JOC *Featured Article*

Enantioselective Total Syntheses of Omuralide, 7-*epi*-Omuralide, and (+)-Lactacystin

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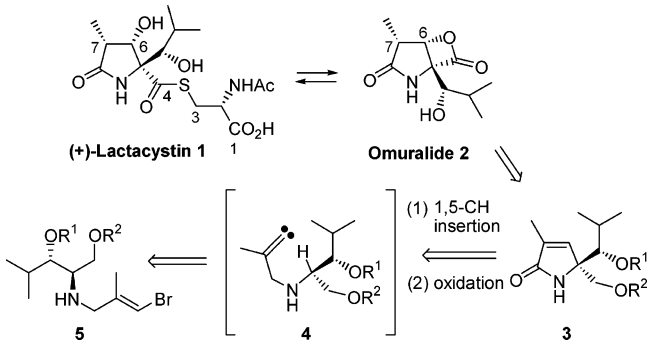

An alkylidene carbene 1,5-CH insertion has been used as a key step in an enantioselective total syntheses of omuralide, its C7-epimer, and (+)-lactacystin. An additional noteworthy feature of the synthesis is the use of a novel oxidative deprotection procedure, utilizing DMDO, for the conversion of a late-stage benzylidene acetal into a primary alcohol and a secondary benzoate ester.

Introduction

(+)-Lactacystin **1** was isolated from the bacterial strain *Streptomyces* sp. OM-6519 by Õmura et al. in 1991 during a screening program for small molecule mimics of nerve growth factors.[1] Lactacystin was later found to be a specific inhibitor of the 20S proteasome found in mammalian and bacterial cells.[2] The proteasome is responsible for the routine degradation of cellular proteins and also the removal of damaged and mutated proteins, and **1** has played a significant role in the study of its function. The remarkable biological activity and intriguing structure of **1** has stimulated much interest over recent years, and a number of syntheses have been published to date.[3] Lactacystin **1** spontaneously and reversibly forms omuralide **2** in the extracellular medium (Scheme 1), and it is this β-lactone that penetrates the cell and acylates an active-site threonine residue leading to inhibition of the proteasome. Other closely related β-lactone-containing lactams have recently been isolated, and synthetic interest in these molecules continues to grow due to their therapeutic potential.[4] In addition to serving as the biologically active form of lactacystin **1**, omuralide **2** has also served as a synthetic precursor to the natural product **1** itself, and the enantioselective synthesis of **2** has become an important synthetic challenge in its own right.

A variety of synthetic strategies have been employed in the previous syntheses of lactacystin,[3] and asymmetric construction of the nitrogen-bearing quaternary stereocenter presents, perhaps, the most significant challenge. Previous studies in our group have demonstrated the utility of alkylidene carbene 1,5-CH insertion reactions for the construction of 3-pyrrolines,[5] and furthermore, we have shown that the 3-pyrroline products can be readily oxidized to the corresponding pyrrolinones under mild conditions.[6] We decided, therefore, to attempt an enantioselective synthesis of lactacystin **1** using this 1,5-CH insertion/oxidation approach, proceeding through a suitably functionalized pyrrolinone (e.g., **3**). In 2002, we reported a formal synthesis of (+)-lactacystin **1**[3l] by intercepting Baldwin's route[3v] at lactam **3** ($R^1 = R^2 = H$), and this early success demonstrated the

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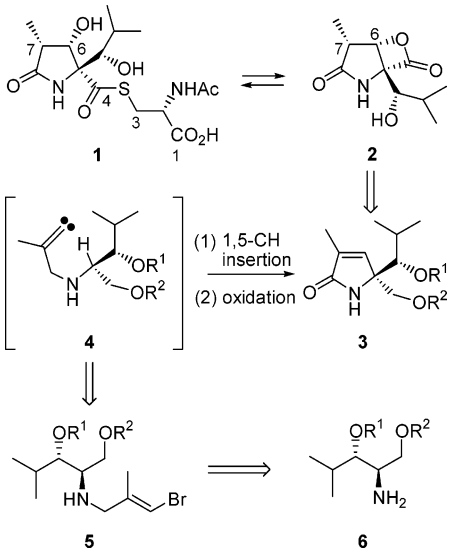
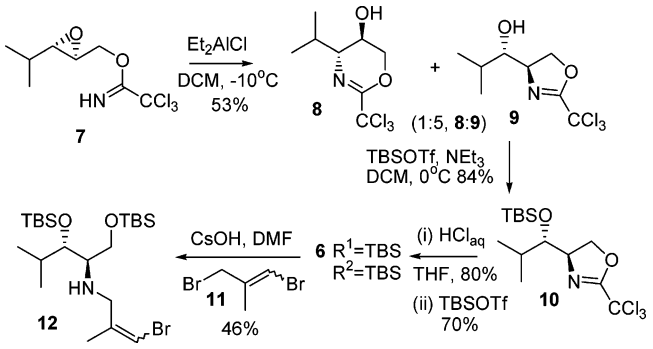
SCHEME 1. Retrosynthetic Analysis of (+)-Lactacystin



validity of our overall synthetic approach. Due to unexpected scale-up problems, however, accessing sufficient quantities of **3** with which to complete a new synthesis of **1** was difficult, so we chose to explore a modified route to the pyrrolinone. Fortunately, the second-generation route was successful, we were able to complete a total synthesis of omuralide **2**,[3f] and we now wish to give a full account of this synthesis and also to report an extension of this work that has resulted in a new total synthesis of (+)-lactacystin **1**.

SCHEME 2. Scale-up of Route Used during 2002 Formal Synthesis



Results and Discussion

The first challenge in our second-generation approach to **1** was to develop a reliable, efficient, and scalable route to the desired alkylidene carbene precursor **5** (Scheme 1). While the methods used during our first formal synthesis (Scheme 2)[3l] were adequate for providing small quantities of **5**, it became immediately obvious that simple scale-up of this chemistry would not provide a viable long-term option for securing multigram quantities of the key CH-insertion precursor. The first problem was that the initial intramolecular epoxide-opening reaction (**7** → **9**)[7] routinely afforded a 5:1 ratio of **9**/**8**, and the desired major isomer could only be separated from the undesired isomer **8** following extensive and tedious column chromatography. In addition to the poor regioselectivity, the overall isolated yield of the desired compound **9** varied considerably from batch to batch (70−45%). The second problem was that alkylation of the primary amine[8] (**6**, $R^1 = R^2 =$ TBS) with the allylic bromide **11** (3:1, *E*/*Z*)[9] was highly capricious (5−45% yield), and despite much effort, we were not able to optimize this reaction further. The highly hindered environment at the primary amine, created by the two neighboring TBS-protecting groups on **6** ($R_1 = R_2 =$ TBS) (Scheme 1), appear to retard the desired alkylation reaction, and we therefore decided to explore the use of an alternative protecting group strategy during our revised route.

Our second-generation route started from the known Sharpless epoxide **13** (Scheme 3),[10] which was ring-opened in a regioselective manner with azide using the recently reported conditions (NaN_3, $B(OMe)_3$, DMF, 50 °C) of Miyashita et al.[11] Under these conditions, the desired azide **14** was produced in good yield (75%) and good regioselectivity (C2/C3 opening, 14:1). The minor 1,2-diol that resulted from C3-opening was removed by treating the mixture with sodium periodate to give the pure 2-azido-1,3-diol **14** in 75% yield.

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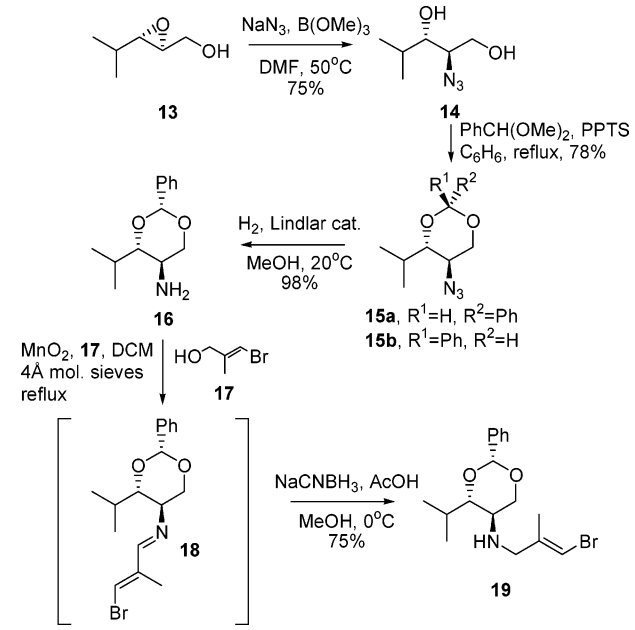
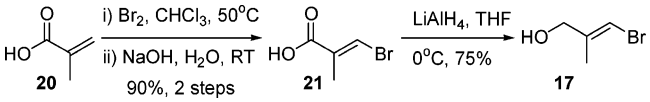
SCHEME 3. Second-Generation Route to Alkylidene Carbene Precursor 19



SCHEME 4. Stereoselective Synthesis of Vinyl Bromide 17



The next steps required were protection of the diol **14** and reduction of the resulting azide **15a**. Benzylidene acetal protection of the diol was chosen as it was hoped that tethering the diol away from the resulting amine would reduce steric hindrance and hence improve the yield of the subsequent *N*-alkylation. Thus, treatment of **14** with benzaldehyde dimethyl acetal in the presence of PPTS (6 mol %) in benzene with 4 Å molecular sieves at reflux gave **15a** and **15b** as a 2:1 mixture of isomers at the benzylic position. However, allowing the system to equilibrate to the thermodynamic product (**15a**) by not using molecular sieves increased this ratio to >25:1, and azide **15a** was isolated in 78% yield.

