ORGANIC LETTERS

2007
Vol. 9, No. 7
1359−1362

Synthesis of the Oxygenated Pactamycin Core

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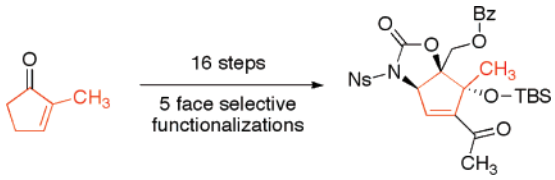
Received January 31, 2007

ABSTRACT



Pactamycin, one of the most complex and densely functionalized aminocyclitol antibiotics known, presents synthetic challenges that include reactivity and sterics, relative and absolute stereochemistry, and functional group compatibility and protection. An approach is reported that features four different types of (cyclopentane) face selective functionalization reactions and results in a polyfunctionalized and appropriately protected intermediate that incorporates all the core carbons and the oxygenated functionality of the target.

Pactamycin (**1**), isolated from a fermentation broth of *Streptomyces pactum* var *pactum*,[1−3] exhibits potent broad-range cytotoxicity both in vitro and in vivo. It interacts with the smaller ribosomal subunit[4,5] and functions as a potent and universal inhibitor of translocation.[6] The unique structure,[7] elucidated crystallographically in 1972,[8] features a nine-carbon core bearing seven vicinally related functionalities (three amino and four hydroxyl), three of which are modified by further N/O substitution, and six stereogenic carbons (all five of the cyclopentane and one off ring). The total synthesis of **1**, arguably among the most complex aminocyclitol assemblages known, can be taken as a challenge to existing and new methods of cyclopentane ring functionalization and amino/hydroxyl protection and manipulation.[9−12]

Functionalization of cyclohexenes and cyclohexanones can often be carried out by relying on preferential pseudoaxial approach of electrophiles and nucleophiles. Cyclopentenes and cyclopentanones, however, enjoy no such general conformational preferences, and so other stereoselective methods for reliably introducing or modifying functionality must be employed. These could include such tactics as the use of a bulky reagent that approaches from the less-hindered cyclopentane face, use of a chiral reagent with inherent enantioface selectivity, use of a coordinating or hydrogen-bonding *syn*-directing group,[13] and use of a tethered nucleophile.[14] We present an approach to the synthesis of **1** that includes stereoselective reactions belonging to each of these

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10.1021/ol0702472 CCC: $37.00
Published on Web 03/06/2007

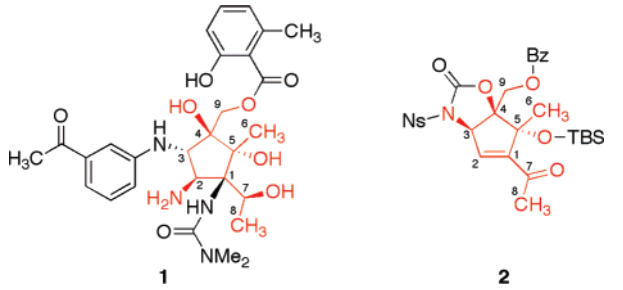
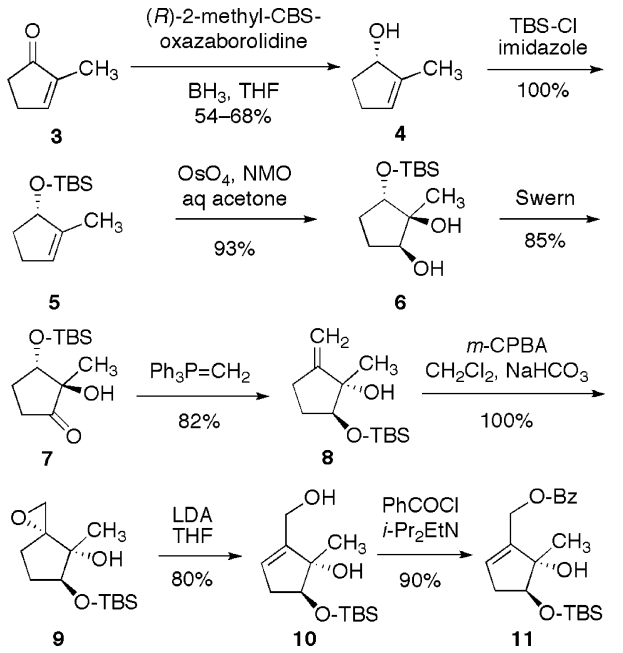


Figure 1. Structures of pactamycin (**1**) and the oxygenated pactamycin core (**2**).

four types of cyclopentyl modifications and results in an advanced intermediate (**2**) bearing all of the core carbons and affiliated oxygenated functionality (Figure 1).

