

# Practical Synthesis of Iboxamycin, a Potent Antibiotic Candidate, in Amounts Suitable for Studies in Animal Infection Models

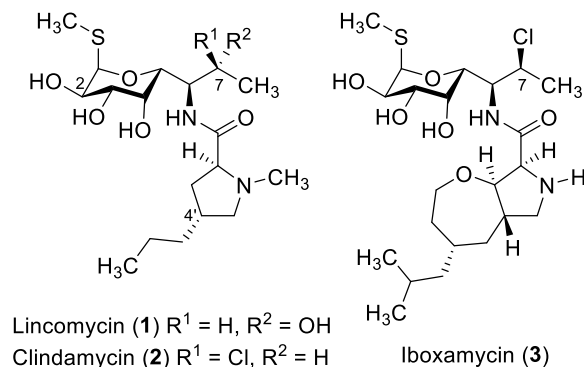
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**ABSTRACT:** A gram-scale synthesis of iboxamycin, an antibiotic candidate bearing a fused bicyclic amino acid residue, is presented. A pivotal transformation in the route involves an intramolecular hydrosilylation–oxidation sequence to set the ring-fusion stereocenters of the bicyclic scaffold. Other notable features of the synthesis include a high-yielding, highly diastereoselective alkylation of a pseudoephedrine amide, a convergent  $sp^3$ – $sp^2$  Negishi coupling, and a one-pot transacetalization–reduction reaction to form the target compound’s oxepane ring. Implementation of this synthetic strategy has provided ample quantities of iboxamycin to allow for its *in vivo* profiling in murine models of infection.

## INTRODUCTION AND BACKGROUND

The lincosamide antibiotics are orally available, non-toxic, bacteriostatic agents that act to inhibit translation by binding to the 23S subunit of the bacterial ribosome, near the peptidyl transferase center.<sup>1</sup> The founding member of the class, lincomycin (**1**, Figure 1), was isolated in 1963 by scientists at The Upjohn Company from a culture of the soil bacterium *Streptomyces lincolnensis*.<sup>2</sup> Lincomycin quickly gained FDA approval (1964) for the treatment of infections caused by Gram-positive pathogens. The semisynthetic derivative clindamycin (**2**), prepared by selective, stereoinvertive deoxychlorination of lincomycin at C7, showed improved *in vitro* and *in vivo* activity relative to lincomycin and was approved for use in humans in 1970.<sup>3</sup> In addition to its antibacterial properties, clindamycin can also be used for the treatment of *P. falciparum* malaria.<sup>4</sup> Clindamycin is commonly used to treat dental infections<sup>5</sup> and osteomyelitis,<sup>6</sup> and in topical form as an anti-acne agent,<sup>7</sup> but its widespread oral and parenteral administration (the latter in the form of the 2-phosphate ester prodrug) is contraindicated due to the risk of promotion of secondary *Clostridioides difficile* infections.<sup>8</sup> In addition, as with most antibiotics in use for decades, multiple bacterial resistance genes have evolved and are now widespread in bacteria within the community.<sup>9</sup> In spite of much effort, no new members of the lincosamide class have advanced to the clinic in the past five decades, which has possibly promoted a self-sustaining perception that the class has little to offer in terms of future antibiotics.<sup>10</sup>

