ON THE CHEMISTRY OF THE 18-DEOXYCYTOCHALASIN H, HIV-1 PROTEASE INHIBITOR, L-696,474. 1:[1] DEGRADATION STUDIES LEADING TO THE 2-ISOINDOLONE CORE

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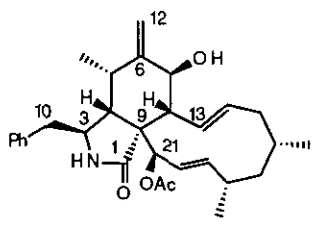
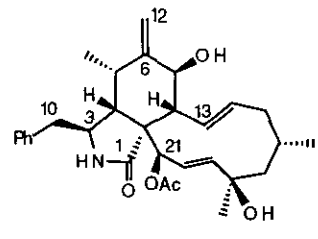
Abstract - Degradation studies of 18-deoxycytochalasin H, a 3 μM HIV-1 protease inhibitor, led to a 2-isoindolone core with conservation of functional groups on the bicyclic ring.

HIV-1 protease (HIV PR) has been recognized as one of the most attractive therapeutic targets for the treatment of acquired immunodeficiency syndrome (AIDS).[2] Our continuing effort to find novel non-peptide leads as HIV-PR inhibitors led to the discovery of the 18-deoxycytochalasin H (**1**) (L-696,474).[3] This cytochalasin, which is active against HIV PR (IC_{50} of 3 μM), was isolated from the fermentation of a bark-inhabiting ascomycete, *Hypoxylon fragiforme*.[3] As an HIV PR antagonist, the cytochalasin structure represents a unique departure from the traditional peptidomimetic transition state isosteres which in most cases lack oral bioavailability.[4] For this reason, a degradation study of this novel lead was undertaken to aid in defining the structural requirements for HIV PR antagonism and to access supplies of key intermediates for subsequent structure-activity relationship investigations.[5]



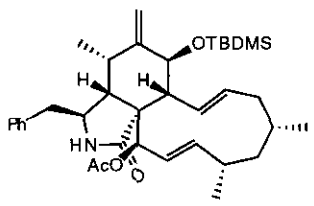
1, L-696,474



Cytochalasin H

Due to their interesting biological activities,[6] cytochalasins have been the subject of numerous synthetic efforts.[7,8] The structure of the cytochalasin family is characterized by a 2-isoindolone core and a fused macrocycle. One subgoal in the degradation study of **1** was to obtain the 2-isoindolone core with a maximum preservation of functionality on the bicyclic ring and to uphold the integrity of the configuration at C(21). It was anticipated that the degradation product(s) could also serve as versatile synthetic intermediates for other naturally occurring cytochalasins. Herein, we report an efficient pathway leading from **1** to the 2-isoindolone core structure (**12**) utilizing as a key step a highly regioselective cleavage of the C(19)-C(20) double bond.

To begin, the 7-hydroxyl group of **1** was protected as *tert*-butyldimethylsilyl ether (**2**) (*tert*-butyldimethylsily chloride, imidazole, DMF, room temperature, 15 h, 95% yield). Our attempts to remove the 11-membered ring portion of **2** by cleaving all three olefinic bonds using various oxidative cleavage methods to provide an isoindolone core structure such as **3** or **4** were not successful. In most instances, the C(13)-C(14) double bond was observed to be resistant to oxidation.



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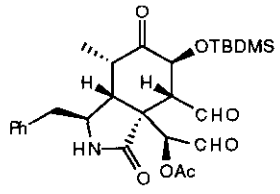

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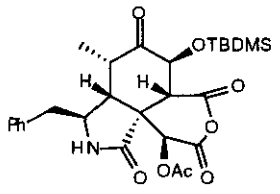

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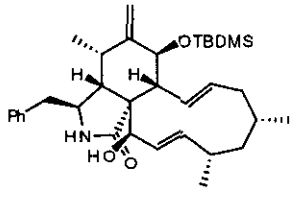
We then focused our attention on regioselective cleavage of one of the double bonds in the 11-membered ring in the presence of the exocyclic C(6)-C(12) methylidene unit. Our initial studies revealed that, in the case of alcohol (**5**),[1] the C(19)-C(20) double bond was the most accessible to various reagents. For example, hydrogenation (H_2, Pd/C in 2-methoxyethanol) and epoxidation (mCPBA, CH_2Cl_2) of the alcohol (**5**) led to regioselective production of **6** and **7**,[9] respectively.



