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Efforts towards the Identification of Simpler Platensimycin Analogues—The Total Synthesis of Oxazinidinyl Platensimycin

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The discovery of platensimycin (**1**; Figure 1),[1] a novel antibiotic produced by *Streptomyces platensis*, has generated

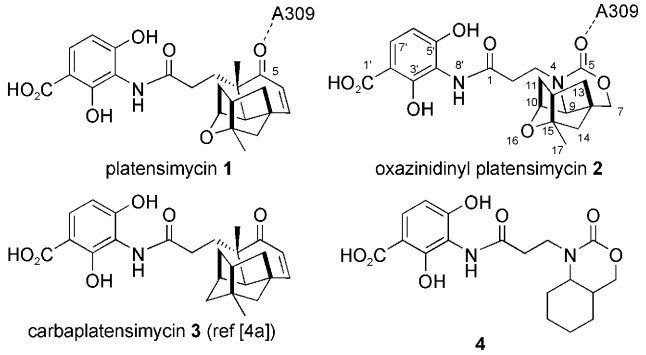


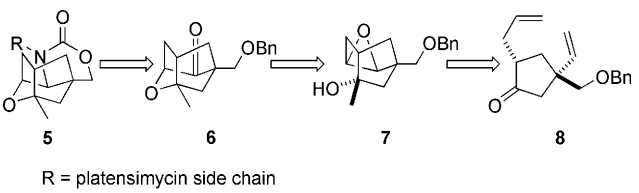
Figure 1. Structures of platensimycin and analogues and interactions of the C5 carbonyl moiety of **1** and **2** with the amide hydrogen atom of A309 of ecFabF(C163Q).

excitement in the scientific community due to its potent antibacterial activity against Gram-positive bacteria including vancomycin-resistant *Enterococcus faecalis* (VREF) and methicillin-resistant *Staphylococcus aureus* (MRSA). Platensimycin, a specific inhibitor of the bacterial FabF enzyme, is the first new class of antibiotic discovered in more than four decades.[2] Due to platensimycin's unprecedented complex architecture and remarkable in vitro activity, several groups have embarked on the total syntheses of this molecule.[3]

Analysis of the X-ray crystal structure of platensimycin in a complex with a mutant version of the ecFabF enzyme reveals several polar interactions between the highly polar benzoic acid moiety of **1** and the FabF residues.[1] Also, the tetracyclic core of compound **1** makes both polar and van der Waals interactions within the enzyme's active site. The extensive interactions between platensimycin and the FabF enzyme account for the high affinity of platensimycin to the FabF enzyme.[1] Platensimycin has a low in vivo activity when administered by conventional routes.[1] This has been attributed to the drug's poor pharmacokinetic properties. Because of platensimycin's poor pharmacokinetics, we and others have initiated programs to study the structure–activity relationship of platensimycin with the aim of identifying parts of the molecule that are amenable to modifications or deletion without adversely affecting biological activity.[4] These studies should ultimately lead to simpler analogues that are easier to synthesize and also with enhanced pharmacokinetics.

Herein, we report the total synthesis and biological testing of oxazinidinyl platensimycin **2**, the methyl ester analogue **32**, and the simplified oxazinidinyl analogue **4** (Figure 1). This limited set of analogues was designed to answer two questions: a) Could the enone moiety of platensimycin be replaced with the oxazinidinyl ring to create a potential bioisostere compound **2**?[5] b) Could the tetracyclic core structure of platensimycin be replaced with other motifs that are synthetically easier to access?

We envisioned that the core structure of oxazinidinyl platensimycin **2** could be obtained by the strategy outlined in Scheme 1. To afford tricycle **10** by pathway **a** as opposed to



Scheme 1. Retrosynthetic analysis of oxazinidinyl platensimycin.