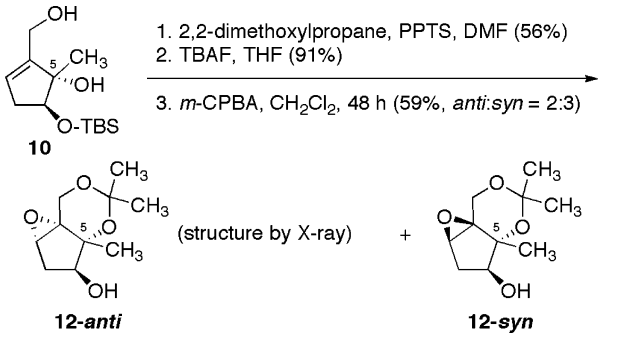
Scheme 1. Cyclopentenol Manipulations



Commercial 2-methyl-2-cyclopenten-1-one (**3**, Scheme 1) was reduced from the desired enantioface (here, β) with borane and catalytic (*R*)-2-methyl-CBS-oxazaborolidine,[15,16] leading to the allylic alcohol **4** on a 5 gram scale (90% ee as determined by Mosher ester analysis[17,18]). Protection of the hydroxyl as the *tert*-butyldimethylsilyl ether[19] (**5**) provided sufficient steric bulk on the α face such that osmylation[20] of **5** proceeded entirely from the opposite side. The resulting diol **6** was selectively oxidized under Swern conditions to ketone **7**, and then **7** was homologated with methylenetriphenylphosphorane[21] to produce the allylic alcohol **8**. Efficient hydroxyl-directed epoxidation of **8** with *m*-CPBA gave the α-epoxide **9** exclusively. Isomerization of **9** to the ene-diol **10** was achieved by treatment with lithium diisopropylamide (LDA) in THF solution.[22] O-Protected versions of **9** did not undergo this ring-opening reaction, which suggests a role for the tertiary hydroxyl in the successful conversion. The primary hydroxyl was selectively protected as the benzoate (**11**).

Although other protecting group schemata were considered for ene-diol **10**, the subsequent desired β face epoxidation could not be achieved selectively. For example, epoxidation of the acetonide-protected homoallylic alcohol derived from **10** gave substantial amounts of the undesired isomer **12-*anti*** (Scheme 2), the structure of which was determined by

Scheme 2. Proof of C-5 Stereochemistry



crystallographic analysis. The homoallylic hydroxyl is evidently not well positioned to *syn*-direct the epoxidation with *m*-CPBA. Nevertheless, the structure of **12-*anti*** proves that the stereochemistry at C-5 has been established correctly.

Protection of the tertiary hydroxyl of **11** as the *tert*-butyldimethysilyl ether (**13**, Scheme 3) provided a bulky group on the α-cyclopentane face and also allowed enough conformational freedom so that the desired H-bonding interaction with *m*-CPBA might occur during epoxidation. Indeed, selective deprotection of the secondary hydroxyl, followed by *m*-CPBA treatment of the resulting homoallylic alcohol **14**, gave the epoxy alcohol **15** with 9:1 *syn*/*anti* stereoselectivity.

The stereochemistry of **15-*syn*** was established by comparison with **12-*anti*** and **12-*syn***, and with *syn*- and *anti*-4-hydroxycyclopentene oxide (**18** and **19**, respectively, Figure 2).[23,24] Both **15-*syn*** and **18** exist in an *endo*-hydroxy

