Diastereocontrolled Construction of Pactamycin's Complex Ureido Triol Functional Array
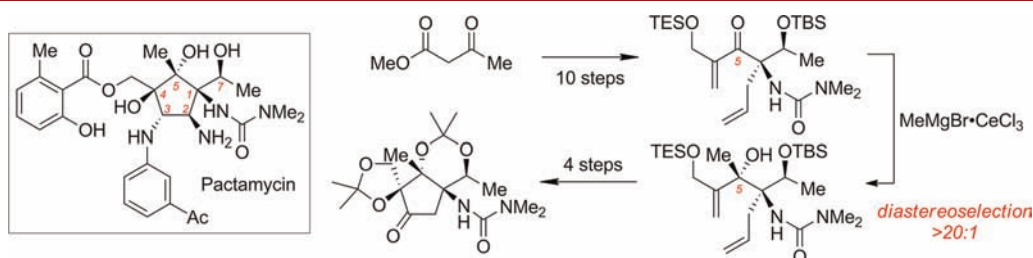
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ABSTRACT

An advanced intermediate in a projected synthesis of pactamycin has been prepared. Early installation of the C1-dimethylurea functionality allows for its participation in a diastereoselective, chelation-controlled addition of organometal nucleophiles to the C5 prochiral ketone. Four of the molecule's six stereocenters are set with a ketone functional handle provided for subsequent manipulation.

First isolated in 1961 from a fermentation broth of *Streptomyces pactum* var. *pactum*, pactamycin (**1**) is a potent, universal inhibitor of translocation.[1,2] Through use of its aniline and salicylate moieties, pactamycin mimics a dinucleotide, interacting with stem loops in the 16S RNA, garnering its antitumor, antimicrobial, antiviral, and antiprotozoal activity.[3] The unique stereochemically and functionally dense structure was proposed in 1970[4] and revised after X-ray analysis in 1972.[5]

Pactamycin's cyclopentane core features stereogenic carbons at each position with an additional side chain stereocenter at C7. The molecule is heteroatom-rich and contains urea, salicylate, and aniline functionality about the densely substituted core. The synthetic challenge posed by this complex target had only received limited attention

in the literature with two synthetic studies,[6] until the first total synthesis was realized in 2011 by Hanessian and co-workers.[7] This Letter details progress on a pactamycin core synthesis, specifically highlighting issues associated with the diastereoselective construction of the C5 tertiary carbinol.

Our retrosynthesis is outlined in Scheme 1. We envisaged access to **1** through selective manipulation of alcohol and amine functionality at C4 and C3, respectively, from stereochemically complete core **2**. The C4 tertiary alcohol and C2/C3 diamine moiety could be installed through allylic and alkene functionalization of cyclopentene **3**, which would be constructed employing ring-closing metathesis of diene **4**. Prior to cyclopentene formation, we believed the C1, C5, and C7 stereocenters could be installed with high diastereoselectivity in the acyclic form. We proposed formation of the C5 stereocenter via functionalized vinyl addition to methyl ketone **5**. The first stereocenter, C1, would be introduced employing an enantioselective allylation followed by

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(5) Duchamp, D. J. *Abstracts, American Crystallographic Association Winter Meeting*; Albuquerque, NM, 1972; 23.

(6) (a) Knapp, S.; Yu, Y. *Org. Lett.* **2007**, *9*, 1359. (b) Tsujimoto, T.; Nishikawa, T.; Urabe, D.; Isobe, M. *Synlett* **2005**, 433.

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diastereoselective ketone reduction at C7 of a substrate derived from methyl acetoacetate.

