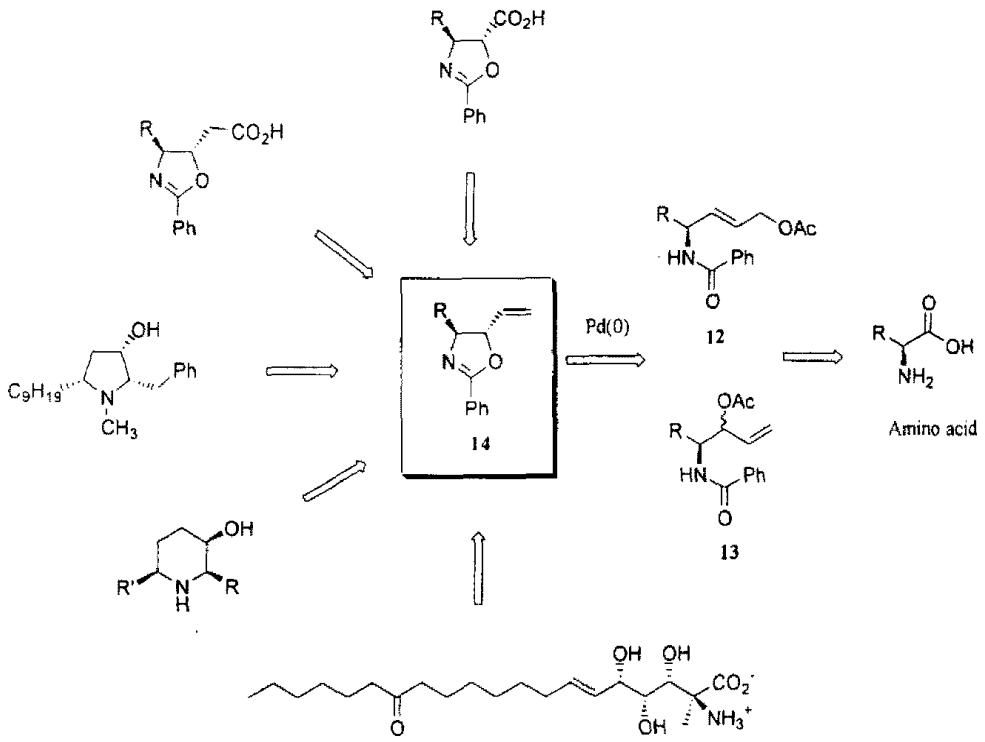
Spectaline, 11

The difficulties of creating stereochemistries and the noted biological activity of these products led us to develop a general strategy to these series.

In a previous paper[8], we described a new Pd(0)-catalyzed procedure for the stereoselective formation of a oxazoline ring from an acyclic allylic and homoallylic amide having a benzoyl substituent as an *N*-protection group. The most significant point of this method is that it is based on the *trans*-oxazoline ring formation in palladium(0)-catalyzed conditions.

In this seminar, we describe our complementary investigations of oxazoline ring formation as well as its conversion to amino hydroxy acid via oxidative degradation of the vinyl group, protected as the oxazoline. Also, we will discuss our synthetic efforts toward sphingosine, preussin, and functionalized piperidine (scheme 1).

Scheme 1



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