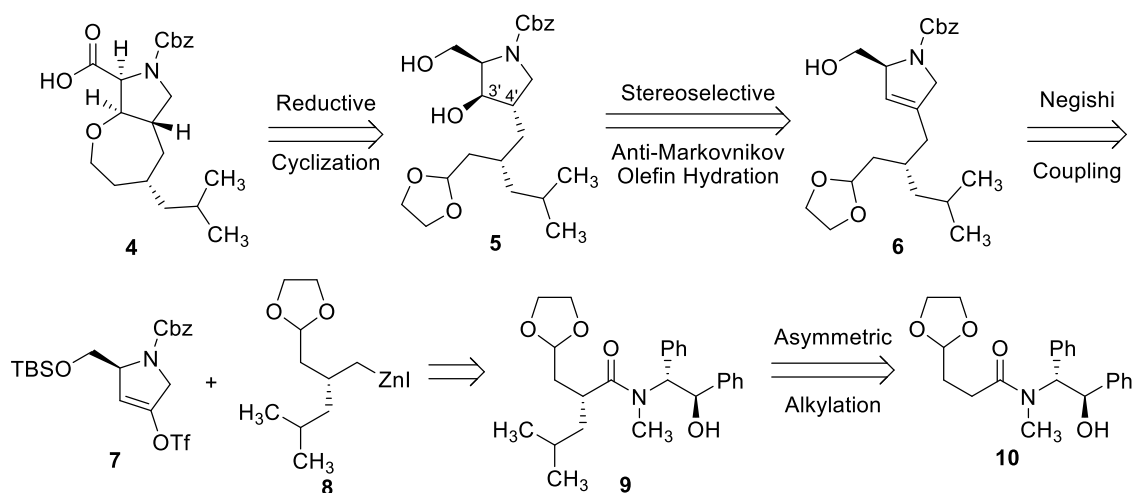
Over a period of more than 5 years, our laboratory has been involved in the continuous development of new methodology for the chemical synthesis of novel lincosamides in a search for next-generation antibiotic candidates that (1) are effective against current multi-drug resistant clinical isolates and (2) have the potential to overcome the *C. difficile* liability of clindamycin. In his PhD research, Dr. Matthew Mitcheltree pioneered new chemistry permitting fully synthetic construction of novel lincosamides with modified aminocytose subunits and initiated the discovery and construction of novel bicyclic scaffolds to replace the 4'-*n*-propyl hygric acid residue of lincomycin and clindamycin.<sup>11</sup> The PhD thesis research of Drs. Katherine Silvestre and Ioana Moga permitted



**Figure 1.** Structures of lincomycin (**1**), clindamycin (**2**), and the novel bicyclic analog iboxamycin (**3**), whose gram-scale synthesis is outlined herein.

an extensive investigation of scaffold substituents, resulting in a large expansion of our synthetic lincosamide library (currently >500 members), with >80% of the analogs having demonstrable antibacterial activity.<sup>12</sup> Dr. Katherine Silvestre discovered the molecule which bears the name iboxamycin (**3**), whose remarkable antibacterial effects, ribosomal-binding studies, and promise in animal infection models will be detailed elsewhere in a parallel submission for publication.<sup>13</sup> The original synthetic route to iboxamycin (**3**) provided quantities of material that were sufficient for extensive minimum inhibitory concentration assays against various bacterial strains (~50 mg, isolated as its formic acid salt after purification by RP-HPLC), but the sequence was lengthy and laborious as it had been designed as a discovery engine, not for efficient synthesis of iboxamycin (**3**) specifically. Considerable efforts were made to improve and substantially scale the discovery route so as to provide the greater quantities of iboxamycin that would be necessary to explore its efficacy in animal infection models. However, this work ultimately only reinforced the sense that an entirely new and different sequence would have to be developed to produce iboxamycin. Here, we present that route, its development and refinement, and implementation to produce >1 g of iboxamycin (**3**), an amount more than sufficient to support ongoing murine infection studies. Should it be warranted, we believe the route presented could provide the basis of a manufacturing route.