A few methods were found to reduce azide **15a** to the corresponding amine **16** (e.g., Ph_3P/H_2O; $ZnBH_4$), but the most reliable and convenient method was found to be catalytic hydrogenation. Exposure of **15a** to 10% Pd/C in MeOH gave the amine **16** in 77% yield, but it was evident from TLC and ^{1}H NMR of the crude material that a small amount of benzylidene acetal deprotection had occurred.[12] Instead, hydrogenation in the presence of Lindlar's catalyst in MeOH worked very cleanly to give the desired product **16** in near-quantitative yield.

As an alternative to the original *N*-alkylation (Scheme 1), we decided to explore the use of a reductive amination procedure for installation of the vinyl bromide-containing *N*-substituent as this would avoid the preparation of the reactive allylic bromide **11**. First, it was necessary to prepare 3-bromoprop-2-enal, and it was thought that the easiest route would be from allylic alcohol **17**. After some preliminary investigations, it was found that the alcohol **17** could be made in high yield as the pure *E*-isomer from methacrylic acid **20** in three steps in 68% overall yield (Scheme 4).[13]

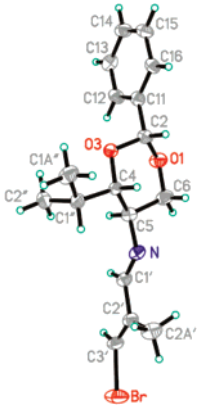


FIGURE 1. X-ray crystal structure of the imine **18**.

A few methods to convert the alcohol **17** to the aldehyde were examined (e.g., Dess−Martin periodane, TPAP/NMO),[14] but the best method found was oxidation with activated manganese dioxide.[15] However, the aldehyde decomposed quickly and needed to be used immediately. It was thought that the one-pot allylic alcohol oxidation, imine formation, and reduction procedure published by Taylor[16] was a promising method for this reductive amination. This method involved stirring an allylic or benzylic alcohol in DCM with manganese dioxide in the presence of an amine, 4 Å molecular sieves, and sodium borohydride. Although this procedure seemed perfect for our substrate, our initial attempts gave disappointing yields of vinyl bromide **19**. The ^{1}H NMR of the crude material showed that the imine **18** and the desired product **19** were present, but no alcohol **17** or the corresponding aldehyde remained. Obviously, oxidation of **17** and condensation with **16** had occurred efficiently, but reduction of the imine **18** was incomplete. Imine **18** could be isolated cleanly from the reaction of **16** and **17** with manganese dioxide as colorless crystals in 50% yield, and an X-ray crystal structure was obtained, thus confirming all regiochemical and stereochemical assignments (Figure 1).

In an attempt to optimize the one-pot oxidation/reductive amination procedure, purified imine **18** was reduced with various reducing agents. It was found that sodium triacetoxyborohydride was ineffective, and sodium borohydride, even in the presence of acetic acid, did not give a good conversion to the amine **19**. Fortunately, sodium cyanoborohydride in the presence of acetic acid (1 equiv) proved to be an excellent reagent combination, and this was adopted for the one pot procedure. It was important to add the acetic acid last as it hindered the oxidation of the alcohol if it was added at the start of the reaction, presumably by deactivating the manganese dioxide. Hydrolysis of the imine back to starting materials was observed if acetic acid was added before the reducing reagent. Using these modified reduction conditions, the vinyl bromide **19** was isolated in 75% yield as a single isomer from the one-pot reductive alkylation (Scheme 2).

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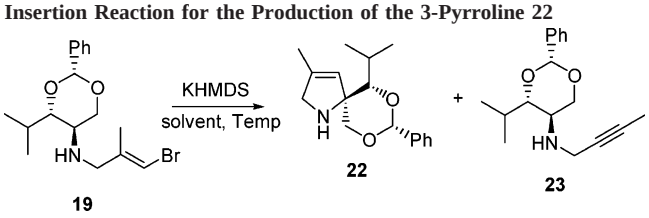
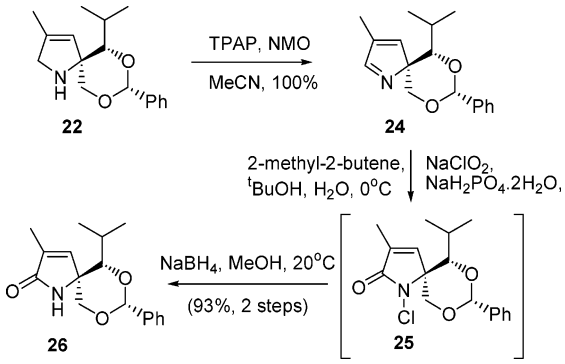
TABLE 1. Optimization of the Alkylidene Carbene 1,5-CH Insertion Reaction for the Production of the 3-Pyrroline 22



entry	solvent	T (°C)	% yield of **22**	% yield of **23**
1	Et_2O	23	54	26
2	THF	23	68	24
3	THF	−30	83	13

SCHEME 5. Oxidation of 3-Pyrroline 22 to 3-Pyrrolinone 26



With a convenient route to vinyl bromide **19** in hand, it was possible to investigate the key alkylidene carbene 1,5-CH insertion reaction in some detail. The KHMDS-mediated[17] α-elimination conditions used in our previous formal synthesis route (Table 1, entry 1) gave 3-pyrroline **22** and acetylene **23** in 54% and 26% isolated yields respectively. This was already an improvement on the yields obtained from insertion precursor **12** in our previous route.[3l] An extensive optimization study was carried out in order to increase the yield of the desired 3-pyrroline **22** and minimize the formation of the unwanted alkyne **23**, which resulted from a competitive 1,2-alkyl shift of the alkylidene carbene. A range of alternative solvents were examined (e.g., DME, toluene, DMF, THF), and it was found that THF gave the greatest improvement in isolated yield of **22** at room temperature (Table 1, entry 2). The best result, however, was obtained when the reaction was conducted in THF at −30 °C, giving **22** in 83% isolated yield and **23** in a much reduced 13% yield. This considerable improvement in the yield of **22** meant that we could routinely access enough material with which to complete the syntheses of **1** and **2**.

Having successfully developed a reliable route to the key 3-pyrroline **22**, our next task was to access the required 3-pyrrolinone (e.g., **3**, Scheme 1). Pleasingly, this could be achieved using our previously described procedure,[6] which involved conversion of **22** to the cyclic imine **24** using catalytic TPAP/NMO (100%) followed by treatment of **24** with a buffered solution of sodium chlorite (Scheme 5).

As we had observed in our earlier studies, the major product from the sodium chlorite oxidation was the *N*-chlorolactam **25** but this did not present any problems as the crude material could be treated with sodium borohydride during the workup to provide the desired 3-pyrrolin-2-one **26** in 93% yield over the two steps. The relative stereochemistry of **26** was determined by X-ray crystallography (Figure 2), and as the absolute stereochemistry could be traced back from the X-ray structure of imine **18**, we could show that the 1,5-CH insertion had taken place with retention of stereochemistry as expected.

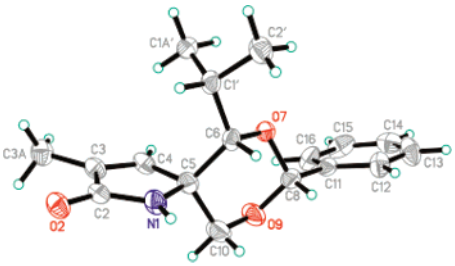
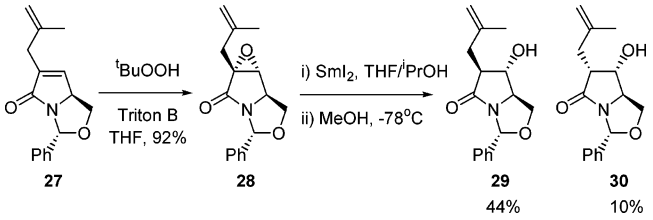
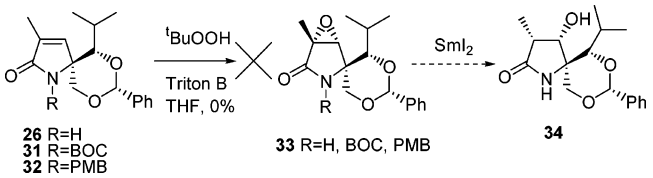


FIGURE 2. X-ray structure of 3-pyrrolinone **26**.

SCHEME 6. Jao and Bogen's Epoxidation of the Electron-Deficient Alkene of 27



SCHEME 7. Failed Epoxidation Attempt on Pyrrolinones



A number of methods appeared available for installing the C-6 alcohol, and the first to be examined was epoxidation followed by reductive epoxide opening. Precedent for this sequence was provided by Jao and Bogen, who had shown previously that the hydroxylactams **29** and **30** could be accessed from the pyrrolinone **27** using this approach (Scheme 6).[18] Unfortunately, however, the pyrrolinone **26**, and its protected versions **31** and **32**, failed to epoxidize under their conditions (^{t}BuOOH/Triton B, THF) and only recovered starting material was observed (Scheme 7). Further epoxidation reactions with *m*-CPBA,[19] DMDO, and ^{t}BuOOLi[20] were also attempted, but once again no epoxidation was observed.