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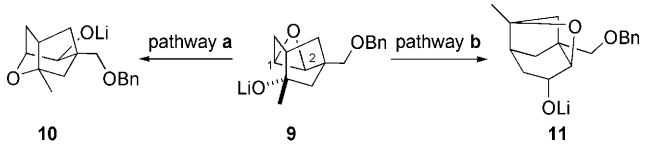
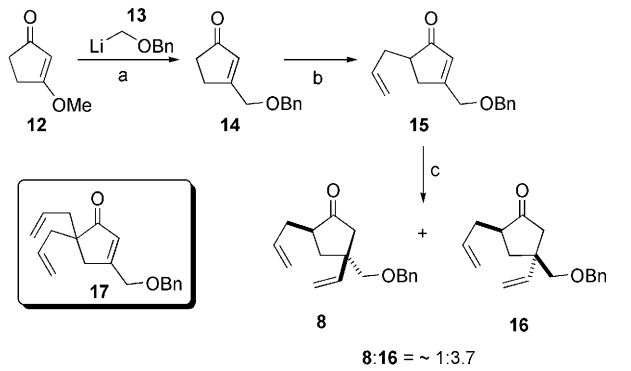
forming **11** by pathway **b**, a regioselective epoxide ring-opening of intermediate **9** to afford tricycle **10** was desired (see Scheme 2). DFT calculations indicated that the activation energy of pathway **a** (Scheme 2) was 9.8 kcal mol^{-1}



Scheme 2. 6-*exo-tet* (pathway **a**) versus 5-*exo-tet* cyclization (pathway **b**).

lower than that of pathway **b** (see the Supporting Information). This suggests that pathway **a** is more favorable than pathway **b**. Also, for the optimized ground state geometry of compound **9**, the distance between the oxygen nucleophile and the C1 atom was 3.2 Å, whereas the oxygen nucleophile was 3.7 Å away from C2. Together, these analyses gave us the confidence that one of our key steps towards the synthesis of oxazinidinyl platensimycin **2** was viable and worth pursuing.

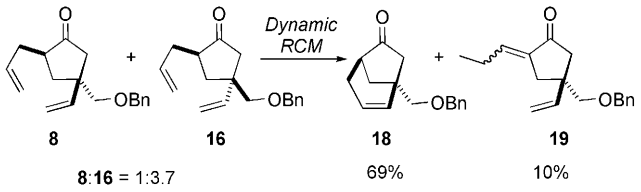
Initially, we set out to make bis-alkene **8**, the requisite substrate for the ring-closing metathesis reaction. Treatment of commercially available vinylogous ester **12** with anion **13**, generated from a stannane precursor by a lithium–tin exchange gave enone **14** in good yield (84%). The next step involved the allylation of enone **14** with allyl halide. Allyl bromide gave the desired product in only a meager 34% yield accompanied by a substantial amount of diallylated product **17** (44% yield). Interestingly, changing the allylation reagent to allyl iodide improved the yield to 62%, and the formation of the diallylated product was somewhat suppressed. Conjugate addition of vinyllithium to enone **15**, in the presence of $BF_3{\cdot}Et_2O$ resulted in a 1:3.7 mixture of racemic **8** and **16**, respectively (Scheme 3). Unfortunately, the major product **16** was not suitable for the subsequent ring-closing metathesis because the alkene moieties were *trans* to each other. The low overall yield of the desired *cis*-bis-alkene **8** led us to investigate the epimerization of compound **16** to give **8**. Subjecting compound **16** to 30 mol% DBU in toluene yielded an epimeric mixture of **16**: **8** in a 10:8 ratio after 21 h (see the Supporting Information). It therefore appears that the undesired bis-alkene **16** is both the kinetic and thermodynamic product.



Scheme 3. a) $LiCH_2OBn$, THF, −78 °C→RT, 12 h, 84%; b) LDA, HMPA, allyl iodide, 62% (67% based on starting material); c) $Sn(CHCH_2)_4$, *n*BuLi, CuCN, $BF_3{\cdot}Et_2O$, 85%. LDA = lithium diisopropylamide, HMPA = hexamethyl phosphoramide.