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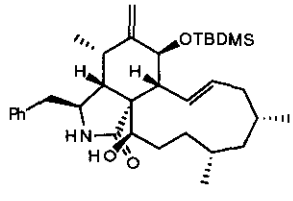

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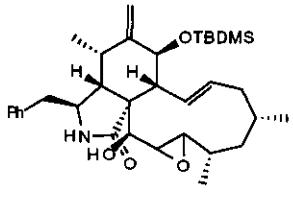

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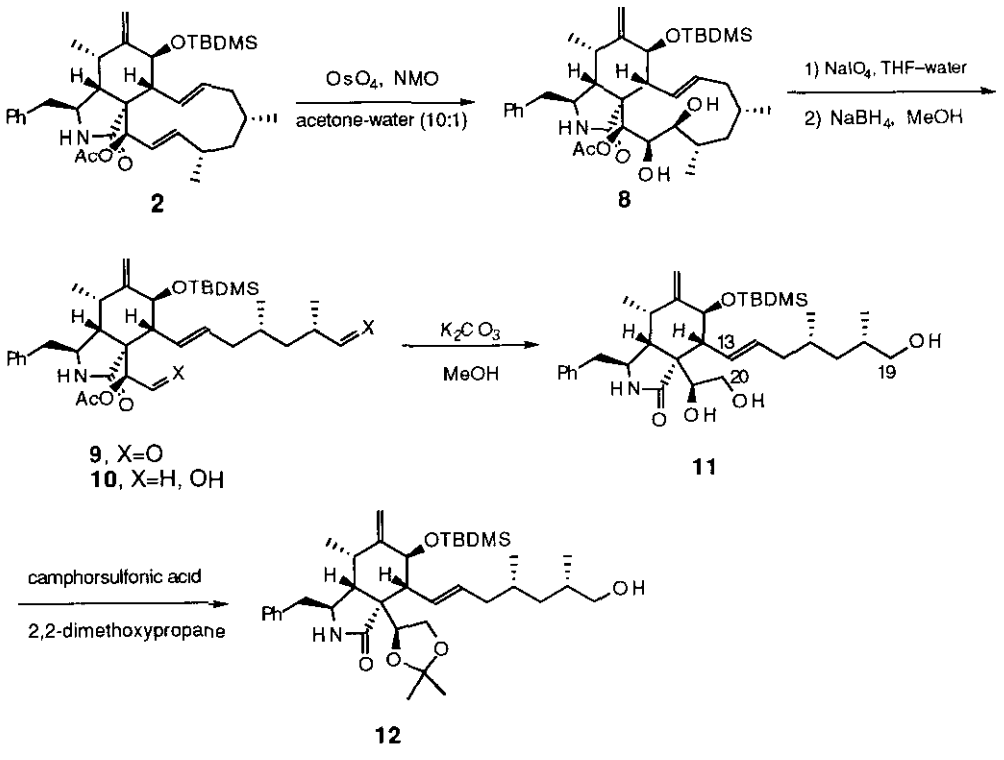
Encouraged by these results, we treated acetate (**2**) under osmium-catalyzed dihydroxylation conditions with 1.5 equiv of *N*-methylmorpholine *N*-oxide[10] and were pleased to find diol (**8**) as the almost exclusive product (mp 136-139° C, 82% yield after recrystallization from 10% EtOAc/Hexane)[11] as depicted in Scheme 1. Although the absolute configuration of this diol was not determined, it was assumed to be as shown based on the conformation of the 11-membered ring in the X-ray crystal structure of **1**.[3b] This diol was smoothly cleaved to the corresponding dialdehyde (**9**) (89% yield) using $NaIO_4$ in THF-water (1:1).[12] In order to protect the C(20) and C(21) oxygen functionalities while preserving the configuration of the C(21) acetate, the acetoxymethylformyl unit in **9** was converted to an acetonide according to the following three step process: (1) reduction of the dialdehyde **9** using $NaBH_4$ to diol acetate (**10**) (95%); (2) methanolysis of the diol acetate (**10**) (K_2CO_3, MeOH) to give triol (**11**) (92%),[13] and (3) protection of the C(20)-C(21) glycol unit as an acetonide (**12**) by treatment of **11** with a catalytic amount of camphorsulfonic acid in the presence of 2,2-dimethoxypropane (88%).[14]

Scheme 1



2 **8**

9, X=O
10, X=H, OH

11

12

It is particularly noteworthy that compound (**12**) can now serve as a versatile intermediate not only for structure-activity relationship studies for the inhibition of HIV-PR but also for the synthesis of a variety of natural

cytochalasins.[15] Initial attempts to further cleave the C(13)-C(14) double bond of **12** in the presence of the C(6)-C(12) double bond have not been successful.[16] Nevertheless, the primary alcohol of **12** is readily amenable to further manipulation which should provide access to various cytochalasins and this possibility is presently being investigated.

In summary, an efficient degradation method has been developed to produce the 2-isoindolone core structure (**12**) as a valuable synthetic intermediate from the HIV-1 PR inhibitor lead, **1**, L-696,474. Structure-activity studies on the resulting 2-isoindolone system towards HIV-1 PR inhibition are now in progress and will be reported in due course.