Undeterred by the resistance of **26** to epoxidation, we were hopeful that dihydroxylation would be possible. Initially, **26** was exposed to the Upjohn conditions,[21] but this only resulted in a low conversion and a poor isolated yield of the desired diol **35**. During a search for more forcing conditions, we were struck by the recent work of the Sharpless group on the dihydroxylation

(17) (a) Taber, D. F.; Christos, T. E.; Neubert, T. D.; Batra, D. *J. Org. Chem.* **1999**, *64*, 9673.(b) Auty, J. M. A.; Churcher, I.; Hayes, C. J. *Synlett* **2004**, 1443.

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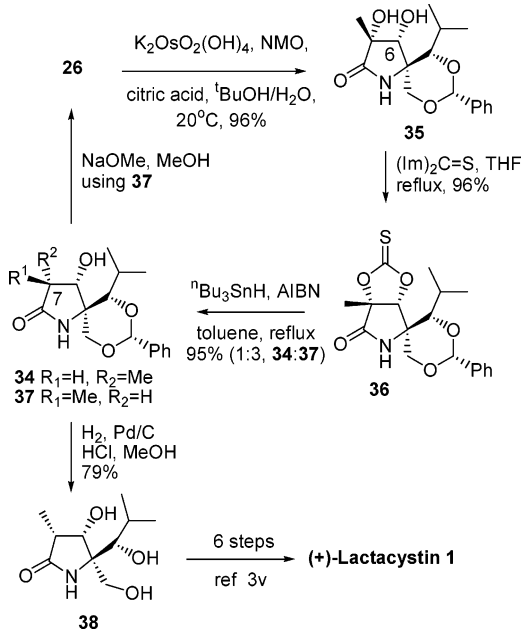
SCHEME 8. Formal Synthesis of (+)-Lactacystin via Dihydroxylation and Deoxygenation of 26



of difficult substrates, including α,β-unsaturated amides.[22] During these studies it was found that performing the Upjohn-style dihydroxylation in a slightly acidic medium (e.g., citric acid) gave much improved yields of diols from α,β-unsaturated amides and we decided to apply these conditions to our pyrrolinone **26**. Under these conditions **26** underwent efficient dihydroxylation and the diol **35** crystallized from the reaction mixture as a single diastereoisomer in 88% yield (Scheme 8). Furthermore, additional diol **35** could be isolated from the aqueous filtrate giving a combined overall yield of 96%. This dramatic improvement was a very pleasing result and we were able to obtain a single-crystal X-ray structure of **35** to confirm its relative stereochemistry (Figure 3).

As the desired stereochemistry at the C6-hydroxyl had been obtained during the dihydroxylation reaction, all that was required to complete functionalization of the lactam was deoxygenation at C7. This transformation was readily achieved by first treating **35** with thiocarbonyl diimidazole to produce the thiocarbonate **36**. Treatment of **36** with $^nBu_3SnH$ and AIBN in toluene using Baldwin's procedure[3v] then gave the deoxygenated products **34** and **37** as a 1:3 mixture, respectively, in 95% yield.

Attempted epimerization of the trans isomer **37** to the cis isomer **34** using Baldwin's previously described procedure

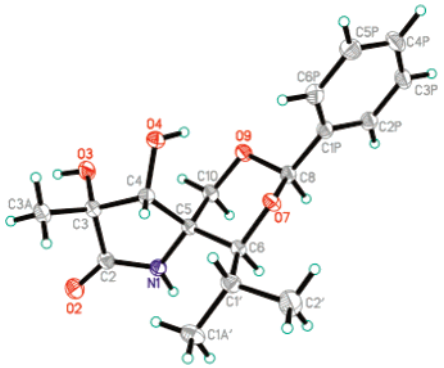
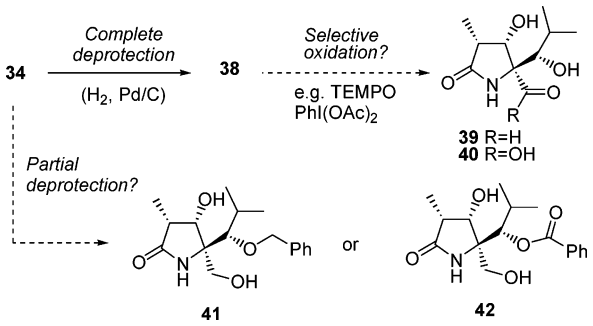


FIGURE 3. X-ray crystal structure of diol **35**.

SCHEME 9. Proposed Selective Oxidation of 38 and Partial Deprotection of 34



(NaOMe/MeOH) gave a slightly improved ratio of 1:2 (**34**/**37**), but no further improvements could be made to this equilibration as both extended reaction times and increased reaction temperatures led to the production of the pyrrolinone **26**, which represents the thermodynamic sink of the reaction. In order to avoid wasting precious material, the two isomers **34** and **37** were separated using reversed-phase HPLC, and the unwanted isomer **37** was recycled to **26** via based mediated elimination (NaOMe, MeOH) in quantitative yield. This material was then used in subsequent rounds of dihydroxylation and deoxygenation to produce more of the desired isomer **34**. Our stereochemical assignment of **34** was confirmed by removal of the benzylidene acetal (H_2, Pd/C, MeOH) to give the triol **38**, which was a known intermediate in Baldwin's earlier synthesis of lactacystin.[3v] Gratifyingly, our spectroscopic data for **38** were identical to that reported, and hence, we had completed our second formal synthesis of (+)-lactacystin. This new route to **38** proceeded in 11 synthetic steps from the known epoxide **13** in 26% overall yield, and six further steps are required to access (+)-lactacystin **1** (i.e., 17 steps in total). This route is considerably shorter (by 9 steps) than our previous formal synthesis, and it also compared well with Baldwin's original route to **38**, which was accomplished in 14 steps from (*R*)-glutamic acid.

Although we were delighted to have completed a synthesis of the triol **38**, we wished to move beyond this point and complete our own synthesis of (+)-lactacystin. A brief examination of the known six-step route required to convert **38** into **1** reveals that four of the six steps involve protecting group manipulations. It was hoped that a selective oxidation of the primary alcohol **38** to either the aldehyde **39** or the known carboxylic acid precursor to lactacystin **40** would remove the need for protecting groups on the secondary alcohols and hence reduce the number steps required to get to **1** (Scheme 9). A number of selective oxidations of **38** to **39** were attempted (e.g., Dess−Martin periodinane, TEMPO/$PhI(OAc)_2$),[23] but these reactions were unsuccessful due in large part to the highly polar nature and low organic solubility of **38**. The benzylidene acetal-protected lactams **34** and **37**, however, were soluble in a wide range of organic solvents, with the aromatic ring presumably playing a major role in the increased solubility. We therefore decided to explore a selective deprotection strategy for **34** which would lead to the formation of either the benzyl protected triol **41** by reductive cleavage or the benzoyl protected triol **42** by oxidative cleavage (Scheme 9).

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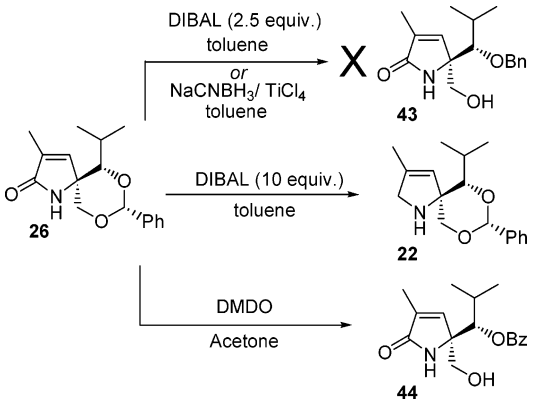
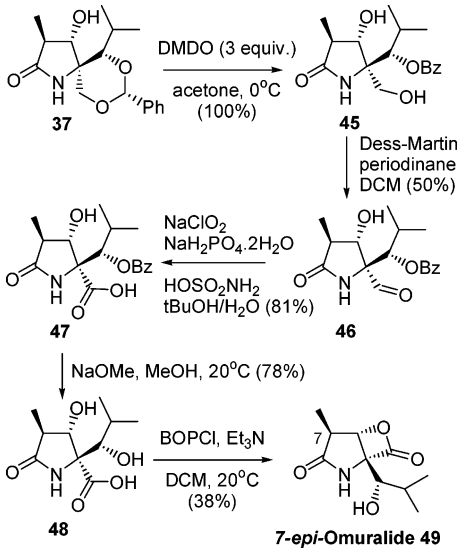
SCHEME 10. Exploratory Partial Deprotections of Benzylidene Acetal 26



Common examples of reductive cleavage use a reducing agent in combination with a Lewis acid, for example, $LiAlH_4/AlCl_3$,[24] $AlH_3/AlCl_3$, $NaCNBH_3/TiCl_4$,[25] and DIBAL.[26] Under these conditions, benzylidene acetals will usually cleave to reveal a primary alcohol and a secondary benzyl ether. Our early results using these reductive conditions on 3-pyrrolin-2-one **26** were not promising (Scheme 10). No reaction occurred when **26** was treated with DIBAL (2.5 equiv), and when the number of equivalents was increased (10 equiv) only reduction to the 3-pyrroline **22** was observed. Based on these preliminary results, it was felt that the reductive cleavage approach was not appropriate for lactam **34** and that an alternative oxidative approach might be more fruitful.

