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New Cytochalasins: Synthetic Studies of a Novel HIV-1 Protease Inhibitor.

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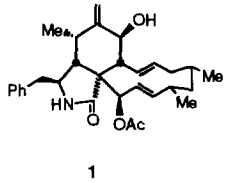
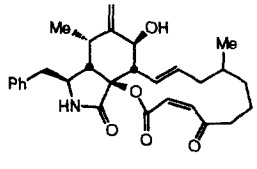
Abstract: By using a benzyl copper reagent (e.g. **10**→**11**) in combination with titanium enolate chemistry (e.g. **12**→**13**) a concise sequence has been developed for the rapid introduction of functionality found in the cytochalasin HIV protease inhibitor (**1**). Copyright © 1996 Elsevier Science Ltd

During the course of an active screening program for non-peptide leads of HIV-1 protease, the lactam (**1**) was identified as an inhibitor.[1] Inhibition of this crucial viral enzyme offers an attractive strategy for the treatment of HIV infected individuals because of its critical role in viral maturation. Both peptide mimetic and structurally novel inhibitors have been shown to prevent viral spread in cell culture.[2] In addition, site directed mutagenesis experiments have demonstrated that delineation of the active site aspartic acid residues leads to the production of non-infectious viral particles. This aspartyl protease is responsible for the cleavage of the viral *gag* and *gag-pol* polyproteins and proper processing of these gene products is essential.[3] Our interest in (**1**) was heightened since it was a competitive inhibitor and represented a significant reduction in peptide character from most inhibitors reported thus far.[4] Our excitement, however, was tempered by the broad range of biological activity this family of cytotoxic mold metabolites can have on cellular processes.[5] Although the precise mechanism of cytotoxicity by these compounds is not known for all members, certain congeners have profound effects on specific cellular events. For example, cytochalasins **A** and **B** inhibit glucose transport, while cytochalasin **E** appears to be devoid of such activity.[6] Additionally, cytochalasin **B** retards actin formation while cytochalasin **D** inhibits RNA and protein synthesis[7] (see Chart 1). Indeed the ubiquitous activity found in this class of compounds has made them useful biological probes despite their lack of any therapeutic objective at this point.[8] Thus, despite the structural similarities between **1** and other cytochalasins, **1** did not have any overt cytotoxicity. We therefore sought to identify a synthetic route that would help us elucidate some of the key structural elements responsible for its enzyme inhibiting property.[9]