## Scheme 1. Retrosynthetic Analysis of the *N*-Protected Amino Acid Component 4



## RESULTS AND DISCUSSION

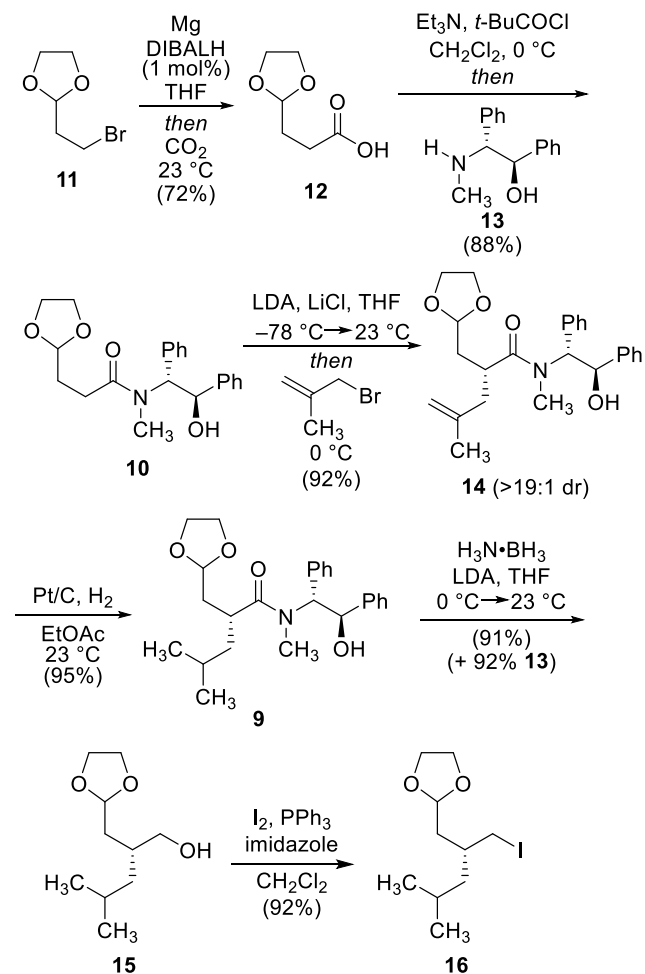
**Retrosynthetic Analysis.** Simplification of the novel bicyclic amino acid component of iboxamycin (in *N*-Cbz protected form, subtarget **4**) was reimagined along the lines presented in the retrosynthetic analysis shown in Scheme 1. Our initial disconnection targeted the oxepane ring, which we proposed might be constructed in a reductive cyclization reaction of the dihydroxy acetal **5**. This, in turn, was considered to arise from an anti-Markovnikov, suprafacial hydration of the alkene **6**, which we anticipated would require methodological development, but was considered strategic because it would set the stereochemistry of positions 3' and 4' in one operation. Disconnection of **6** by targeting the alkene appendage using a Negishi coupling<sup>14</sup> transform gave rise to the known vinyl triflate **7**<sup>15</sup> and the elaborated organozinc reagent **8** as starting materials. The latter was envisioned to arise from a straightforward sequence initiated in the synthetic direction by an asymmetric alkylation reaction of (*R,R*)-pseudoephedrine derivative **10** toward  $\alpha$ -substituted amide **9**, as depicted.<sup>16</sup>

**Implementation of an Asymmetric Alkylation Protocol to Construct the Direct Precursor to the Elaborated Organozinc Reagent 8.** By modifying literature protocols, we were able to prepare the carboxylic acid **12** in multi-decagram quantities (Scheme 2).<sup>17</sup> Specifically, we learned that formation of the Grignard reagent from the commercially available alkyl bromide **11** was best achieved by activation of the magnesium metal turnings using 1 mol% of diisobutylaluminum hydride according to the procedure of Tilstam and Weinmann.<sup>18</sup> After sparging with carbon dioxide with care to control the exotherm, the carboxylic acid **12** was obtained as an amorphous white solid after extractive isolation (35.7 g, 72%). Amide bond formation between **12** and (*R,R*)-pseudoephedrine derivative **13**<sup>19</sup> by mixed anhydride activation of **12** with pivaloyl chloride provided pseudoephedrine derivative **10** as white needles after extractive isolation and recrystallization from 1:1 ethyl acetate–hexanes (56.0 g, first crop, mp 111–112 °C, 8.0 g, second crop, 84% total). An additional 3.3 g of product (4%, total yield 88%) was obtained by flash chromatography of the residue obtained from concentration of the mother liquors using acetone–hexanes as eluent.

We found that neither isobutyl iodide nor isobutyl triflate were sufficiently reactive as substrates for high-yielding alkylation of the lithium enolate of pseudoephedrine derivative **10**, but methyl bromide provided excellent results.

Thus, formation of the lithium enolate using the standard protocol (LiCl, 6 equiv, LDA, 2.1 equiv, tetrahydrofuran (THF),  $-78\text{ }^{\circ}\text{C}\rightarrow 0\text{ }^{\circ}\text{C}\rightarrow 23\text{ }^{\circ}\text{C}\rightarrow 0\text{ }^{\circ}\text{C}$ ) followed by addition of methyl bromide (2 equiv) at 0 °C provided the alkylation product **14** as a colorless gum in 92% yield after extractive isolation and purification by flash column chromatography.<sup>16</sup> The product was shown to have a dr of >19:1 by using the oxazolium triflate method.<sup>20</sup>