There are numerous methods for performing oxidative cleavage of benzylidene acetals. These include NBS,[27] ozone,[28] ^tBuOOH with Pd(II),[29] Cu(II),[30] PDC,[31] or hypervalent iodine species,[32] $KMnO_4$ and phase transfer catalyst,[33] Oxone,[34] bipyridinium chlorochromate/*m*-CPBA,[35] $NaBrO_3/Na_2S_2O_4$,[36] and O_2/Co(II).[37] Unfortunately, none of these methods are particularly well suited to our needs as they either produce unwanted functionality (i.e., alkyl bromides when NBS is used) or the wrong regiochemistry (i.e., production of primary benzoates in the case of bipyridinium chlorochromate/*m*-CPBA). During our earlier epoxidation studies on **26**, we observed that DMDO oxidized the benzylidene acetal to give the secondary benzoate ester **44** as the major new product.[38] At the time, this was an unwanted and unexpected outcome, but if this same oxidation could be performed on the acetal **34** then it could be exploited in our new synthesis of (+)-lactacystin **1**. In order to conserve our supply of **34**, we decided to perform the initial exploratory experiments on its C7-epimer **37**.

SCHEME 11. Total Synthesis of 7-*epi*-Omuralide 49



We were pleased to find that upon treatment with an excess of DMDO (0.06 M, 3 equiv), the benzylidene acetal **37** gave the corresponding secondary benzoate ester **45** as the only isolable product (Scheme 11). Presumably, this reaction involves oxidative CH-insertion into the benzylidene acetal methine to produce a hemi-orthoester intermediate, which then collapses to afford the benzoate ester and the primary hydroxyl in a subsequent step. The origin of the high degree of selectivity for the formation of the secondary, rather than the primary, benzoate ester is not yet clear, and further work in our laboratory is being directed to understanding the course of this reaction. The selective oxidation of **45** with Dess−Martin periodinane was successful, and aldehyde **46** was isolated in good yield. Although the aldehyde was often clean enough to take onto the next step, it was better to carry out column chromatography prior to the next reaction as the subsequent products required little or no chromatography and it was best to remove minor impurities at this stage. Aldehyde **46** was cleanly converted into the acid **47** in 81% yield by the use of sodium chlorite under buffered conditions. Treatment of the acid **47** with a dilute solution of sodium methoxide in methanol (0.1 M) for 3 days gave the dihydroxy acid **48** in good yield. Using the procedure developed by Corey, the acid **48** was finally converted into 7-*epi*-omuralide **49**.[39]

Having successfully developed a synthesis of 7-*epi*-omuralide **49** from the benzylidene acetal **37**, attention was turned to repeating the same chemical steps on acetal **34** in order to complete total syntheses of omuralide **2** and (+)-lactacystin **1**.

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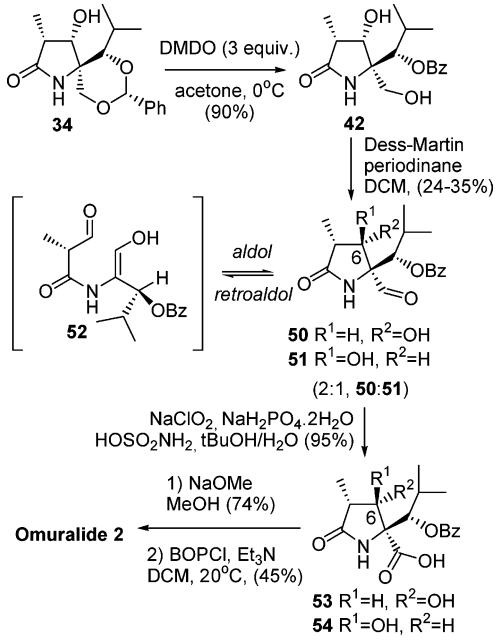
SCHEME 12. Total Synthesis of Omuralide 2 Using First-Generation Endgame

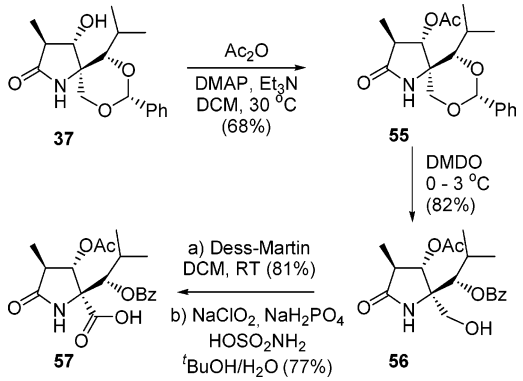


These studies began well, with the acetal **34** being cleanly oxidized to the secondary benzoate **42** using DMDO. Unfortunately, however, treatment of **42** with Dess−Martin periodinane only afforded a low yield (35%) of the corresponding aldehyde. Furthermore, the aldehyde was formed as an inseparable 2:1 mixture of diastereoisomers **50** and **51**. The unwanted C6-epimer **51** most likely forms via a retroaldol/aldol sequence (via **52** or equivalent charged species). As it was particularly difficult to purify this mixture of aldehydes by column chromatography, the 2:1 mixture was oxidized with buffered sodium chlorite to give the acids **53** and **54** in excellent yield (95%) in the same 2:1 ratio of α/*β* C6-epimers. The resulting mixture of acids was treated with sodium methoxide for several days to give dihydroxy acid **40** (2:1 ratio of C6-epimers). Pleasingly, the ^{1}H NMR and ^{13}C NMR spectra of the major epimer matched that previously reported for the dihydroxy acid **40**.[3s] The 2:1 mixture of C6-epimers was then treated with BOPCl under Corey's conditions, and the major α-C6-epimer cyclized to afford omuralide **2** (45%) (Scheme 12). The minor *β*-C6-epimer of **40** is unable to form a *β*-lactone structure as its C6-hydroxyl and C5-carboxylic acid are in a trans arrangement, and this material could be separated at this stage.

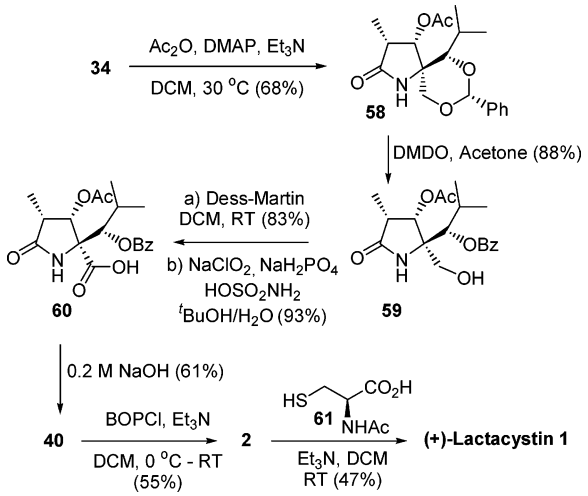
Having achieved our first objective of synthesizing omuralide **2**, we were very keen to go one step further and complete a total synthesis of (+)-lactacystin **1**. In order to provide material for this task, a more efficient endgame from **34** had to be sought. We reasoned that protection of the C6-secondary alcohol would both increase the yield of the Dess−Martin oxidation of **42** and also prevent the unwanted retroaldol reaction of **50**. An acetate protecting group was chosen as it could be introduced with ease, and more importantly, it could be removed under the same conditions that were already going to be used to remove the benzoate later in the synthesis. This protection adds one extra step to the synthesis, but the potential increase in overall yield should provide adequate compensation for this effort.

The lactam **37** was once again selected as a model system with which to test the reaction conditions (Scheme 13). Thus, exposure of **37** to Ac_2O, DMAP, and Et_3N in DCM gave the

SCHEME 13. Model Study for Revised C6-Protection/Oxidation Endgame



SCHEME 14. Completion of the Total Synthesis of (+)-Lactacystin 1



acetate **55** in reasonable yield and gratifyingly the DMDO-mediated acetal cleavage proceed smoothly to give alcohol **56** in excellent yield. Sequential oxidation with Dess−Martin periodinane (81%) and then sodium chlorite gave the desired acid **57** (77%) in good overall yield.

Having gained confidence in the revised protecting group strategy, **34** was acetylated to give **58**, and DMDO oxidation of this material proceeded cleanly to give the primary alcohol **59** in excellent yield (88%). Sequential Dess−Martin periodinane and sodium chlorite oxidations then gave the desired carboxylic acid **60** in excellent yield and purity. Hydrolysis of **60** (0.2 M NaOH, 2 days) then gave the known dihydroxy acid **40** as a single diastereoisomer, and gratifyingly, the spectroscopic data matched that previously reported.[3s] Treatment of **40** with BOPCl then gave omuralide **2** (55%), and opening of this *β*-lactone with *N*-acetyl-L-cysteine **61** according to Corey's procedure finally gave (+)-lactacystin **1** in 47% yield (Scheme 14).

In conclusion, we have successfully completed an enantioselective total synthesis of (+)-lactacystin **1** in 16 steps using an alkylidene carbene 1,5-CH insertion reaction to install the key quaternary stereogenic center in high yield. Our route can readily be adapted to provide analogues of lactacystin and omuralide that have different sidechains at C7 and C5. We are currently examining synthetic approaches to the salinosporamide family of related natural products, and progress in this area will be published in due course. During our synthesis, we have also

shown that a regioselective DMDO-mediated oxidative cleavage of a benzylidene acetal can be used to provide differentially protected diol products. This transformation warrants further study, and we hope to develop it into a general synthetic tool.

