Total Synthesis

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Hidden Symmetry Enables a 15-Step Total Synthesis of Pactamycin**

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Over the last half century since its isolation from *Streptomyces pactum* by Argoudelis et al.,[1] the natural product pactamycin (**1**, Figure 1) has been acknowledged as a formidable challenge to practical chemical total synthesis. Certainly, many researchers focused on the total synthesis of complex

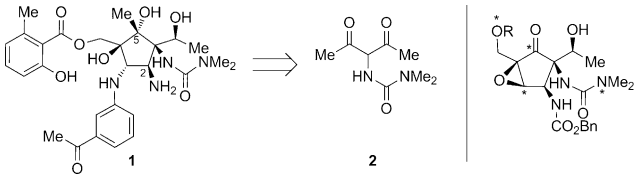

Figure 1. Left: Pactamycin and the starting urea in the Johnson synthesis. Right: A key late-stage intermediate; sites of modification are marked by asterisks (vide infra).

natural products have tackled targets much larger than **1**. However, the density of functional groups on the pactamycin cyclopentanoid core (six contiguous stereocenters, a primary amine, and a urea moiety) makes it an unusually challenging synthetic target. Not only is pactamycin an interesting target from a purely synthetic standpoint, there is also substantial incentive to identify a practical blueprint for its synthesis that would enable a more in-depth study of its multifarious antiproliferative biological activity, which is rooted in its function as a universal inhibitor of translocation.[2]

The excitement generated by the bioactivity of **1**, which includes antitumor, antimicrobial, and antiviral properties is, however, tempered by the compound's toxicity.[3] Recently, genetic engineering has provided several analogues of **1** that show reduced toxicity, which has reinvigorated interest in additional biological studies.[4] As is often the case with many complex natural products (including **1**), opportunities to study the biological activity of not only the natural product, but of related compounds is severely hampered by an inability to access meaningful quantities. Although pactamycin is available by isolation from the natural source, synthetic biology has provided only a limited subset of analogues, which leaves a practical total synthesis as the only recourse to access significant quantities of related analogues in a reasonable timeframe. Recently, an important step toward this eventual goal has been achieved by a landmark 15-step total synthesis of pactamycin by Johnson and co-workers,[5] which is the focus of this Highlight.

The total synthesis of a natural product of the complexity of pactamycin requires careful strategic planning, the implementation of this strategy in a most efficient manner using powerful modern methods, and a healthy dose of serendipity, which are all to be found in the Johnson total synthesis of **1**. Furthermore, Johnson's work was aided by invaluable insight and lessons provided by the first completed synthesis of pactamycin, which was achieved by Hanessian and co-workers.[6] The strategy utilized by Johnson et al. is brimming with modern concepts for synthesis including avoiding the unnecessary use of protecting groups, using functional groups innate to the target (e.g., a urea group) to direct the installation of stereocenters, and taking advantage of latent symmetry elements to simplify the approach to **1**. As has been well recognized in many complex-molecule syntheses (exemplified by the syntheses of carpanone[7] and the endiandric acids),[8] the recognition of latent symmetry in a complex target can drastically simplify the task at hand. For the Johnson synthesis of **1**, this was the recognition of an amino acetylacetone grouping (**2**, see Figure 1) as a part of the cyclopentanoid core.

Symmetric urea derivative **2** (Scheme 1) is available in two steps from commercially available acetylacetone. The use of this urea enabled the introduction of over half of the core carbon atoms present in the natural product in a single operation. If employed at this juncture, different amide or urea substrates would lead to diversification of the target structure. The Johnson synthetic route featured an early asymmetric Mannich reaction using cinchonidine as a catalyst, which was inspired by the method of Schaus et al.[9] This resulted in the formation of adduct **5** (70% yield, 98:2 e.r.) and introduced a new stereocenter, which was "incorrect" with respect to the natural product but served, in a twist of fate, to direct the correct installation of additional stereocenters.

With the carbon framework (i.e., **5**) assembled, attention was directed to the desymmetrization of the Mannich product. Faced with the task of selectively accessing one of