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9. However, directed epoxidation of **5** under $VO(acac)_2$/TBHP conditions (K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, **1973**, *95*, 6136) did not provide the same epoxide (**7**). Epoxidation under these conditions is believed to proceed transannularly on C(13)-C(14) double bond (B. M. Kim, unpublished results).

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11. Diagnostic ^1H nmr spectra and other physical data of compound (**8**): ^1H nmr ($CDCl_3$, 400 MHz) 2.77 (H_8, dd, J=9.7, 9.5 Hz), 2.84 (H_{10}, dd, J=13.2, 6.2 Hz), 2.90 (H_{10}, dd, J=13.4, 8.8 Hz), 3.28 (H_{19}, m), 4.01 (H_7, d, J=9.3 Hz), 4.89 (H_{12}, dd, J=0.9, 0.7 Hz), 4.92 (H_{20}, dd, J=8.8, 8.1 Hz), 5.00 (H_{12},

s), 5.21 (H_{21}, d, J=7.1 Hz), 5.48 (H_{14}, ddd, J=15.0, 11.5, 3.7 Hz), 5.55 (NH, s), 5.97 (H_{13}, dd, J=15.0, 9.9 Hz); mp 136-139° C; HRFABms (M+H) 626.3867 calcd for $C_{36}H_{56}NO_6Si$ 626.3877.

12. Reaction of **2** under Lemieux-Johnson conditions (R. Pappo, D. S. Allen Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **1956**, *21*, 478) also provided the dialdehyde (**9**) but not as cleanly as the two step procedure.

13. Diagnostic ^{1}H nmr spectra and MS of triol **11**: ^{1}H nmr ($CDCl_3$) 3.60 (H_{20B}, dd, J=11.0, 7.7 Hz), 3.90 (H_{20A}, dd, J=11.0, 4.9 Hz), 4.11 (H_7, d, J=4.4 Hz), 4.18 (1H, m), 4.54 (1H, br d, J=9.2 Hz), 5.02 (H_{12}, s), 5.10 (H_{12}, s), 5.15 (H_{13}, dd, J=15.0, 10.4 Hz), 5.48 (H_{14}, ddd, J=14.8, 9.5, 5.3 Hz), 5.94 (NH, s); HRFABms (M+H) 586.3920 calcd for $C_{34}H_{55}NO_5Si$ 586.3928

14. ^{1}H nmr spectra and ms of acetonide (**12**): ^{1}H nmr ($CDCl_3$) -0.03 (3H, s), 0.00 (3H, s), 0.82 (9H, s), 0.89 (1H, m), 0.92 (3H, d, J=6.6 Hz), 1.03 (3H, d, J=6.0 Hz), 1.36 (3H, s), 1.44 (1H, m), 1.53 (3H, s), 1.64 (1H, m), 1.72 (1H, m), 1.98 (1H, m), 2.23 (H_9, t, J=9.9 Hz), 2.35 (H, dd, J=4.6, 3.9 Hz), 2.74 (1H, m), 2.80 (H_{10B}, dd, J=13.2, 4.2 Hz), 2.86 (H_{10A}, dd, J=13.2, 9.9 Hz), 3.22 (H_3, m), 3.41 (H_{19}, dd, J=10.4, 6.2 Hz), 3.49 (H_{19}, dd, J=10.4, 5.1 Hz), 3.65 (H_{20}, dd, J=8.2, 8.0 Hz), 3.98 (H_7, d, J=9.2 Hz), 4.13 (H_{20}, dd, J=7.9, 6.0 Hz), 4.61 (H_{21}, dd, J=7.9, 6.8 Hz), 4.99 (H_{12}, br s), 5.09 (H_{12}, br s), 5.32 (NH, s), 5.35 (H_{14}, ddd, J=14.3, 8.6, 5.5 Hz), 5.93 (H_{13}, dd, J=15.2, 9.9 Hz), 7.17 ($2H_{10\text{-}Ph\text{-}o}$, d, J=~7 Hz), 7.23 ($H_{10\text{-}Ph\text{-}p}$, t, J=~7 Hz), 7.32 ($2H_{10\text{-}Ph\text{-}m}$, t, J=~7 Hz); HRFABms (M+H) 626.4256, calcd for $C_{37}H_{60}NO_5Si$ 626.4241

15. Various [11]cytochalasins such as cytochalasin D, cytochalasin O, and zygosporin E are viable synthetic targets from **12**.

16. The low reactivity of C(13) aldehyde unit, due to severe steric hindrance, was similarly demonstrated in the synthesis of [11]cytochalasins. See, M. Boutellier, D. Wallach, and C. Tamm, *Helv. Chim. Acta*, **1993**, *76*, 2515.

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