Experimental Section

((*E*)-3-Bromo-2-methylallyl)-((2*R*,4*R*,5*R*)-4-isopropyl-2-phenyl-[1,3]-dioxan-5-yl)amine (19). A solution of alcohol **17** (3.79 g, 24.9 mmol) in DCM (100 mL) was added via cannula to a stirring supension of MnO_2 (22.0 g, 247 mmol) and powdered activated 3 Å molecular sieves (5.0 g) in DCM (50 mL) at room temperature under Ar. This was followed by addition of a solution of amine **16** (6.0 g, 27 mmol) in DCM (100 mL) via cannula. The reaction mixture was heated to reflux for 50 h and then cooled to 0 °C. Sodium cyanoborohydride (4.71 g 74.9 mmol) in MeOH (50 mL) was added via cannula over 30 min at 0 °C and then allowed to reach room temperature, upon which acetic acid (1.50 mL, 24.7 mmol) was added. The mixture was stirred for 6 h and was then filtered through Celite. The filtrate was concentrated in vacuo to give a yellow solid. The solid was partitioned between Et_2O (200 mL) and a saturated aqueous solution of Na_2CO_3 (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 200 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, and concentrated in vacuo to give a yellow solid. The crude material was purified by column chromatography using petroleum ether/Et_2O (2:1) to give *vinyl bromide* **19** (6.57 g, 18.6 mmol, 75%) as colorless crystals. A small portion was further purified by recrystallization from petroleum ether for analysis: mp 55−56 °C (petroleum ether); $[\alpha]^{26}_D$ −56.0 (*c* 0.51 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 2964, 1099; δ_H (400 MHz; $CDCl_3$) 7.51−7.48 (2H, m), 7.40−7. 34 (3H, m), 6.17 (1H, *J* 1.2), 5.46 (1H, s), 4.37 (1H, dd, *J* 10.6 and 4.8), 3.44 (1H, app t, *J* 10.6), 3.36 (1H, dd, *J* 9.6 and 2.0), 3.32 (1H, d, *J* 13.8), 3.26 (1H, d, *J* 13.8), 2.80 (1H, app td, *J* 10.0 and 4.8), 2.19 (1H, qqd, *J* 7.0, 6.9 and 2.0), 1.84 (3H, d, *J* 1.2), 1.09 (3H, d, *J* 7.0), 1.00 (3H, d, *J* 6.9); δ_C (100 MHz; $CDCl_3$) 140.6 (C) 138.7 (C), 128.8 (CH), 128.3 (CH), 126.2 (CH), 104.2 (CH), 101.0 (CH), 85.7 (CH), 71.5 (CH_2), 53.8 (CH_2), 51.1 (CH), 28.0 (CH), 20.2 (CH_3), 17.9 (CH_3), 15.5 (CH_3); *m*/*z* (CI, NH_3) 356 (M + H^+, 60), 354 (M + H^+, 61), 248 (M + H^+ − PhCHO, 13); $C_{17}H_{25}{}^{81}BrNO_2$ requires 356.1048, found 356.1044; $C_{17}H_{25}{}^{79}BrNO_2$ requires 354.1069, found 354.1062. Anal. Calcd for $C_{17}H_{24}BrNO_2$: C, 57.63; H, 6.83; N, 3.95. Found: C, 57.60; H, 6.84; N, 3.96.

[(*E*)-3-Bromo-2-methylprop-2-en-(*E*)-ylidene]-(2*R*,4*S*,5*R*)-4-isopropyl-2-phenyl-[1,3]-dioxan-5-yl)amine (18). A solution of amine **16** (500 mg, 2.26 mmol) in DCM (10 mL) was added via cannula to a stirring suspension of MnO_2 (1.96 g, 22.5 mmol) and 3 Å molecular sieves (300 mg) in DCM (30 mL) at room temperature under Ar, followed by a solution of alcohol **17** (330 mg, 2.2 mmol) in DCM (10 mL). The reaction mixture was heated to reflux for 18 h and then cooled to room temperature, filtered through Celite, and washed with DCM (50 mL). The organic solvents were removed in vacuo to give a pale yellow solid. The crude material was recrystallized from petroleum ether to give *imine* **18** (0.43 g, 56%) as a colorless crystalline solid, from which an X-ray crystal structure was obtained (see Figure 1): mp 79−80 °C (petroleum ether); $[\alpha]^{30}_D$ −79.3 (*c* 0.91 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 2965, 1627 (C═N); δ_H (400 MHz; $CDCl_3$) 7.96 (1H, s), 7.54 − 7.52 (2H, m), 7.41 − 7.33 (3H, m), 6.80 (1H, d, *J* 1.2), 5.60 (1H, s), 3.96 (1H, d, *J* 6.3), 3.95 (1H, d, *J* 9.1), 3.88 (1H, dd, *J* 9.4 and 2.5), 3.46 (1H, app td, *J* 9.1 and 6.5), 2.00 (3H, d, *J* 1.2) 1.77 (1H, app septd, *J* 6.9 and 2.5), 1.05 (3H, d, *J* 6.9), 0.93 (3H, d, *J* 6.9); δ_C (100 MHz; $CDCl_3$) 162.9 (CH), 142.1 (C), 138.7 (C), 128.9 (CH), 128.3 (CH), 126.2 (CH), 120.5 (CH), 101.1 (CH), 84.3 (CH), 71.0 (CH_2), 65.4 (CH), 28.8 (CH), 19.9 (CH_3), 15.4 (CH_3), 14.7 (CH_3); *m*/*z* (CI) 352 (M + H^+, 51), 354 (M + H^+, 44); $C_{17}H_{23}{}^{79}BrNO_2$ requires 352.0912, found 352.0901. Anal. Calcd for $C_{17}H_{22}BrNO_2$: C, 57.96; H, 6.29; N, 3.98. Found: C, 57.96; H, 6.29; N, 3.99.

(5*R*,6*S*,8*R*)-6-Isopropyl-3-methyl-8-phenyl-7,9-dioxa-1-azaspiro-[4.5]dec-3-ene (22) and But-2-ynyl(2*R*,4*S*,5*R*)-4-isopropyl-2-phenyl-[1,3]-dioxan-5-yl)amine (23). KHMDS (0.5 M in toluene, 57.0 mL, 28.5 mmol) was added dropwise over 30 min to a stirring solution of vinyl bromide **19** (5.00 g, 14.2 mmol) in THF (80 mL) at −30 °C. The red solution was allowed to reach room temperature over 6 h and then quenched with a saturated aqueous solution of Na_2CO_3 (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, and concentrated in vacuo to give a yellow oil. The crude material was purified by column chromatography using a pentane and EtOAc (6:1) with 1% Et_3N to give *acetylene* **23** (0.51 g, 13%) as a colorless oil, and the polarity was increased to pentane and EtOAc (2:1) to give *3-pyrroline* **22** (3.20 g, 83%) as a colorless oil: 3-Pyrroline **22**: $[\alpha]^{26}_D$ −8.47 (*c* 0.938 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 2960, 2840, 1666, 1382, 1096; δ_H (400 MHz; $CDCl_3$) 7.5 −7.51 (2H, m), 7.41−7.32 (3H, m), 5.82 (1H, m), 5.53 (1H, s), 3.90 (1H, d, *J* 10.4), 3.73 (1H, dq, *J* 15.1 and 1.0), 3.67 (1H, dq, *J* 15.1 and 1.0), 3.65 (1H, d, *J* 10.4), 3.39 (1H, d, *J* 4.4), 1.95 (1H, qqd, *J* 6.9, 6.8 and 4.4), 1.77 (3H, m), 1.45 (1H, br, s), 1.06 (3H, d, *J* 6.9), 1.01 (3H, d, *J* 6.7); δ_C (100 MHz; $CDCl_3$) 138.9 (C), 137.2 (C), 128.7 (C), 128.3 (CH), 126.2 (CH), 125.4 (CH), 101.4 (CH), 89.2 (CH), 78.1 (CH_2), 68.8 (C), 56.9 (CH_2), 29.1 (CH), 22.0 (CH_3), 18.5 (CH_3), 14.3 (CH_3); *m*/*z* (ES, +ve) 274 (M + H^+, 100), 168 (M + H^+ − PhCHO, 80); $C_{17}H_{25}NO_2$ requires 274.1807, found 274.1805. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.51; H, 8.50; N, 4.82. Acetylene **23**: $[\alpha]^{26}_D$ −56.3 (*c* 1.05 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 2965, 2923, 2877, 1679, 1306, 1099; δ_H (400 MHz; $CDCl_3$) 7.53−7.50 (2H, m), 7.40−7.32 (3H, m), 5.47 (1H, s), 4.45 (1H, dd, *J* 10.7 and 4.8), 3.39 (1H, dd, *J* 10.7 and 10.0), 3.46 − 3.35 (3H, m), 3.05 (1H, app td, *J* 10.0 and 4.8), 2.18 (1H, qqd, *J* 6.9, 6.8 and 2.0), 1.83 (3H, s), 1.10 (3H, d, *J* 6.9), 1.05 (3H, d, *J* 6.8); δ_C (100 MHz; $CDCl_3$) 138.7 (C), 128.7 (CH), 128.2 (CH), 126.1 (CH), 100.9 (CH), 85.3 (CH), 79.5 (C), 71.0 (CH_2), 50.7 (CH), 36.8 (CH_2), 27.8 (CH), 20.1 (CH_3), 15.2 (CH_3), 3.5 (CH_3); *m*/*z* (ES, +ve) 274 (M + H^+, 16), 168 (M + H^+ − PhCHO, 100); $C_{17}H_{25}NO_2$ requires 274.1807, found 274.1821. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.67; H, 8.53; N, 5.09.