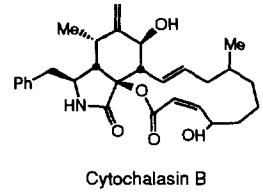
Chart 1



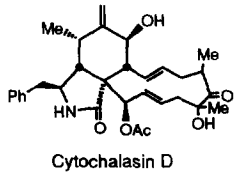
1



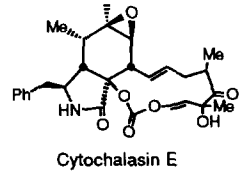
Cytochalasin A



Cytochalasin B



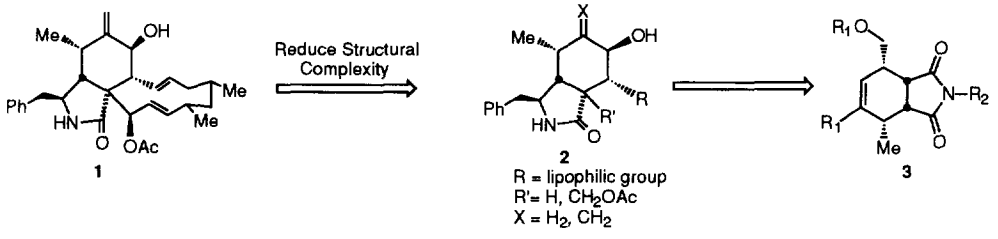
Cytochalasin D



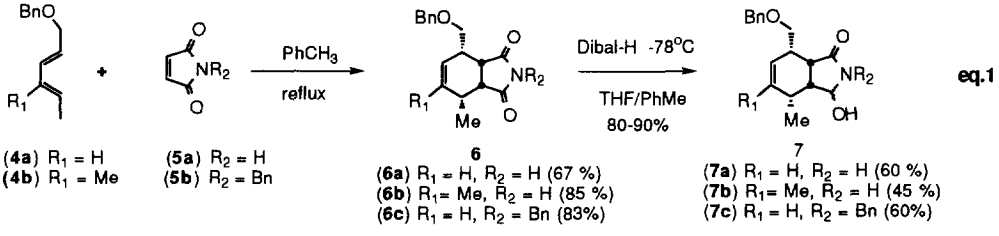
Cytochalasin E

Scheme 1 illustrates our retrosynthetic analysis highlighted by the major simplification of removing the 11 member unsaturated ring found in the natural product. This gives rise to the advanced intermediate (2). We felt appropriate arrangement of the functional groups in this intermediate would serve our needs to assess the relevant binding elements responsible for biological activity in this portion of our lead compound. We were particularly interested in imides related to (3) which were used in a strategy discussed by Weinreb.[10] The availability of (3) from dienes (4) and imides (5) made this approach very attractive for structure activity studies and the synthesis of analogs.[11] This report describes modifications of the Weinreb approach and demonstrates the value of an intermediate such as (3). We chose to incorporate the protected hydroxymethyl substituent in (3), since this would give us the greatest flexibility for derivatizing this position as well as providing an appropriate oxidation level to install the lipophilic side chain if necessary.

Scheme 1



Dienes **4a** and **4b** were prepared from commercially available materials with only slight modification of literature reports. Diels-Alder adducts (**6a**, **6b** and **6c**) and their corresponding lactols were prepared in 5-10 gram quantities in an analogous manner to that described by Weinreb[10] (equation **1**). Conversion of lactols (**7**) to the methoxy aminals as described by Weinreb proved to be capricious in our hands and resulted in elimination and produced varying amounts of unsaturated amides.



(**4a**) R_1 = H
(**4b**) R_1 = Me

(**5a**) R_2 = H
(**5b**) R_2 = Bn

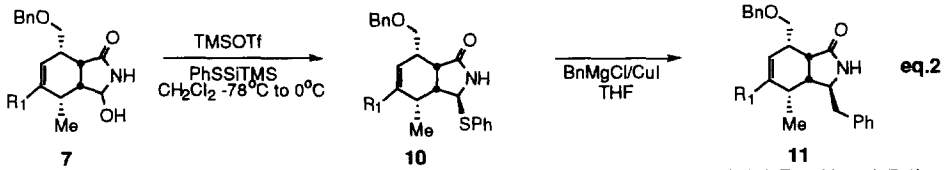
6
(**6a**) R_1 = H, R_2 = H (67 %)
(**6b**) R_1 = Me, R_2 = H (85 %)
(**6c**) R_1 = H, R_2 = Bn (83%)

7
(**7a**) R_1 = H, R_2 = H (60 %)
(**7b**) R_1 = Me, R_2 = H (45 %)
(**7c**) R_1 = H, R_2 = Bn (60%)

In a parallel set of experiments (not shown) we found that simply treating lactol (**7**) with trimethylsilyltrifluoromethanesulfonate (TMSOTf) and allyltrimethylsilane led in good yield to allylated materials directly.[12] Although not relevant to the target structure, these compounds did give us the opportunity to modify the functional groups on the periphery. We found under these reaction conditions the N-H derivative (**7a**) was just as effective as the N-benzyl (**7c**) derivative, therefore, we concentrated our synthetic efforts on lactols **7a** and **7b**. We turned our attention to finding an iminium ion precursor that would be more compatible to a broader range of carbon nucleophiles other than allylsilanes. One convenient source for iminium ions appeared to be an α-thioamide which can be trapped under appropriate reaction conditions.[13] We were gratified to observe that the thioaminal (**10**) could be obtained in good yield using trimethylsilylthiophenol (TMSSPh) in the presence of TMSOTf (CH_2Cl_2, 0°C). This reaction produced the desired thiophenyl derivative (single isomer as judged by

^{1}H NMR) with minimal amounts of the α,β unsaturated amide which occurred to varying degrees using other types of methods (e. g. use of Lewis acids).