We wondered if we could perform the ring-closing metathesis in the presence of DBU. Should the ruthenium catalyst be compatible with the amine base, then a dynamic ring-closing resolution should ensue and both diastereomers **8** and **16** would be suitable for the ring-closing reaction. To the best of our knowledge, a dynamic ring-closing metathesis involving epimerization has not been reported in the literature.

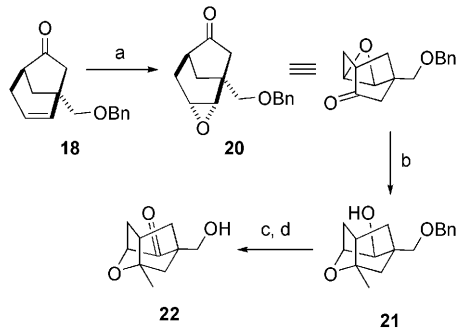
Pleasingly, subjecting an epimeric mixture of compounds **8**:**16** (ratio of 1:3.7) to Hoveyda–Grubbs II catalyst in the presence of DBU and benzoquinone afforded the ring-closed product in 69% yield (83% based on the starting material; Scheme 4). In contrast, in the absence of DBU, the desired product could be obtained in a meager 20% yield. The benzoquinone additive was important for minimizing the formation of the enone by-product **19**.[6]



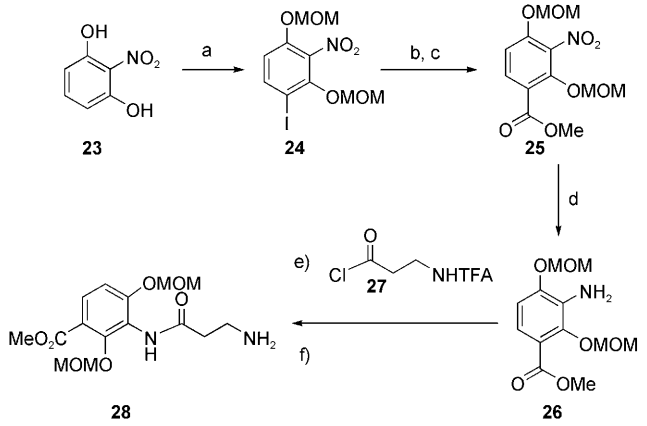
Scheme 4. Dynamic ring-closing metathesis. Reaction conditions: Grubbs–Hoveyda II catalyst (five portions; each portion = 3.2 mol%), DDQ (20 mol%), DBU (46 mol%), toluene, reflux, 69% (83% based on starting material). DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

With bicyclic compound **18** in hand, in gram quantities, we proceeded with the epoxidation reaction using *m*CPBA. The epoxide **20**, obtained in 64% yield, was then subjected to a tandem nucleophilic MeLi addition followed by a subsequent epoxide ring-opening to afford tricycle **21** in 70% yield. In line with our expectation, the alternative tricycle **11** (see Scheme 2) was not obtained. Oxidation of compound **21** with Dess–Martin periodinane was followed by debenzylation with Pd/H_2 to afford **22** without any incident (Scheme 5). The aromatic side chain of compound **4** was synthesized following the strategy shown in Scheme 6.

The stage was now set to couple the aromatic side chain **28** with the tricyclic ring core **22**. The reductive amination intermediate **29** has two sterically similar faces (shown as faces *A* and *B* in Figure 2) and it appeared at first glance that a mixture of diastereomers would be obtained during the reductive amination step. We however postulated that because one face (face *B*) contained oxygen, subtle stereoelectronic factors could swing the selectivity towards the desired product. The Felkin–Anh model[7] for the addition of nucleophiles to iminium **29** favors addition from face *A* (Figure 2) due to favorable interactions between the nucleo-



Scheme 5. a) *m*CPBA, dichloromethane, 0°C→RT, 12 h, 64%; b) MeLi, THF, −78°C→RT, 5 h, 70%; c) Dess–Martin reagent, dichloromethane, 12 h, 95%; d) 10 mol%, Pd/C, H_2, MeOH, RT, 12 h, 90%. *m*CPBA = 3-chloroperoxybenzoic acid.