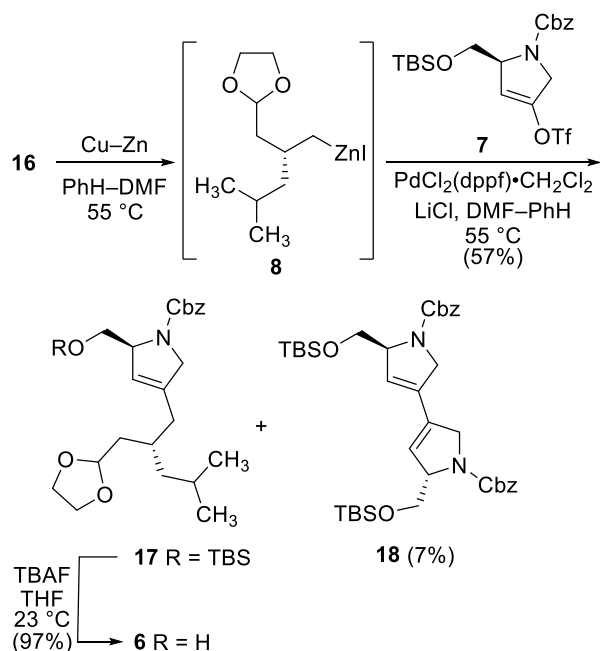
## Scheme 2. Synthesis of Alkyl Iodide 16



In a single experiment, we also evaluated the alkylation conditions recently reported by Collum and co-workers<sup>21</sup> (sodium diisopropylamide as base at  $-78\text{ }^{\circ}\text{C}$  rather than LiCl–LDA at  $0\text{ }^{\circ}\text{C}$ ) and found them to be effective as well as convenient, providing **14** in 83% yield (287 mg) with  $>19:1$  dr. The isobutenyl side chain of amide **14** was hydrogenated (Pt/C catalysis) in ethyl acetate as solvent to provide the saturated product **9** in 95% yield (30.5 g) as a thick, colorless oil. Reduction of **9** with lithium amidotrihydroborate<sup>22</sup> provided the primary alcohol **15** in 91% yield (12.5 g), and (*R,R*)-pseudoephedrine (**13**) was recovered in 92% yield by a simple extractive isolation. Using the Mosher ester method<sup>23</sup> we ascertained that the transformation of **9** to **15** had proceeded without detectable epimerization (dr  $>19:1$ ). Exposure of alcohol **15** to a combination of iodine, triphenylphosphine, and imidazole under the usual conditions<sup>24</sup> provided the desired primary iodide **16** in 92% yield (18.0 g) as a colorless oil.

**Formation of Elaborated Zinc Reagent 8 and Negishi Coupling.** In exploring methods to transform the primary iodide **16** into the elaborated organozinc reagent **8** we found that use of chlorotrimethylsilane and/or 1,2-dibromoethane as metallic zinc activators<sup>25</sup> was not easily reproduced on scales above a half-gram (Scheme 3). In contrast, when we employed freshly prepared 2% copper–zinc couple<sup>26</sup> in lieu of zinc metal, we found that organozinc formation proceeded smoothly at  $55\text{ }^{\circ}\text{C}$  (benzene–*N,N*-dimethylformamide (DMF) as solvent) and was easily reproduced on scales of as much as 10 g (larger scales were not attempted). Negishi coupling between the elaborated organozinc reagent **8** (formed *in situ* using 10.0 g of **16**) and the vinyl triflate **7** (17.4 g, 1.1 equiv, prepared by slight modifications of literature procedures,<sup>15</sup> see Supporting Information) in the presence of lithium chloride (1.5 equiv)<sup>27</sup> using [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane ( $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ ) as catalyst (0.02 equiv) in benzene–DMF as solvent at  $55\text{ }^{\circ}\text{C}$  afforded the coupled product **17** as a colorless oil in 57% yield (9.5 g)

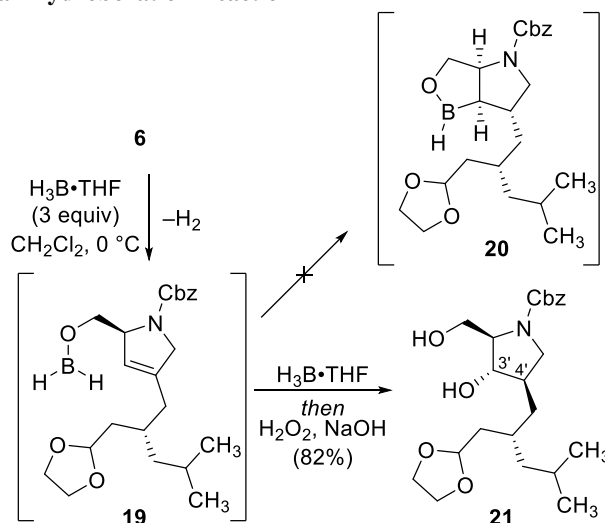
### Scheme 3. Organozinc Formation and Negishi Coupling