Scheme 1. Retrosynthetic Analysis of Pactamycin

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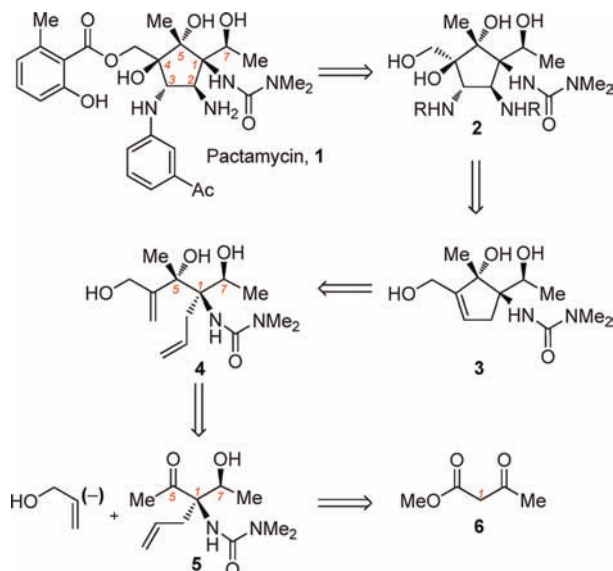
Rather than advancing the unusual C1 dimethyl urea in a protected form, we were intrigued by possible directing or chelating effects that this Lewis base might exert during key bond constructions. To this end, we elected to install this C1 functionality *in its final desired form* early in the synthesis. Diazo transfer onto methyl acetoacetate with *p*-acetamidobenzenesulfonyl azide (*p*-ABSA)[8] proceeded in excellent yield to give α-diazo methyl acetoacetate (**7**, Scheme 2). A Rh-catalyzed N−H insertion reaction adapted from the method reported by Janda[9] was then used for installation of the dimethylurea (**8**). This pronucleophile was subjected to the allylation conditions developed by Ito[10] to provide the C1 stereocenter ((±)-**9**). An unoptimized asymmetric variant of this reaction using the Ito conditions provided enantioenriched (*R*)-**9** (er 92:8, Scheme 3). The allylation was followed by a diastereoselective L-selectride reduction which provided the desired diastereomer in 72% yield.[10] Silyl protection of the C7 alcohol with TBSOTf proceeded in excellent yield to give methyl ester **10**.

Conversion of the methyl ester **10** to a methyl ketone was unsuccessful under standard conditions (MeMgBr, MeLi, Cp$_2$TiMe$_2$) due to a lack of reactivity attributed to congestion at the adjacent C1 center; however, TMSCH$_2$Li was shown to possess unique nucleophilicity, smoothly providing ketone **11** after a methanol quench (Scheme 4).[11]
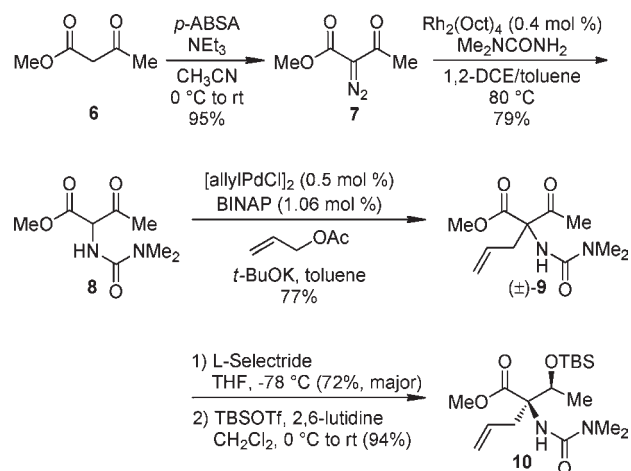
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Scheme 2. Diastereoselective Assembly of the C1 and C7 Stereocenters

With the desired C5 ketone in hand we tested a variety of nucleophilic additions to evaluate reaction efficiency, diastereoselectivity, and influence of the C1 urea during formation of the C4−C5 bond.

**Scheme 3.** Enantioselective Tsuji−Trost Allylation
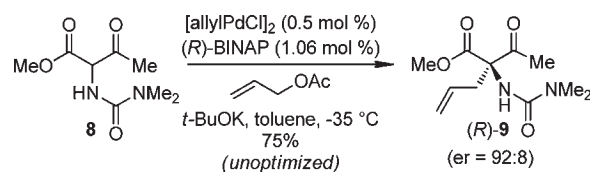
Standard nucleophilic additions to **11** were unsuccessful. Recovered starting material suggested an extreme degree of steric hindrance and/or competitive enolization of the methyl ketone. To overcome this impasse, cerium trichloride was deployed to both activate the ketone and render the organometal nucleophiles less basic.[12,13] An isopropenyl Grignard was used as a model nucleophile and, when used with added CeCl$_3$, provided tertiary carbinol **12** with 2.7:1 diastereoselectivity and 59% isolated yield (major isomer). Ring-closing metathesis with Grubbs's second generation catalyst provided cyclopentene **13**; nOesy analysis on this rigidified structure revealed the undesired *syn* relationship between the C5 hydroxyl and C1 urea.[14]

The conversion of **11** to **12** demonstrated that organometal additions to a hindered α-ureido ketone were

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(14) See Supporting Information for nOesy analysis.