Scheme 6. a) NIS, TFA, RT, 12 h, 100%, then, MOMCl, Hünig base, dichloromethane, RT, 12 h, 97% ; b) $CNCO_2Me$, PhMgBr, −78°C→RT, THF, 12 h, 78%; c) MOMCl, Hünig base, dichloromethane, RT, 12 h, 78%; d) H_2, 10 mol% Pd/C, MeOH, 69%; e) pyridine, benzene, RT→50°C, 5 h, 95%; f) K_2CO_3, MeOH: H_2O = 3: 1, RT, 10 h, 99%. NIS = *N*-iodosuccinimide, TFA = trifluoroacetic acid.

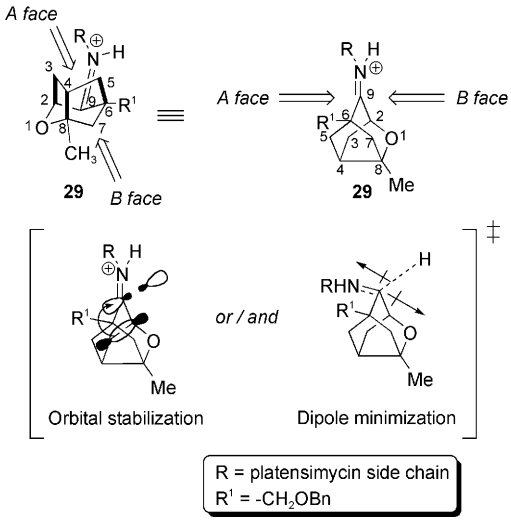
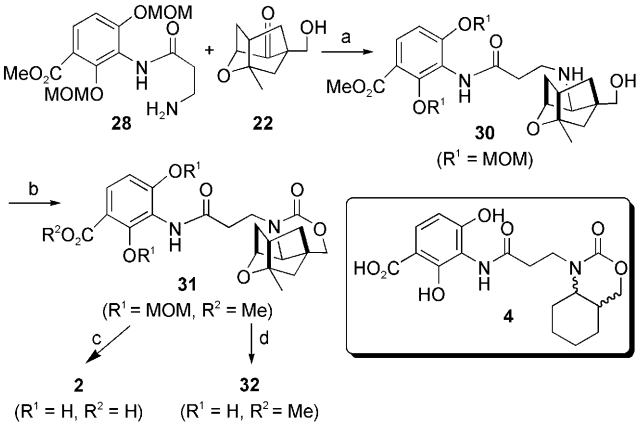


Figure 2. Facial selectivity of the reductive amination reaction.

phile and the low-lying bond. However, literature examples[8] indicated that for tricyclic systems such as **29**, a Cieplak model[9] would be a more appropriate predictor for product distribution: A hydride approach from face *B* would lead to two σ_{C-C} interacting favorably with the developing bond, whereas a hydride approach from face *A* will only lead to one σ_{C-C} interacting favorably with the developing σ^*_{C-H} bond. σ_{C-O} bonds are low lying and not expected to make any significant hyperconjugative contribution. Additionally, transition-state dipole minimization between the C–O bond and the forming C–N bond dictates that approach from face *B* should predominate.[10] Together, these arguments strengthened our conviction that the desired product would be obtained by reductive amination. Model studies using a simplified side chain confirmed our prediction that hydride attack from face *B* predominates (see the Supporting Information).

The end game of our synthesis proceeded smoothly. Reacting compounds **22** and **28** in methanol in the presence of sodium cyanohydride gave compound **30**; which was not purified but subjected to carbonyldiimidazole cyclization to afford **31** in 76% yield. Deprotection of the methyl ester and the MOM groups led to oxazinidinyl platensimycin **2** in 80% yield over two steps. Oxazinidinyl cyclohexaplatensimycin **4** was synthesized following the strategy outlined in Scheme 7 (see the Supporting Information).