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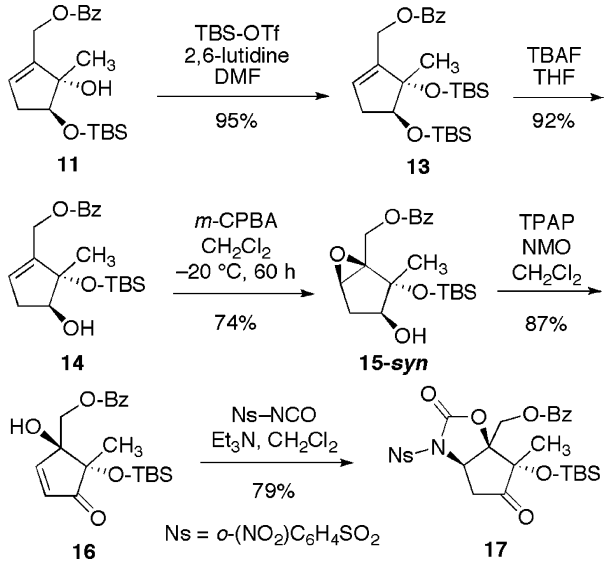
Scheme 3. Tethered Nitrogen Delivery

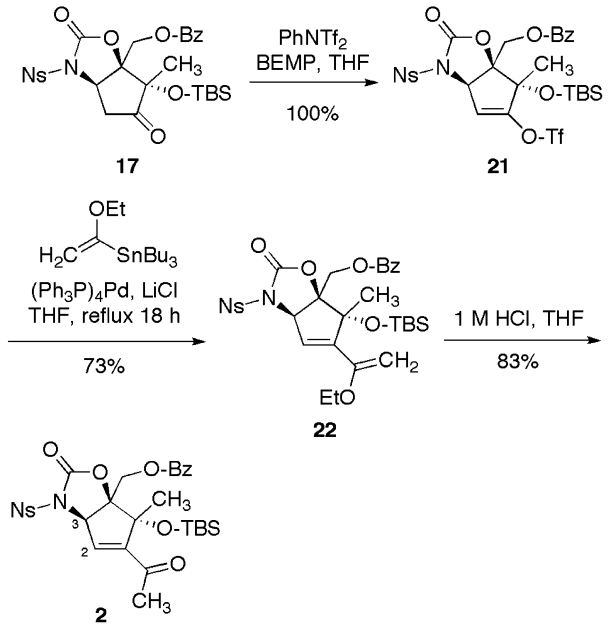


pseudoboat conformation in $CDCl_3$ solution, as illustrated by **20**, with nearly identical H-3_{cis}/H-4 and H-3_{trans}/H-4 coupling constants [$J_{3,4}$ = 5.2 (**18**) vs 5.8 (**15-*syn***) and 1.0 (**18**) vs ~0 (**15-*syn***) Hz, respectively]. In contrast, respective J values of **19** (also a pseudoboat, $J_{3,4}$ = 7.3 and 7.0 Hz) are a poor match with those of **15-*syn*** but are close to those of **15-*anti*** (8.8 and 7.2 Hz). The conformations and ^{1}H NMR spectra of the isopropylidene derivatives **12-*anti*** and **12-*syn*** are also in complete accord: **12-*anti*** exists in a pseudoboat conformation in the solid state, according to the crystallographic analysis, and exhibits H-3_{cis}/H-4 and H-3_{trans}/H-4 coupling constants of 7.6 and 7.2 Hz, matching those of **15-*anti*** and **19**. In contrast, the corresponding coupling constants of **12-*syn*** (6.6 and ~0 Hz) match those of **15-*syn*** and **18**.

Oxidation of **15** under weakly basic conditions led directly to the hydroxyenone **16**; the epoxide ring evidently opens subsequent to ketone formation.[25] The tertiary hydroxyl situated on the β face is now positioned to deliver a tethered nitrogen nucleophile in conjugate fashion to the unsaturated ketone. Treatment of **16** with 2-nitrobenzenesulfonylisocyanate[26−28] gave the N-protected[29] *cis*-fused oxazolidinone **17** as a single isomer. Although the nitrogen nucleophile is delivered β at C-3 (pactamycin numbering), this N is bound for C-2 in the target **1** and thus is already on the appropriate face.

The remaining core carbons of **1** were installed by first converting **17** to the vinyl triflate **21** (Scheme 4). The

Scheme 4. Cyclopentanone 2-Carbon Extension



hindered phosphazene base BEMP,[30] added last, was key for this transformation; sodium hexamethyldisilazide[31] failed to give complete conversion. Palladium-promoted coupling[32] of **21** with ethyl 2-(tri-*n*-butylstannyl)vinyl ether furnished diene **22**, and then acid hydrolysis gave the oxygenated pactamycin core target **2**.