(5*R*,6*S*,8*R*)-6-Isopropyl-3-methyl-8-phenyl-7,9-dioxa-1-azaspiro-[4.5]dec-3-en-2-one (26). A suspension of 3-pyrroline **22** (1.33 g, 4.87 mmol), TPAP (85.6 mg, 0.243 mmol), NMO (2.11 g, 18.0 mmol), and powdered 4 Å molecular sieves (625 mg) in MeCN (16 mL) was stirred at room temperature for 4 h. The suspension was filtered through Celite and then silica and eluted with EtOAc to give *imine* **24** (1.32 g, 100%) as a black oil: $[\alpha]^{21}_D$ +4.1 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} ($CHCl_3$) 2865, 1351, 1082, 975; δ_H (400 MHz; $CDCl_3$) 7.99 (1H, s), 7.59−7.55 (2H, m), 7.47 (1H, s), 7.47−7.35 (3H, m), 5.72 (1H, s), 4,48 (1H, d, *J* 10.5), 4.28 (1H, d, *J* 4.9), 3.28 (1H, d, *J* 10.5), 2.05 (3H, s), 1.48−1.37 (1H, qqd, *J* 6.8, 6.7 and 4.9), 0.86 (3H, d, *J* 6.7), 0.81 (3H, d, *J* 6.8); δ_C (400 MHz; $CDCl_3$) 169.4 (C), 150.8 (CH), 138.4 (C), 137.8 (C), 128.9 (CH), 128.3 (CH), 126.2 (CH), 102.0 (CH), 86.4 (CH), 84.0 (C), 74.2 (CH_2), 29.7 (CH), 21.1 (CH_3), 19.2 (CH_3), 12.1 (CH_3). A solution of sodium chlorite (1.38 g, 12.3 mmol) and sodium dihydrogen orthophosphate hydrate (1.53 g, 9.80 mmol) in water (12 mL) was added dropwise to a stirring solution of imine **24** (1.32 g, 4.87 mmol) in *tert*-butyl alcohol (12 mL) and 2-methyl-2-butene (10 mL) at 0 °C. The solution was stirred for 18 h and then concentrated in vacuo. The product was partitioned between water (50 mL) and Et_2O (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo to give a colorless solid. The crude material was dissolved in MeOH (48 mL), and sodium borohydride (370 mg, 9.80 mmol) was added slowly. The solution was stirred for 1 h and then

concentrated in vacuo to give a colorless solid. The product was partitioned between water (50 mL) and Et_2O (50 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined layers were dried over $MgSO_4$ and concentrated in vacuo to give a colorless solid. The crude material was purified by column chromatography using petroleum ether and EtOAc (1:1) to give *3-pyrrolinone* **26** (1.31 g, 93%) as a colorless crystalline solid. The solid was recrystallized from EtOH, and an X-ray crystal structure was obtained (see Figure 2): mp 157−159 °C (EtOH); $[\alpha]^{25}_D$ −30.2 (*c* 1.00 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 2966, 1649 (C═O), 1099; δ_H (400 MHz; $CDCl_3$) 7.86 (1H, br, s), 7.54−7.51 (2H, m), 7.43−7.51 (3H, m), 7.26 (1H, s), 5.61 (1H, s), 4.09 (1H, d, *J* 10.9), 3.81 (1H, d, *J* 5.6), 3.79 (1H, d, *J* 10.9), 1.93 (3H, s), 1.80−1.68 (1H, qqd, *J* 6.8, 6.7 and 5.6), 0.94 (3H, d, *J* 6.7), 0.93 (3H, d, *J* 6.8); δ_C (400 MHz; $CDCl_3$) 174.7 (C), 144.5 (C), 137.8 (C), 134.7 (C), 129.1 (CH), 128.3 (CH), 126.1 (CH), 101.7 (CH), 86.3 (CH), 74.3 (CH_2), 61.3 (C), 28.9 (CH), 21.2 (CH_3), 19.0 (CH_3), 10.9 (CH_3); *m*/*z* (ES, +ve) 288 (M + H^+, 100); $C_{17}H_{22}NO_3$ requires 288.1600, found 288.1591. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.85; H, 7.23; N, 5.01.

(3*R*,4*R*,5*S*,6*S*,8*R*)-3,4-Dihydroxy-6-isopropyl-3-methyl-8-phenyl-7,9-dioxa-1-azaspiro[4.5]decan-2-one (35). Citric acid (597 mg, 2.84 mmol), potassium osmate dihydrate (103 mg, 0.280 mmol), and NMO (367 mg, 3.12 mmol) were added successively to a suspension of 3-pyrrolinone **26** (816 mg, 2.84 mmol) in *tert*-butyl alcohol (2.8 mL) and water (2.8 mL) at room temperature. The resulting olive green solution was stirred for 48 h. The product precipitated out of solution and was filtered and washed with water (50 mL) to give pure *diol* **35** (523 mg) as a colorless powder. The filtrate was treated with solid sodium sulfite and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo to give diol (110 mg) as a single diastereoisomer. The products were combined to give *diol* **35** (878 mg, 96%) as a colorless powder. A small sample was recrystallized from EtOH, and an X-ray crystal structure was obtained (see Figure 3): mp 228−230 °C (^{t}BuOH/H_2O); $[\alpha]^{23}_D$ −32.0 (*c* 0.513 in MeOH); ν_{max}/cm^{-1}(solid) 3428, 3306, 1703 (C═O); δ_H (400 MHz; CD_3OD) 7.51−7.49 (2H, m), 7.38−7.33 (3H, m), 5.53 (1H, s), 4.64 (1H, d, *J* 11.5), 4.24 (1H, s), 3.66 (1H, d, *J* 11.5), 3.53 (1H, d, *J* 8.0), 2.10−2.03 (1H, dqq, *J* 8.0, 6.8 and 6.5), 1.36 (3H, s), 1.11 (3H, d, *J* 6.5), 0.96 (3H, d, *J* 6.8); δ_C (400 MHz; CD_3OD) 177.3 (C), 139.7 (C), 129.8 (CH), 129.0 (CH), 127.4 (CH), 102.7 (CH), 87.4 (CH), 74.9 (C), 74.4 (CH), 72.7 (CH_2), 57.9 (C), 30.2 (CH), 22.4 (CH_3), 21.0 (CH_3), 20.7 (CH_3); *m*/*z* (ES, +ve) 322 (M + H^+,100); $C_{17}H_{24}NO_5$ requires 322.1654, found 322.1657. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.22; H, 7.46; N, 4.12.

(3*R*,4*R*,5*S*,6*S*,8*R*)-6-Isopropyl-3-methyl-8-phenyl-7,9,11,13-tetraoxa-12-thiocarbonyl-1-azaspiro[4.5]decan-2-one (36). A yellow solution of diol **35** (587 mg, 1.83 mmol) and thiocarbonyl diimidazole (814 mg, 2.74 mmol) in THF (9 mL) was heated to reflux for 6 h. The solution was cooled to room temperature and concentrated in vacuo to give a brown oil. The residue was purified by column chromatography using petroleum ether and EtOAc (1:2) to give *thiocarbonate* **36** (637 mg, 96%) as a colorless foam: mp 176−179 °C; $[\alpha]^{28}_D$ +60.6 (*c* 0.500 in $CHCl_3$); ν_{max}/cm^{-1} 3404, 3198, 2968, 1726 (C═O), 1314 (C═S); δ_H (400 MHz; $CDCl_3$) 7.85 (1H, br, s), 7.52−7.48 (2H, m), 7.42−7.38 (3H, m), 5.60 (1H, s), 5.30 (1H, s), 4.26 (1H, d, *J* 11.5), 3.80 (1H, d, *J* 11.5), 3.59 (1H, d, *J* 8.4), 1.79 (3H, s), 1.76−1.69 (1H, dqq, *J* 8.4, 6.6 and 6.5), 1.10 (3H, d, *J* 6.5), 0.99 (3H, d, *J* 6.6); δ_c (100 MHz; $CDCl_3$) 188.5 (C), 170.2 (C), 137.0 (C), 129.4 (CH), 128.4 (CH), 126.2 (CH), 102.0 (CH), 88.7 (C), 86.5 (CH), 85.1 (CH), 70.7 (CH_2), 60.1 (C), 28.7 (CH), 21.6 (CH_3), 19.9 (CH_3), 18.3 (CH_3); *m*/*z* (ES, +ve) 386 (M + Na^+, 100), 364 (M + H^+, 42); $C_{18}H_{22}NO_5S$ requires 364.1219, found 364.1223.