Scheme 7. a) $NaBH_3(CN)$, MeOH, pH 4, RT, 5 h, 75%; b) $(im)_2CO$, 20 mol% DMAP, benzene, 50°C, 12 h, 76%; c) 1 N LiOH, MeOH: H_2O = 2:1, RT, 12 h, then, 2 N HCl, MeOH: H_2O = 2:1, RT, 24 h, 80%; d) 2 N HCl, MeOH:H_2O = 3:1, RT, 24 h, 92%. DMAP = 4-dimethylaminopyridine.

Oxazinidinyl platensimycin **2** has a minimum inhibitory concentration (MIC) of 90 $\mu g\,mL^{-1}$[11] for all of the three bacterial strains tested; *Staphylococcus aureus* (Newman), *Streptococcus agalactiae* (2603 V/R), and *Bacillus subtillis* (3160). MICs of oxazinidinyl platensimycin methyl ester **32** and the platensimycin analogue with simpler core structure **4** were greater than 512 $\mu g\,mL^{-1}$ for all of the three bacterial strains.

Despite its structural mimicry of platensimycin, oxazinidinyl platensimycin **2** is two orders of magnitude less potent.

Carbaplatensimycin **3**, an analogue that has the ethereal oxygen of platensimycin replaced with carbon, has a MIC of 1–2 $\mu g\,mL^{-1}$ (MRSA), which is close to that of the parent compound.[4b] Our work and that of the Nicolaou and the Merck groups suggest that the enone moiety of platensimycin is more important than the ethereal oxygen with regard to antibiotic activity.[4b,12] The lack of antibiotic potency of the methyl ester analogue **32**, even at millimolar concentrations, suggests that bacterial esterases are unable to hydrolyze the ester analogues of platensimycin into active drugs.[13]

In conclusion, we have presented novel strategies such as the dynamic ring-closing metathesis reaction and nucleophilic addition to a ketone followed by tandem epoxide ring-opening reaction to construct the tricyclic core structure found in platensimycin. These strategies should be applicable to the construction of other polycyclic motifs found in other natural or non-natural molecules. Our synthesis of oxazinidinyl platensimycin is concise and involves only 11 steps, starting from commercially available vinylogous ester **12**. We also show that the enone moiety of platensimycin's core structure is sensitive to modifications.

Acknowledgements

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Keywords: antibiotics · enzymes · ring-closing metathesis · medicinal chemistry · platensimycin · total synthesis

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[5] The carbamate moiety of the oxazinidinyl ring can maintain the hydrogen-bonding interactions with A309 of ecFabF. The oxazinidinyl ring is however not strictly an isosteric replacement of the enone ring core of platensimycin due to the lack of the C4 methyl group found in the parent compound.

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[10] The reductive amination was conducted in the polar protic solvent, MeOH; therefore dipole minimization might not play as great a role in product distribution.

[11] Using the conventional and usual twofold dilution method, the MIC of oxazinidinyl platensimycin **2** for all the strains would be 128 $\mu g\,mL^{-1}$ because the determined MIC value of 90 $\mu g\,mL^{-1}$ lies between 64 and 128 $\mu g\,mL^{-1}$.

[12] Dihydroplatensimycin, an analogue that lacks the enone moiety, is less active than platensimycin. Also, this keto analogue is unstable and forms cyclized products. See: S. B. Singh, H. Jayasuriya, J. G. Ondeyka, K. B. Herath, C. Zhang, D. L. Zink, N. N. Tsou, R. G. Ball, A. Basilio, O. Genilloud, M. T. Diez, F. Vicente, F. Pelaez, K. Young, J. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 11916–11920; S. B. Singh, H. Jayasuriya, J. G. Ondeyka, K. B. Herath, C. Zhang, D. L. Zink, N. N. Tsou, R. G. Ball, A. Basilio, O. Genilloud, M. T. Diez, F. Vicente, F. Pelaez, K. Young, J. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 15547.

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