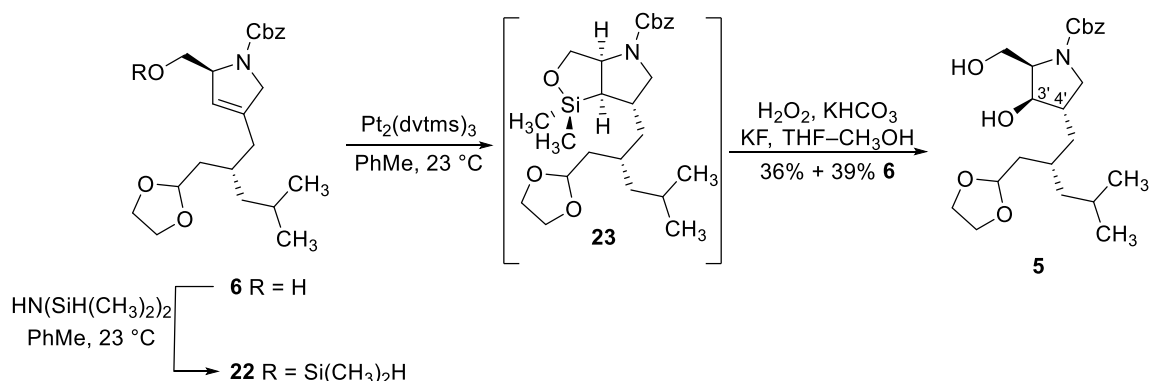
after extractive isolation and purification by flash-column chromatography. In separate chromatography fractions, we also recovered the vinyl triflate **7** (38%) and a dienyne dimerization product (**18**, 7% yield). Desilylation of coupling product **17** with tetra-*N*-butylammonium fluoride (TBAF) in THF at  $23\text{ }^{\circ}\text{C}$  gave rise to the key homoallylic alcohol intermediate **6** as a light-yellow oil (97% yield, 7.2 g).

**Stereo- and Regioselective Hydration of Homoallylic Alcohol 6.** The next and, as it transpired, greatest challenge in the synthetic route was to affect a suprafacial, anti-Markovnikov hydration of the alkene function within homoallylic alcohol **6** from its more hindered face—that which bears the hydroxymethyl group appendage (Scheme 4). The notion of using the homoallylic alcohol function to direct the addition was obvious but challenging to implement. Initially, we hoped that borane or another boron hydride reagent might first engage the hydroxyl group, evolving dihydrogen, and that the putative alkoxyboron hydride intermediate **19** might then undergo intramolecular hydroboration of the adjacent alkene.<sup>28</sup> We recognized that the resulting [3.3.0]-bicyclooctane-type intermediate **20** would likely suffer from a degree of strain, but we hoped that this might be mitigated by proximity. In the event, it was not, for only the diol arising from addition to the less hindered face of the alkene (i.e. **21**) was obtained after treatment with alkaline peroxide. Addition of a solution of borane THF complex to alcohol **6** led to instantaneous evolution of gas, certainly dihydrogen, suggesting that the alkoxyboron hydride intermediate **19** had likely formed, but intermolecular hydroboration of the less hindered face of the alkene was apparently faster than the desired course of reaction.<sup>29</sup> Attempts to induce the desired transformation using equimolar quantities of borane THF complex at elevated temperatures, as well as exploration of a number of other boron hydride reagents (hexylborane, chloroborane, to name two) were not successful, and led to the recovery of starting material or to the formation of the undesired diol **21** (see Supporting Information). When exposed to the species arising from the combination of borane dimethyl sulfide complex and trifluoromethanesulfonic acid, **6** was observed to undergo reductive opening of the acetal protective group.<sup>30</sup> After much additional experimentation not detailed here, we turned our focus to an alternative strategy to accomplish the desired transformation.