Scheme 4. 2-Propenide Addition to a C5 Methyl Ketone

GII = Cl$_2$(PCy$_3$)(IMes)Ru=CHPh

Scheme 5. Methide Addition to a C5 Functionalized Enone
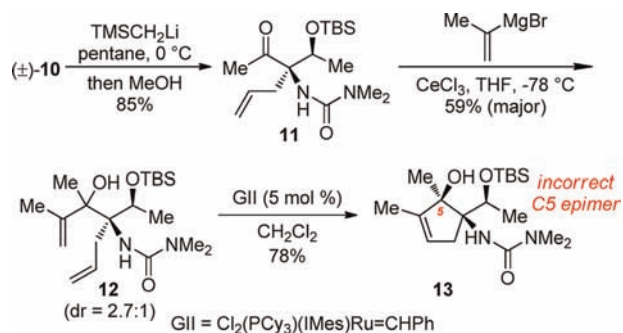
feasible and potentially diastereoselective, dictated by the C1/C7 stereodiad. Since the C5 alcohol arises from two consecutive organometal additions to a carbonyl electrophile, it occurred to us that reversing the order of nucleophile additions (functionalized vinyl, then methyl) might deliver the desired stereochemical outcome. To this end, we set out to synthesize a functionalized C5 enone electrophile.

A reduction/oxidation sequence of methyl ester **10** with DIBAL-H and Dess–Martin periodinane proved most reliable in providing aldehyde **14** (Scheme 5). The aldehyde functionality at C5 permitted addition of lithiated 2-bromopropenol[15] (**15**) in good yield to give diol **16**.[16] A selective triethylsilylation of the primary alcohol followed by Dess–Martin oxidation yielded α,β-enone **17**.

Methyl Grignard addition in the presence of CeCl$_3$ proceeded in excellent yield providing the 1,2-addition product as a single diastereomer (**18**). Ring-closing metathesis gave cyclopentene **19**; nOesy analysis showed the desired stereochemistry at C5, confirming our hypothesis. Notably, this second-generation route allowed for the facile introduction of a critical hydroxymethylene functionality at C4.

The stereochemical outcome of C5 ketone nucleophilic additions may be analyzed in the context of the following transition state proposal (**20**, Scheme 6). A five-membered chelate involving the urea, ketone, and metal (M = CeX$_2$, MgX) could lock the electrophile in a conformation wherein the bulky, branched *tert*-butyldimethylsilyloxyethyl group shields addition from the *Si* face providing a modest preference in the methyl ketone case, and exclusive *Re* facial addition in the functionalized ketone system. This chelation effect has been invoked sporadically in additions to fully substituted *cyclic* α-amino ketones (to an α-oxo-azaspirocyle[17] and an α-amino cyclobutanone[18]). Two conclusions flow from this analysis: (1) the identity of the nucleophile has little effect on the stereochemical outcome,
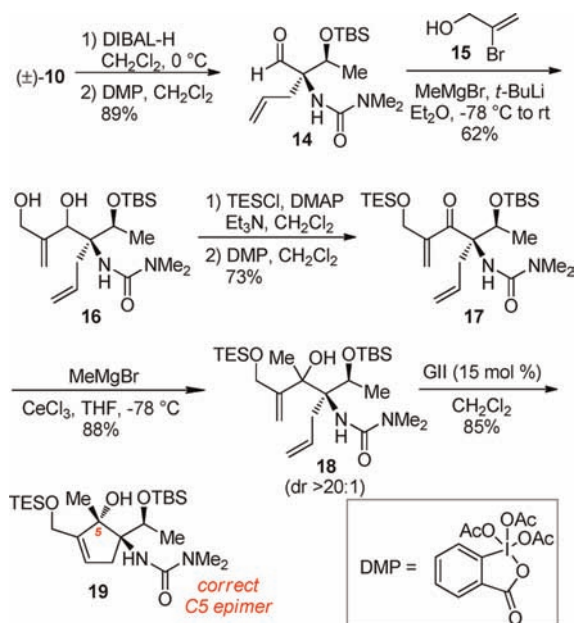
and (2) the decision to incorporate the dimethylurea early is crucial in achieving the proper C5 stereochemistry via this synthetic route. The enhanced diastereocontrol with the more sterically demanding enone **17** might be consistent with "nonvertical" approach trajectories that accentuate the influence of chiral information in the electrophile.[19]