(3*S*,4*R*,5*S*,6*S*,8*R*)-4-Hydroxy-6-isopropyl-3-methyl-8-phenyl-7,9-dioxa-1-azaspiro[4.5]decan-2-one (37) and (3*R*,4*R*,5*S*,6*S*,8*R*)-4-Hydroxy-6-isopropyl-3-methyl-8-phenyl-7,9-dioxa-1-azaspiro-[4.5]decan-2-one (34). A degassed solution of AIBN (57 mg, 0.37 mmol) in toluene (50 mL) was added in two portions over 2 h to a degassed solution of thiocarbonate **36** (1.05 g, 2.89 mmol) and ^{n}Bu_3SnH (1.3 mL, 5.78 mmol) in toluene (90 mL). The solution was reluxed for 16 h and cooled to room temperature. The colorless solution was treated with a 10% aqueous solution of KF (30 mL) and a saturated aqueous solution of $NaHCO_3$ (30 mL). The layers were separated, and the extraction was repeated. The combined aqueous layers was extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo to give a colorless oil. The crude material was purified by column chromatography using petroleum ether and EtOAc (1:1) to give a *lactams* **34** and **37** (839 mg, 95%) as a mixture of isomers (cis/trans, 1:3.6). The epimers were separated by reversed-phase HPLC using MeOH and water (65:35) to give *trans-lactam* **37** and *cis-lactam* **34** as colorless solids. *trans*-Lactam **37**: mp 63−66 °C (DCM); $[\alpha]_D^{27}$ −57.2 (*c* 0.870 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3564, 3484, 2966, 1704 (C═O), 1101; δ_H (500 MHz; $CDCl_3$) 7.48−7.45 (2H, m), 7.42−7.37 (3H, m), 7.35 (1H, br, s), 4.46 (1H, d, *J* 11.4), 4.40 (1H, d, *J* 7.3), 3.71 (1H, d, *J* 11.4), 3.53 (1H, d, *J* 8.3), 3.09 (1H, br, s), 2.66 (1H, app quin *J* 7.3), 2.08 (1H, dqq, *J* 8.3, 6.8 and 6.6), 1.34 (3H, d, *J* 7.3), 1.13 (3H, d, *J* 6.6), 0.95 (3H, d, *J* 6.8); δ_c (126 MHz; $CDCl_3$) 177.7 (C), 137.4 (C), 129.3 (CH, ArH), 128.5 (CH), 126.0 (CH), 101.5 (CH), 87.1 (CH), 76.0 (CH), 71.6 (CH_2), 57.3 (C), 44.1 (CH), 29.0 (CH), 20.8 (CH_3), 20.3 (CH_3), 13.7 (CH_3); *m*/*z* (ES, +ve) 328 (M + Na^+, 26), 306 (M + H^+, 100); $C_{17}H_{24}NO_4$ requires 306.1705, found 306.1710). *cis*-Lactam **34**: $[\alpha]^{30}_D$ −37.6 (*c* 0.585 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3590, 3418, 2964, 1705 (C═O), 1097; δ_H (500 MHz; $CDCl_3$) 7.49−7.47 (2H, m), 7.42−7.37 (3H, m), 6.23 (1H, br, s), 5.56 (1H, s), 4.72 (1H, d, *J* 7.6), 4.45 (1H, d, *J* 11.0), 3.67 (1H, d, *J* 11.0), 3.47 (1H, d, *J* 7.9), 2.72 (1H, dq, *J* 7.6 and 7.5), 2.46 (1H, br, s), 1.95 (1H, dqq, *J* 7.9, 6.6 and 6.6), 1.27 (3H, d, *J* 7.5), 1.07 (3H, d, *J* 6.6), 1.01 (3H, d, *J* 6.6); δ_c (126 MHz; $CDCl_3$) 179.1 (C), 137.6 (C), 129.3 (CH), 128.5 (CH), 126.0 (CH), 101.7 (CH), 87.9 (CH), 71.9 (CH_2), 69.5 (CH), 60.6 (C), 41.7 (CH), 29.0 (CH), 21.8 (CH_3), 20.0 (CH_3), 9.1 (CH_3); *m*/*z* (ES, +ve) 328 (M + Na^+, 75), 306 (M + H^+, 100); $C_{17}H_{24}NO_4$ requires 306.1705, found 306.1720. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.70; H, 7.66; N, 4.49.

(3*R*,4*S*,5*R*,1′*S*)-4-Hydroxy-5-hydroxymethyl-5-(1′-hydroxy-2-methylpropyl)-3-methylpyrrolidin-2-one (38).[3v] A suspension of lactam **34** (2.3 mg, 7.5 μmol), Pd (10% on C, 2.9 mg), and concentrated HCl (15 μL) in MeOH (1.2 mL) was stirred under a H_2 atmosphere at room temperature for 17 h. Solid $NaHCO_3$ (31 mg) was added, and the suspension was filtered through a pad of Celite and washed with MeOH (50 mL). The filtrate was concentrated in vacuo to give a colorless solid. The crude material was purified by column chromatography using $CHCl_3$ and MeOH (4:1) to give triol **38** (1.3 mg, 79%): $[\alpha]^{22}_D$ −9.7 (*c* 1.0 in MeOH) (lit.[3v] $[\alpha]^{22}_D$ −9.7 (*c* 1.0 in MeOH)); ν_{max}/cm^{-1} (film) 3358, 2962, 1673 (C═O); δ_H (270 MHz; CD_3OD) 4.40 (1H, d, *J* 7.6), 3.78 (2H, s), 3.51 (1H, d, *J* 3.4), 2.81 (1H, app quin, *J* 7.6), 2.01−1.90 (1H, qqd, *J* 6.9, 6.7 and 3.4), 1.10 (3H, d, *J* 7.6), 1.03 (3H, d, *J* 6.9), 0.95 (3H, d, *J* 6.7); δ_C (67 MHz; CD_3OD) 181.7 (C), 79.0 (CH), 74.4 (CH), 70.0 (C), 68.3 (CH_2), 42.7 (CH), 30.6 (CH), 22.7 (CH_3), 17.6 (CH_3), 9.5 (CH_3); *m*/*z* (ES, +ve) 218 (M + H^+, 100). The data were identical to that reported by Baldwin.[3v]

(3*S*,4*S*,5*R*,6*S*)-6-Isopropyl-3-methyl-2-oxo-8-phenyl-7,9-dioxa-1-azaspiro[4.5]dec-4-yl Acetate (58). Acetic anhydride (15 μL, 0.16 mmol) was added to a stirring solution of lactam **34** (33.0 mg, 0.108 mmol), DMAP (1.3 mg, 0.010 mmol), and triethylamine (23 μL, 0.17 mmol) in DCM (1 mL) under Ar at 30 °C. The solution was stirred for 1 h and then diluted with DCM (2 mL). HCl (2 M, 3 mL) was added, and the layers were separated. The aqueous layer was extracted with DCM (3 × 3 mL). The organic layers were combined, washed with a saturated aqueous solution of $NaHCO_3$ (3 mL) and brine (3 mL), dried over $MgSO_4$, and concentrated in

vacuo to give a colorless solid. The crude material was purified by column chromatography using petroleum ether and EtOAc (1:2) to give *acetate* **58** (25.3 mg, 68%) as a colorless foam: mp 60−62 °C ($CHCl_3$); $[\alpha]^{25}_D$ +3.8 (*c* 0.64 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3420 (N−H), 3210, 2912, 1744 (s) (C═O), 1704 (s) (C═O); δ_H (500 MHz; $CDCl_3$) 7.43−7.35 (5H, m), 6.01 (1H, d, *J* 7.5), 5.46 (1H, s), 4.34 (1H, d, *J* 11.1), 3.66 (1H, d, *J* 11.1), 3.42 (1H, d, *J* 7.6), 2.81 (1H, dq, *J* 7.5 and 7.4), 1.95 (1H, dqq, *J* 7.6, 6.6 and 6.5), 1.95 (3H, s), 1.68 (1H, br, s) 1.16 (3H, d, *J* 7.4), 1.04 (3H, d, *J* 6.5), 1.00 (3H, d, *J* 6.6); δ_C (126 MHz; $CDCl_3$) 178.6 (C), 169.7 (C), 137.7 (C), 129.2 (CH), 128.4 (CH), 126.5 (CH), 102.6 (CH), 87.6 (CH), 71.2 (CH), 69.9 (CH_2), 60.0 (C), 41.1 (CH), 29.0 (CH), 21.7 (CH_3), 20.7 (CH_3), 19.9 (CH_3), 9.3 (CH_3); *m*/*z* (ES, +ve) 370 (M + Na^+, 100), 348 (M + H^+, 82); $C_{19}H_{25}NNaO_5$ requires 370.1630, found 370.1631.

General Procedure A: Oxidative Cleavage of Benzylidene Acetals with DMDO. Benzylidene acetal was treated with a solution of DMDO (0.06 M in acetone, 3 equiv) and stirred at 0−3 °C for 18 h. The solution was allowed to reach room temperature, dried over $MgSO_4$, and concentrated in vacuo. The product of the reaction was clean enough to be taken onto the next step without further purification unless otherwise stated.

(*S*)-1-((2*R*,3*S*,4*R*)-3-Actetoxy-2-hydroxymethyl-4-methyl-5-oxopyrrolidin-2-yl)-2-methylpropyl Benzoate (59). Using general procedure A: Lactam **58** (49.3 mg, 0.142 mmol) and DMDO solution (8.4 mL, 0.56 mmol) gave alcohol **59**. The material was purified by column chromatography using EtOAc to give *alcohol* **59** (45.2 mg, 88%) as a colorless foam: mp 56−58 °C; $[\alpha]^{24}_D$ −16.2 (*c* 0.520 in $CHCl_3$); ν_{max}/cm^{-1} ($CDCl_3$) 3603, 3418, 2935, 1711 (s)(C═O); δ_H (500 MHz; $CHCl_3$) 8.07−8.04 (2H, m), 7.64−7.60 (1H, m), 7.51−7.47 (2H, m), 6.32 (1H, br, s), 5.80 (1H, d, *J* 8.2), 5.30 (1H, d, *J* 5.2), 3.71 (1H, d, *J* 12.1), 3.67 (1H, d, *J* 12.1), 2.90 (1H, dq, *J* 8.2 and 7.6), 2.21 (1H, app septd, *J* 7.0 and 5.2), 2.01 (3H, s), 1.10 (3H, d, *J* 7.6), 1.07 (3H, d, *J* 7.0), 1.06 (3H, d, *J* 7.0); δ_C (126 MHz; $CHCl_3$) 177.3 (C), 167.0 (C), 166.7 (C), 133.9 (CH), 130.1 (CH), 129.1 (C), 128.9 (CH), 77.1 (CH), 72.4 (CH), 66.5 (C), 63.4 (CH_2), 39.9 (CH), 29.0 (CH), 22.2 (CH_3), 20.5 (CH_3), 18.7 (CH_3), 10.0 (CH_3); *m*/*z* (ES, +ve) 386 (M + Na^+, 100), 364 (M + H^+, 86); $C_{19}H_{26}NO_6$ requires 364.1760, found 364.1761.