### Scheme 4. An Attempt to Achieve a Directed, Intramolecular Hydroboration Reaction



### Scheme 5. Intramolecular Hydrosilylation–Oxidation Sequence



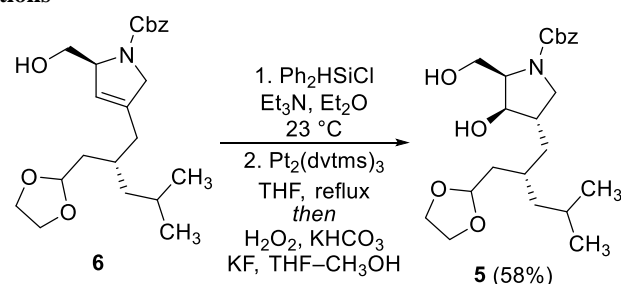
We turned instead to the strategy of intramolecular hydrosilylation followed by C–Si bond oxidation, pioneered by Tamao and Ito.<sup>31</sup> In an early experiment, we exposed homoallylic alcohol **6** to an excess of 1,1,3,3-tetramethyldisilazane (4 equiv) in toluene at 23 °C, and concentration to dryness under vacuum afforded the crude dimethylsilyl ether **22** (Scheme 5). This intermediate was then treated directly with Karstedt's catalyst (platinum-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex, Pt<sub>2</sub>(dvtms)<sub>3</sub>) in toluene at 23 °C to form the putative oxasilacycle **23**, in addition to other unidentified byproducts, and the crude mixture was subjected to alkaline peroxide in the work-up. After purification, we obtained the desired diol **5** in 36% yield. We also recovered 39% of the homoallylic alcohol **6**, which we believe arises from a competing dimerization of the dimethylsilyl ether **22**, which hydrolyzes to **6** upon work-up. Attempts to improve the yield of this transformation by using different transition-metal catalysts (e.g., [Rh(cod)Cl]<sub>2</sub>, Pt(PPh<sub>3</sub>)<sub>4</sub>, and a platinum-*N*-heterocyclic carbene catalyst<sup>32</sup>) or by slow addition of the silyl ether to a solution of the catalyst were not successful (see Supporting Information).

We then explored modifying the substituents on the silicon atom. Di-*tert*-butylsilyl, di-*mesityl*silyl, and di-*ortho*-tolylsilyl ethers proved to be unreactive under a variety of conditions, and the diisopropylsilyl ether proved similar to the dimethylsilyl ether in terms of the final yield of **5**. Among the silyl ethers investigated, the diphenylsilyl ether was found to be optimal. In addition, intermediates and by-products of the diphenylsilyl ether were found to be more stable than those of the dimethylsilyl ether, permitting their isolation and characterization (see Supporting Information). After additional experimentation (see Supporting Information), we found that replacement of toluene as solvent with THF improved the yield and provided a process that could be used to generate multi-gram quantities of **5**.

Thus, the diphenylsilyl ether derived from alcohol **6** was prepared by its reaction with commercially available chlorodiphenylsilane in ethyl ether with triethylamine as a base (Scheme 6). After removal of the resulting triethylammonium chloride precipitate by filtration, the solution was thoroughly dried under vacuum to provide the diphenylsilyl ether as a thick colorless oil. In the optimized intramolecular hydrosilylation process, a dilute (0.025 M) solution of the crude diphenylsilyl ether in THF at reflux was treated with a catalytic amount of Karstedt's catalyst (ca. 0.01 equiv). After consumption of the starting silyl ether (3.5 h), the crude mixture was cooled and directly subjected to Tamao–Fleming oxidation conditions, providing after purification by flash-column chro-

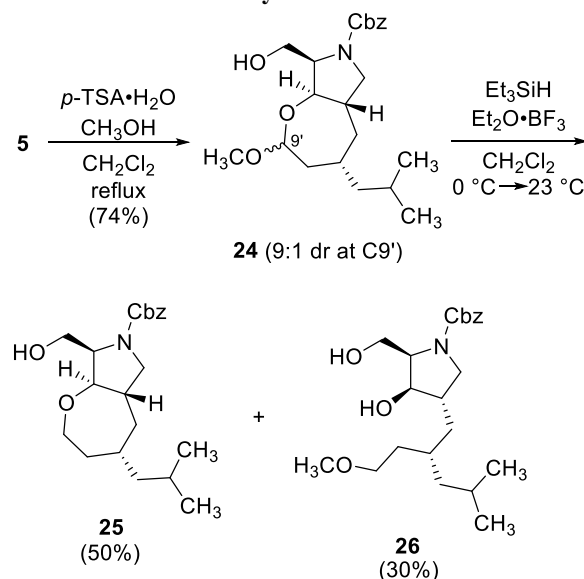
matography, the diol **5** as a colorless oil which solidified upon standing (4.3 g, 58%).