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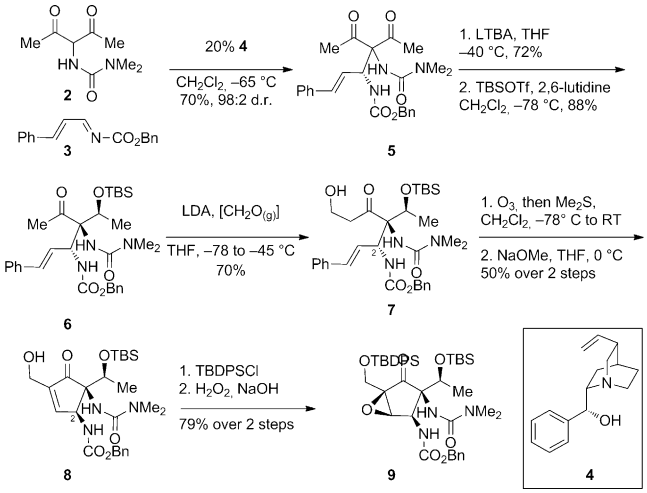
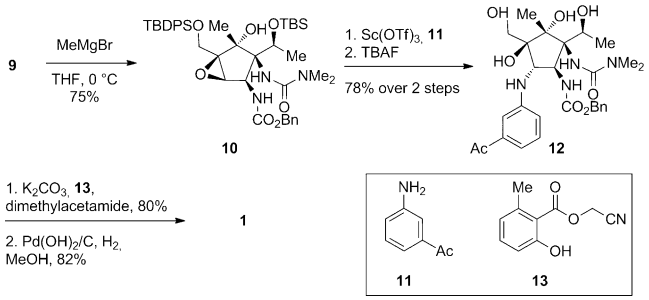


Scheme 1. Accessing the pactamycin core.



Scheme 2. Final functional group incorporation and completion of the synthesis. LDA = lithium diisopropylamide, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, TBDPSCl = *tert*-butyldiphenylchlorosilane.

four possible diastereomers, Johnson et al. found that the use of lithium tri(*tert*-butoxy)aluminum hydride (LTBA) delivered desired stereoisomer **6** in 72% yield in a ratio exceeding 10:1 with respect to the sum of the other three diastereomers, and the resulting hydroxy group was protected as a TBS ether. As previously alluded to, the "incorrect" stereochemistry at C-2 was crucial for this selectivity. In principle, reduction at this stage could be tailored, through either substrate or reagent control, to deliver the other diastereomers, which would in turn lead to stereoisomers of the pactamycin core for further investigation of the structure–activity relationship (SAR). Addition of **6** to formaldehyde proceeded smoothly to afford alcohol **7**.

Formation of the cyclopentenoid core was effected using an aldol condensation, and it was at this juncture that the burden of an undesired stereocenter was relieved. Synthetic chemists are well aware that often, when one encounters the wrong configuration at a given position, a great deal of manipulation may be required to fix the problem. Fortuitously, Johnson and co-workers found that under the conditions necessary for the aldol condensation, not only was the desired enone formed, but they also observed epimerization at C-2, which now mapped correctly onto the natural product. Protection of the primary alcohol group of **8** and Weitz–Scheffer[10] epoxidation delivered epoxide **9** as a single diastereomer. The introduction of a bulky silyl protecting group ensured the diastereoselectivity of methyl-group incorporation at C-5 (**9** to **10**, Scheme 2). This epoxide stands as a key intermediate that they were able to access in gram quantities. Furthermore, three of the subsequent five final steps in the synthesis involve the introduction of modifiable pieces that would aid in the generation of a library of compounds containing the pactamycin core (see Figure 1, sites of modification marked by asterisks).

A modular synthesis is especially significant for the study of pactamycin's bioactivity because data collected from SAR studies of derivatives accessed by synthetic chemistry, in conjunction with data from analogues isolated by genetic engineering, could redeem the natural product's practical worth. Toward this end, recent important work by Hanessian et al. compares the activity of synthetic analogues to that of natural pactamycin across several bacterial and cancer cell lines.[11] Furthermore, Hanessian, Ramakrishnan, and co-workers have started to unveil the pharmacophore of pactamycin through co-crystallization of pactamycin analogues and RNA segments from *Thermus thermophilus*.[12]

To complete the synthesis of pactamycin, Johnson and co-workers incorporate a 3-acetylaniline group by a $Sc(OTf)_3$-mediated epoxide opening in excellent yield. Following the precedent of Hanessian et al., ester **13** was employed for the introduction of the salicylate unit, setting in place the last of the required functional groups. The primary amine was revealed under hydrogenolysis conditions using Pearlman's catalyst in 82% yield, allowing for the total synthesis of pactamycin in 15 steps.

Overall, the importance of the Johnson synthesis arises not only from the ability to access a potent bioactive natural product, but also from the recognition of latent symmetry that drove, and ultimately simplified, the synthetic design of a complex molecule. The use of strategies such as this one emphasizes the capacity of chemical total synthesis to address the challenges that nature presents us with. In the case of pactamycin, the stage is now set for additional SAR studies building on the noteworthy initial studies by the Hanessian group.

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