A variety of benzylic organometallic reagents were then examined that would install the desired C-10 substituent. It was ultimately determined that the reagent combination of 1:1 benzylmagnesium chloride (2M THF) and CuI in THF followed by addition of a THF solution of thioaminal (**10**) led to smooth substitution producing a single diastereomer in >80% yield (eq.**2**). Other reagent combinations (e.g. catalytic CuI) and or Lewis acid catalysis[13] were inferior to the 1:1 stoichiometric combination described here.[14]



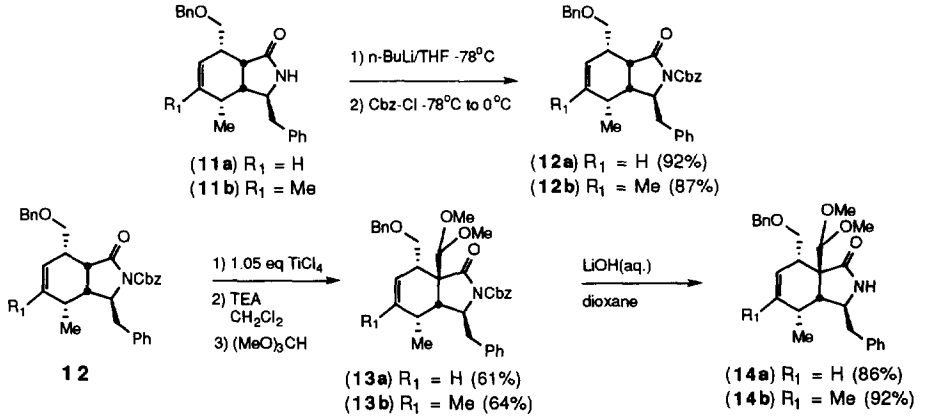
7
(**7a**) R_1 = H
(**7b**) R_1 = Me

10
(**10a**) R_1 = H (50 %)
(**10b**) R_1 = Me (52%)

11
(**11a**) R_1 = H (77%)
(**11b**) R_1 = Me (75%)

We then turned our attention to the problem of functionalizing the bridgehead position. One possible solution that appeared well suited for our needs was to proceed via a titanium enolate. Evan's has described that under appropriate reaction conditions these reactive intermediates can be generated directly from carbonyl compounds.[15] Having achieved installation of the C-10 benzyl group without protection of the amide N-H using aminals **10a** and **10b,** gave us the opportunity to study the feasibility of this strategy from (**11**) with minimal protecting group manipulations. Thus, treatment of amides (**11**) with n-BuLi (-78°C, 30 min) followed by carbobenzyloxychloroformate (-78° to 0°C) produced the mixed imides in excellent yield. We were gratified to observe that using our optimized reaction conditions, treatment of (**12a, 12b**) with $TiCl_4$ (1.05eq.) followed by triethylamine generated a violet solution presumably containing a titanium enolate which on exposure to trimethylorthoformate led to the gradual disappearance of the color. After aqueous workup and chromatography the desired acetals (**13a, 13b**) were obtained. Deprotection of the Cbz-group without saturation of the ring double bond was conveniently achieved using aqueous LiOH in dioxane (Scheme 2).[16]

Scheme 2



(**11a**) R_1 = H
(**11b**) R_1 = Me

(**12a**) R_1 = H (92%)
(**12b**) R_1 = Me (87%)

12

(**13a**) R_1 = H (61%)
(**13b**) R_1 = Me (64%)

(**14a**) R_1 = H (86%)
(**14b**) R_1 = Me (92%)

In conclusion, we have described two useful reactions that have furnished the basic skeleton found in the cytochalasin class of natural products. Benzyl copper reagents in combination with thioaminals (e.g. **10**) are an excellent combination for this ring system. The titanium enolate generated from **12** represents an interesting application of this powerful methodology and is well suited for the synthesis of acetals (**14a** and **14b**). Thus, using the methodology described herein we have achieved a concise synthesis of the core ring system found in

the cytochalasin natural products. Enzyme inhibition studies, unfortunately, resulted in significant loss in activity for all compounds investigated. We have, therefore, established that the macrocyclic ring is required for biological activity of these novel inhibitors of HIV-1 protease. The results of these investigations have been reported elsewhere.[17]

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16. Further manipulations to produce functionalities present in the natural product but lacking the macrocyclic ring were achieved using procedures described in the literature. For example see reference 10b.
17. None of the intermediates shown or analogs which lack the macrocyclic ring were active in the enzyme inhibition assay. Portions of that work has been published in: Advanced ACS Abstracts August 1993.

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