### Scheme 6. Improved Hydrosilylation–Oxidation Conditions



**Oxepane Formation and Completion of the Synthesis.** With multi-gram quantities of diol **5** in hand we turned to formation of the oxepane ring of **4** by a trans-acetalization–reduction sequence. In an initial experiment, the diol **5** was transformed into a 9:1 mixture of C9'-epimeric methoxy oxepane acetals **24** (stereochemistry of the major isomer not determined) upon exposure to methanol in the presence of *p*-toluenesulfonic acid monohydrate (*p*-TSA•H<sub>2</sub>O) at reflux (74% yield after isolation and purification by flash-column

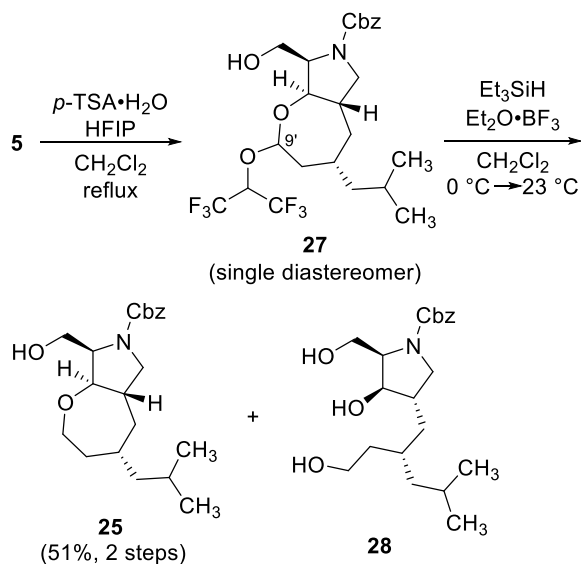
### Scheme 7. Synthesis of Oxepane **25** by Reductive Transacetalization via a Methoxy Acetal



chromatography) (Scheme 7). When a solution of this mixture was treated with triethylsilane and boron trifluoride etherate at 0 °C and warmed to 23 °C, the desired oxepane **25** was obtained in 50% yield. Isolated from separate chromatography fractions was the methyl ether by-product **26** (30%), which must certainly arise from the alternative oxocarbenium ion formation that leads to ring-opening.

By replacing methanol with 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) to form mixed acetal **27** (single diastereomer, stereochemistry not determined), ring opening during the reduction step was suppressed, and oxepane **25** was isolated in 51% yield by a parallel two-step process (Scheme 8). The triol **28** was also observed as a side product in this reaction, suggesting that oxocarbenium capture by adventitious moisture may have been an issue.

### Scheme 8. An Improved Reductive Transacetalization Sequence



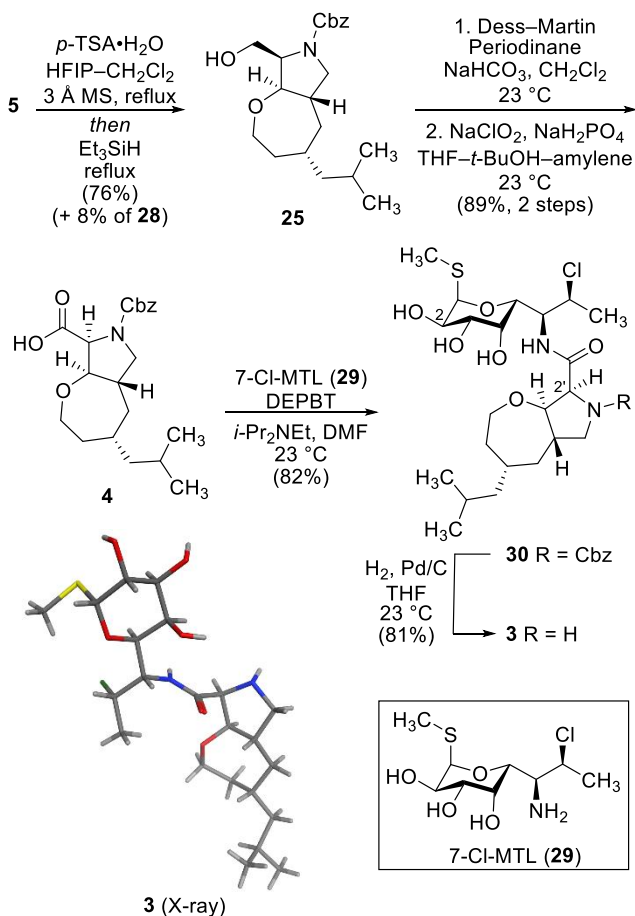
An improved, single-operation process was developed, one in which the diol **5** was held at reflux in a mixed solvent of dichloromethane and HFIP in the presence of  $p\text{-TSA}\cdot\text{H}_2\text{O}$  (1.7 equiv) and freshly activated 3 Å molecular sieves (MS) (Scheme 9). Subsequent addition of triethylsilane (8 equiv) and a second portion of  $p\text{-TSA}\cdot\text{H}_2\text{O}$  (1.7 equiv) to the refluxing mixture with brief further reflux gave rise to oxepane **25** in 76% yield (2.4 g), which was purified by extractive workup and flash-column chromatography. The undesired triol **28** was isolated separately as a side product (8%).