(2*R*,3*S*,4*R*)-3-Acetoxy-2-((*S*)-1-benzoyloxy-2-methylpropyl)-4-methyl-5-oxopyrrolidine-2-carboxylic Acid (60). Dess−Martin periodinane (73.2 mg, 0.173 mmol) was added to a stirring solution of alcohol **59** (40.0 mg, 0.110 mmol) in "moist" DCM (0.55 mL, 10 μL of H_2O in 10 mL of dry DCM) at room temperature. The resulting suspension was stirred for 2 h and then diluted with Et_2O (3 mL). A saturated aqueous solution of sodium thiosulfate (1 mL) and a saturated aqueous solution of $NaHCO_3$ (1 mL) were added, and the mixture was stirred until both layers had become clear. The layers were separated, and the aqueous layer was extracted with Et_2O (4 × 3 mL). The combined organic layers were washed with brine (3 mL), dried over $MgSO_4$, and concentrated in vacuo to give a colorless oil. The crude material was purified by column chromatography using petroleum ether/EtOAc (1:1) to give the *aldehyde* (33.0 mg, 0.091 mmol, 83%) as a colorless oil: $[\alpha]^{27}_D$ +76.1 (*c* 0.305 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3428, 2973, 1722 (s)(C═O); δ_H (500 MHz; $CDCl_3$) 9.66 (1H, s), 8.06−8.03 (2H, m), 7.65−7.61 (1H, m), 7.51−7.48 (2H, m), 6.58 (1H, br, s), 5.80 (1H, d, *J* 6.5), 5.69 (1H, d, *J* 5.5), 2.77 (1H, qd, *J* 7.0 and 6.5), 2.09 (1H, qqd, *J* 7.0, 6.8 and 5.5), 1.00 (3H, d, *J* 6.8,), 0.99 (6H, d, *J* 7.0); δ_C (126 MHz; $CDCl_3$) 195.7 (CH), 177.8 (C), 169.6 (C), 165.6 (C), 134.0 (CH), 130.1 (CH), 129.0 (CH), 128.8 (C), 77.4 (CH), 75.3 (CH), 73.8 (C), 39.9 (CH), 30.2 (CH), 21.1 (CH_3), 20.4 (CH_3), 18.3 (CH_3), 8.9 (CH_3); *m*/*z* (ES, +ve) 362 (M + H^+, 100); $C_{19}H_{24}NO_6$ requires 362.1604, found 362.1596.

Sulfamic acid (49.0 mg, 0.505 mmol), sodium dihydrogen orthophosphate dihydrate (52.5 mg, 0.337 mmol), and sodium chlorite (80%, 57.1 mg, 0.505 mmol) were added sequentially to a stirring solution of the aldehyde (prepared above) (30.4 mg, 0.084 mmol) in ^{t}BuOH/H_2O (1.7 mL, 1:1) at room temperature. The resulting green solution was stirred for 18 h and then concentrated to give a colorless solid. The solid material was partitioned betweenwater (4 mL) and EtOAc (4 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 4 mL) and the combined organic layers were washed with brine (4 mL), dried over $MgSO_4$, and concentrated in vacuo to give a colorless solid. The crude product was purified by column chromatography using 20% MeOH in EtOAc to give *acid* **60** (29.5 mg, 93%) as a colorless solid: mp 223−227 °C (MeOH/EtOAc); $[\alpha]^{21}_D$ +63.5 (*c* 0.400 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3751, 1743, 1601; δ_H (500 MHz; CD_3OD) 8.05−8.02 (2H, m), 7.69−7.65 (1H, m), 7.55−7.51 (2H, m), 5.71 (1H, d, *J* 6.4), 5.62 (1H, d, *J* 6.4), 2.60 (1H, qd, *J* 7.4 and 6.4), 2.09 (1H, qqd, *J* 6.9, 6.7 and 6.4), 1.02 (3H, d, *J* 6.9), 0.96 (3H, d, *J* 6.7), 0.88 (3H, d, *J* 7.4); δ_C (126 MHz; CD_3OD) 179.9 (C), 171.3 (C), 170.8 (C), 166.9 (C), 135.1 (CH), 130.8 (CH), 130.3 (C), 130.1 (CH), 80.9 (CH), 76.1 (CH), 73.8 (C), 41.3 (CH), 31.4 (CH), 20.7 (CH_3), 20.4 (CH_3), 18.9 (CH_3), 9.1 (CH_3); *m*/*z* (ES, +ve) 400 (M + Na^+, 100), 378 (M + H^+, 27); $C_{19}H_{24}NO_7$ requires 378.1553, found 378.1546.

(3*R*,4*S*,5*R*)-4-Hydroxy-5-[(1′*S*)-1′-hydroxy-2′-methylpropyl]-3-methyl-2-pyrrolidinone-5-carboxylic Acid (40).[3q,3s] An aqueous solution of NaOH (0.2 M, 1.0 mL, 0.20 mmol) was added to acid **60** (26.1 mg, 0.689 mmol) at room temperature. The solution was stirred for 3 days at room temperature and then acidified with 2 M HCl. The solution was concentrated in vacuo to give a colorless solid, and the crude material was purified by column chromatography using $CHCl_3$/MeOH (1:1) to give dihydroxy acid **40** (9.7 mg, 61%) as a colorless solid: mp 234 °C dec (lit.[3y] mp 240 °C dec); $[\alpha]^{24}_D$ +20.4 (*c* 0.265 in MeOH); (lit.[3v] $[\alpha]^{21}_D$ +18.5 (*c* 1.0 in MeOH)); δ_H (500 MHz; CD_3OD) 4.43 (1H, d, *J* 5.9), 3.96 (1H, d, *J* 6.4), 2.98 (1H, dq, *J* 7.5 and 5.9), 1.73 (1H, qqd, *J* 6.8, 6.7 and 6.4), 1.07 (3H, d, *J* 7.5), 0.97 (3H, d, *J* 6.7), 0.93 (3H, d, *J* 6.8); δ_C (126 MHz; CD_3OD) 182.2, 175.0, 79.9, 79.5, 76.8, 42.6, 32.3, 20.9, 18.8, 8.8; *m*/*z* (ES, −ve) 230 (M − H, 100). The data were identical to that reported by Chida.[3s]

Omuralide (2).[3q] Using the method described by Corey: BOPCl (23.9 mg, 94.1 μmol) was added to a stirring suspension of dihydroxy acid **40** (14.5 mg, 62.7 μmol) and triethylamine (26 μL, 190 μmol) in DCM (0.9 mL) at room temperature. The suspension was stirred for 30 min, and then water (0.5 mL) was added. The aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$, and concentrated in vacuo to give a colorless solid. The crude material was purified by column chromatography using $CHCl_3$/MeOH (50:1) to elute BOPCl residues and then EtOAc to give omuralide **2** (7.4 mg, 55%): $[\alpha]^{25}_D$ −73 (*c* 0.09 in MeCN) (lit.[3q] $[\alpha]^{21}_D$ −93.9 (*c* 0.53 in MeCN)); ν_{max}/cm^{-1}($CHCl_3$) 1840, 1723; δ_H (500 MHz; C_5D_5N) 10.4 (1H, br, s), 7.84 (1H, br, s), 5.69 (1H, d, *J* 6.1), 4.37 (1H, s), 3.06 (1H, qd, *J* 7.5 and 6.1), 2.15−2.11 (1H, m), 1.48 (1H, d, *J* 7.5), 1.14 (1H, d, *J* 6.9), 1.02 (1H, d, *J* 6.7); *m*/*z* (ES, +ve) 214.1064 ($C_{10}H_{16}NO_4$ requires 214.1079). The data were identical to those reported.[3q]

(+)-Lactacystin (1).[3q] Using the method described by Corey: *N*-Acetyl-L-cysteine **61** was added to a stirring solution of omuralide **2** (6.3 mg, 29.5 μmol) and Et_3N (12 μmol, 86 μL) in DCM (600 μL) at room temperature under Ar. The solution was stirred for 18 h and then concentrated in vacuo. Pyridine (2 mL) was added and then removed by rotary evaporation under reduced pressure. The azeotropic distillation was repeated twice. The free acid was regenerated by treatment with THF/AcOH (5:1, 2 mL), and then the solvent was removed by rotary evaporation under reduced pressure. The azeotropic distillation was repeated twice to give a colorless solid. The crude material was purified by column chromatography using $CHCl_3$/MeOH/AcOH (10:2:1) to give (+)-lactacystin **1** (5.2 mg, 47%): $[\alpha]^{24}_D$ +31 (*c* 0.13 in MeOH) (lit.[3v] $[\alpha]^{21}_D$ +75 (*c* 0.28 in MeOH)); δ_H (500 MHz; C_5D_5N) 9.92 (1H, br, s), 5.48−5.41 (1H, m), 5.37 (1H, d, *J* 7.1), 4.62 (1H, *J* 7.0), 4.09 (1H, dd, *J* 13.5 and 4.7), 3.86 (1H, dd, *J* 13.5 and 6.6), 3.50

(1H, qd, 7.6 and 7.1), 2.27 (1H, dqq, *J* 7.0, 6.8 and 6.6), 2.13 (1H, br, s), 2.06 (3H, s), 1.60 (3H, d, *J* 7.6), 1.28 (3H, d, *J* 6.6), 1.21 (3H, d, *J* 6.8); δ_C (126 MHz; C_5D_5N) 203.4, 181.7, 173.4, 170.6, 81.8, 80.4, 76.4, 53.5, 42.3, 32.5, 32.0, 23.5, 21.9, 20.4, 10.7.[3q]

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Supporting Information Available: Experimental procedures for the preparation of **6**, **9**−**12**, **14**−**17**, **21**, **42**, **45**−**49**, and **53**−**56**, CIF files for X-ray structures of **18**, **26**, and **35**, and copies of ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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