The route to **2** comprises 16 steps, including five that feature cyclopentane-face-selective transformations of various types. Conversion of **2** to pactamycin **1** will require additional face-selective functionalizations (to affix the remaining amino groups), the introduction of heteroatom substituents at N-1,

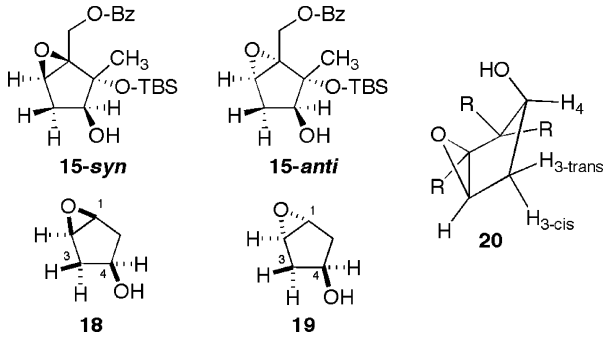


Figure 2. Stereochemistry of homoallylic alcohol epoxidation.

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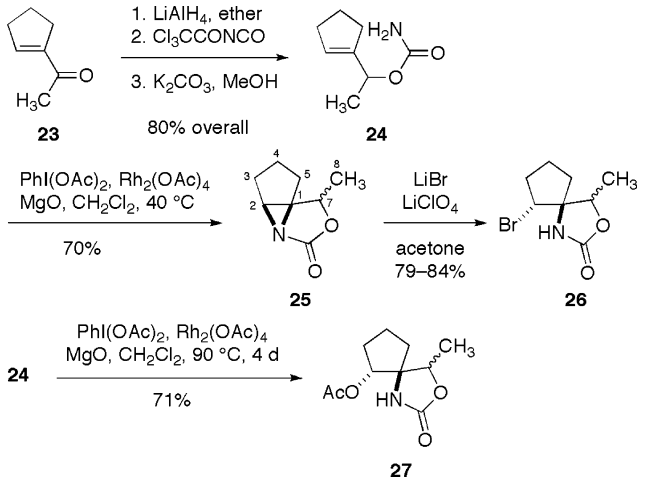
N-3, and O-9, and deprotection. The hindered amino at C-1 of **2** can possibly be introduced by a halo-amination or related reaction. One such method has been studied for a model substrate (Scheme 5).

Scheme 5. Model Study for Introducing the C-1 Amino



1-Acetylcyclopentene **23** was reduced to the racemic secondary alcohol,[33] which was further transformed[34] to the carbamate **24**. A rhodium-catalyzed cyclization following the procedure of Padwa[35−37] produced the *N*-acyl aziridine **25** as a separable mixture of methyl-*exo* and methyl-*endo* isomers (1.2:1, less polar and more polar, respectively). Upon treatment with LiBr, both isomers opened smoothly at C-2 (pactamycin numbering) to give the respective bromo oxazolidinones **26**. Alternatively, cyclization of **24** in a sealed tube under more forcing conditions led directly to a separable mixture of acetoxy oxazolidinones **27**. Either a bromo or a sulfonate (derived from the acetate) at C-2 can potentially serve as a leaving group for generation of a β-situated C-2/C-3 aziridine when the *N*-(2-nitrosulfonyl)oxazolidinone ring of **2** is hydrolyzed. The α-amino substituent at C-3 of **1** can then potentially be delivered to this aziridine by tethering the nucleophile to O-9.

Acknowledgment. We are grateful to Schering-Plough Corp. for financial support, Santosh Nandan (Astra-Zeneca) and Etzer Darout (Rutgers University) for helpful discussion, Tom Emge and David Fash (Rutgers) for crystallographic analysis, and Eric Sorensen (Princeton) and Lucy Stark (Scripps) for supplying a procedure for **4**.

Supporting Information Available: Experimental details and spectroscopic characterization for new compounds, including copies of ^{13}C and ^{1}H NMR spectra, and X-ray crystallographic results (CIF file) for the structure determination of **12-*anti***. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0702472

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