Oxidation of the primary alcohol function of oxepane **25** to a carboxyl group was achieved by a conventional two-step sequence of Dess–Martin periodinane oxidation to form the corresponding aldehyde, followed immediately by oxidation with sodium chlorite.<sup>33</sup> The key carboxylic acid subtarget **4** was thus obtained in 92% yield over the two-step sequence (2.2 g). Coupling of carboxylic acid **4** with (7*S*)-7-deoxychloro methylthiolincosamine (7-Cl-MTL, **29**)<sup>34</sup> was best achieved using 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT)<sup>35</sup> as the coupling reagent and *N,N*-diisopropylethylamine as base with DMF as solvent at 23 °C. While other reagents such as HATU were also effective for this coupling, DEPBT allowed for the most facile purification protocol. After isolation by flash-column chromatography, the amide coupling product **30** was obtained as a white powder in

82% yield (2.8 g). No diastereomer resulting from epimerization at C2' was observed after this coupling. To complete the synthesis of iboxamycin (**3**), all that remained was to cleave the *N*-benzyloxycarbonyl protective group. For this, we employed a full equivalent of 10% palladium on carbon (catalyst poisoning by the methylthio function was believed to be an issue) under 1 atm of dihydrogen in THF as solvent at 23 °C (5 h). Flash-column chromatographic purification using 1% ammonium hydroxide in the eluent afforded the pure, free-base form of iboxamycin (**3**) in 81% yield (1.5 g) as a white powder. Prior to biological evaluation *in vivo*, this material was recrystallized from absolute ethanol to provide iboxamycin as fine white needles (first crop, 78% recovery, mp 205–206 °C). Confirmation of all stereochemistry and structural details of iboxamycin was revealed by single-crystal X-ray analysis (CCDC # 1949345) of a sample obtained after two consecutive recrystallizations from absolute ethanol.

We prepared several salts of iboxamycin (**3**), as well as a 2-phosphate ester prodrug for galenic evaluation. The preparation and characterization of these derivatives is described in the Supporting Information.

### Scheme 9. Completion of the Synthesis



### CONCLUSION

In summary, we have developed a convergent, stereoselective, and potentially scalable synthesis of iboxamycin (**3**), proceeding in 6.7% yield over 15 steps from the commercially available alkyl bromide **11**. Key steps include a Negishi coupling involving the elaborated organozinc reagent **8** and vinyl triflate **7**, a regio- and stereoselective olefin hydration of

homoallylic alcohol **6** by an intramolecular hydrosilylation reaction followed by carbon–silicon bond oxidation, and a single-operation construction of the oxepane ring by trans-acetalization–reduction of diol **5**. The component-based nature of the route (**7**, **8**, **29**) makes fragment substitution quite feasible, and thus the route should provide a means to prepare a large number of additional analogs. The material furnished in these studies has permitted extensive *in vivo* analysis of iboxamycin (**3**) in murine infection models as well as other biological studies that would have been infeasible otherwise.<sup>13</sup>

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Detailed experimental procedures, supplementary tables, and all NMR characterization data (PDF)

X-ray data for iboxamycin (**3**) (CIF)

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### Notes

A.G.M. has filed international patent applications WO/2019/032936 and WO/2019/032956 ‘Lincosamide Antibiotics and Uses Thereof’.

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