Scheme 6. Proposed Transition State for C5 Nucleophilic Addition
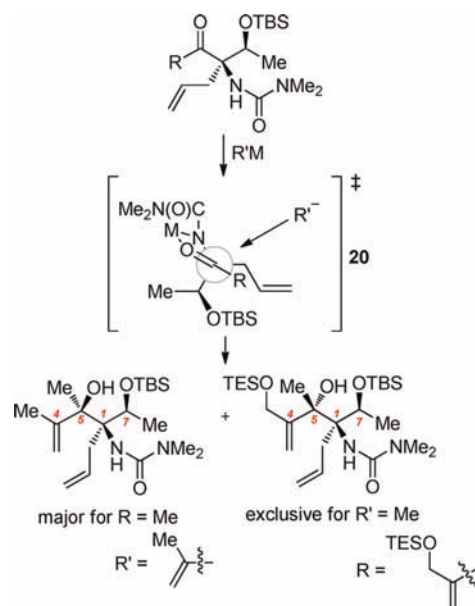
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The C3−C4 alkene was expected to provide a useful handle for elaboration to the remaining functionality in the pactamycin core. Efforts to install an allylic amine or otherwise oxidize the C2 methylene were unsuccessful, so our efforts turned to alkene functionalization. OsO_4-catalyzed dihydroxylation of cyclopentene **19** provided *syn*-diol **21** in good yield as a single diastereomer (Scheme 7).[20] Swern oxidation gave the α-hydroxy ketone **22** in 88% yield and avoided competitive oxidative cleavage that was observed with other oxidants (Dess−Martin periodinane, PCC). Diol **21**, ketone **22**, and their derivatives are expected to be useful intermediates for the introduction of the C2 amine and the C3 aniline.

Scheme 7. Elaboration of the C3−C4 Alkene
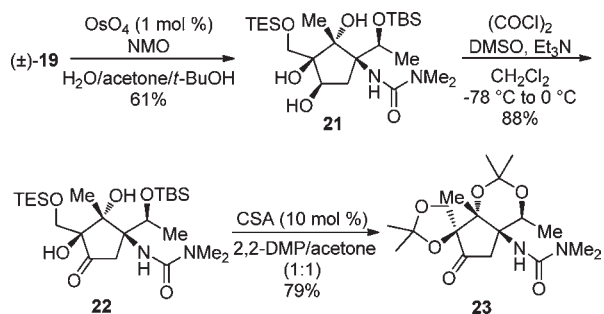
An alternate protecting group scheme was also realized upon treating ketone **22** with 2,2-dimethoxypropane (2,2-DMP) and catalytic acid. Under these conditions, both silyl ethers were cleaved, and the C4 1,3-dioxolane and C1/C7 1,3-dioxane were selectively constructed, conveniently protecting the tetraol (**23**). Diacetonide **23** was highly crystalline and used for X-ray analysis (Figure 1). The crystal structure confirmed our nOesy-based stereochemical assignments and provided insight into the preferred conformation of functional groups, aiding in the planning of further manipulations.[21]

Figure 1. X-ray structure of diacetonide **23**.

In conclusion, we have in 15 steps converted methyl acetoacetate to diacetonide **23**, an advanced intermediate in a projected synthesis of pactamycin. Four of the six stereocenters, including the contiguous fully substituted C1/C5/C4 stereotriad, have been established with high levels of stereocontrol. The stereochemical issues associated with the creation of the C5 tertiary alcohol were studied, and a stereochemical model for organometal additions to highly substituted α-NH-ketones was advanced. A C3 ketone arose from functionalization of the cyclopentene core and provides a functional handle for subsequent manipulation. Ongoing efforts are focused on α-amination of the C3 ketone and elaboration of the ketone to the C3 aniline functionality.

Supporting Information Available. Experimental details and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) CCDC 878935 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallograph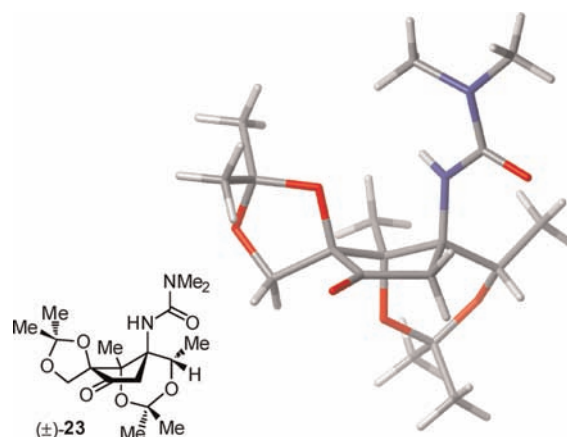ic Centre via www.ccdc.cam.ac.uk/data_request/cif.