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Two Rearrangement Pathways in the Geminal Acylation of 2-Methoxyoxazolidines Leading to Substituted 1,4-Oxazines

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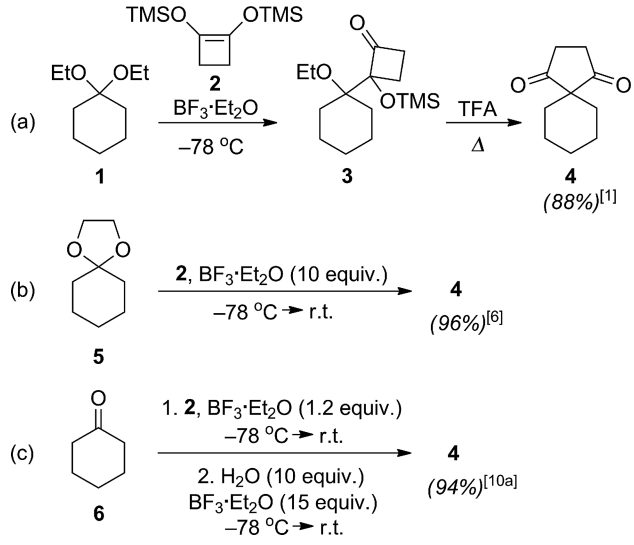
Lewis acid-mediated geminal acylation of 2-methoxyoxazolidines with five- or six-membered acyloins followed by heterocyclization afforded 1,4-oxazines fused to cyclopentenone or cyclohexenone rings. Overall yields ranged from 30 to 73 %. The position of the carbonyl group in the products depended on whether or not water was present during the ring-expanding acyl migration step. The route lacking water during the acyl migration step was best conducted in one pot. The addition of water effected cleavage of a silyloxy group in the intermediate during the initial Mukaiyama aldol reaction prior to the acyl migration.

Introduction

Geminal acylation of ketones, ketals and acetals has been established as an efficient method for the formation of cyclopentane- and cyclohexane-1,3-diones. The initial procedure by Kuwajima and co-workers[1] involved Lewis acid-promoted Mukaiyama aldol reaction of a ketal, such as **1**, with acyloin 1,2-bis(trimethylsilyloxy)cyclobutene,[2] **2**, to produce a cyclobutanone intermediate (**3**). Then, in a separate operation, a ring-expanding acyl migration of **3** to give 1,3-cyclopentanedione **4** was carried out in trifluoroacetic acid under reflux (Scheme 1, a). This two-step method, using Amberlyst-15 instead of trifluoroactic acid for the second step, is still the method of choice for geminal acylation of acetals[3] and of ketals and ketones that are α-substituted by halogens.[4] This two-step method has been employed a number of times in synthesis.[5] A simpler way of geminally acylating ketals, e.g. **5**, is to use a one-pot method with a large excess of the Lewis acid, $BF_3{\cdot}Et_2O$, which then mediates both the Mukaiyama aldol and the acyl migration (Scheme 1, b).[6–8] There are numerous examples of this method being employed in synthesis.[9]

Ketones are usually geminally acylated poorly using these two methods. It appears that the Mukaiyama aldol reaction does occur, but the cyclobutanone intermediate akin to **3** does not rearrange with acid. Instead, C–C bond fragmentation of the intermediate regenerates the ketone substrate. It was discovered that, after the formation of the intermediate, addition of roughly 10 equiv. of water to the



Scheme 1. Three general methods for geminal acylation with acyloin **2** (TFA = trifluoroacetic acid).

CH_2Cl_2 solution along with a large excess of $BF_3{\cdot}Et_2O$ tips the course of reaction towards the desired acyl migration, and it is likely that this is related to cleavage of the silyloxy group on the cyclobutanone intermediate. The yields of geminally acylated products by this "two-step one-pot" method are excellent with substrates such as ketone **6** (Scheme 1, c).[10] This method has been particularly useful for the geminal acylation of aromatic ketones[11] and some ynones.[12]

Two simple orthoesters had given products derived by geminal acylation, but in yields of less than 20 %.[7] Maulide and Markó[13] discovered that, with $ZnCl_2$ as the Lewis acid, the Mukaiyama aldol reaction of **2** with orthoester **7** (with the orthoester in excess) could be carried out in good

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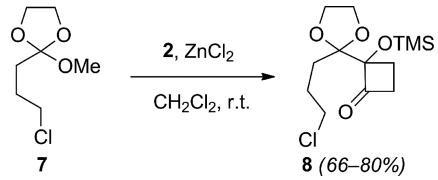
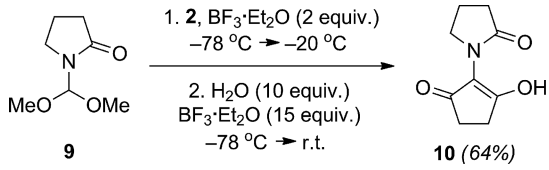
yield to give **8** (Scheme 2). The reaction took place with the loss of the extra-annular oxygen of the orthoester. However, under these conditions, ring-expanding acyl migration of **8** was not observed. No orthoamide has been geminally acylated. We were motivated to attempt this transformation for two reasons. First, we envisioned that the reactions with orthoamides could lead to nitrogen-containing compounds that might, in turn, be cyclized to produce bicyclic heterocycles. As heterocycles are ubiquitous in numerous drug scaffolds,[14] novel methods for their production are of considerable importance. We secondly envisaged probing the question of how the geminal acylation might proceed. Geminal acylation requires the sequential rupture of two carbon–heteroatom bonds. Would these rupture sites be C–O or C–N bonds? The results of our research are described below.



Scheme 2. Mukaiyama aldol reaction of orthoester **7** with acyloin **2**.[13]

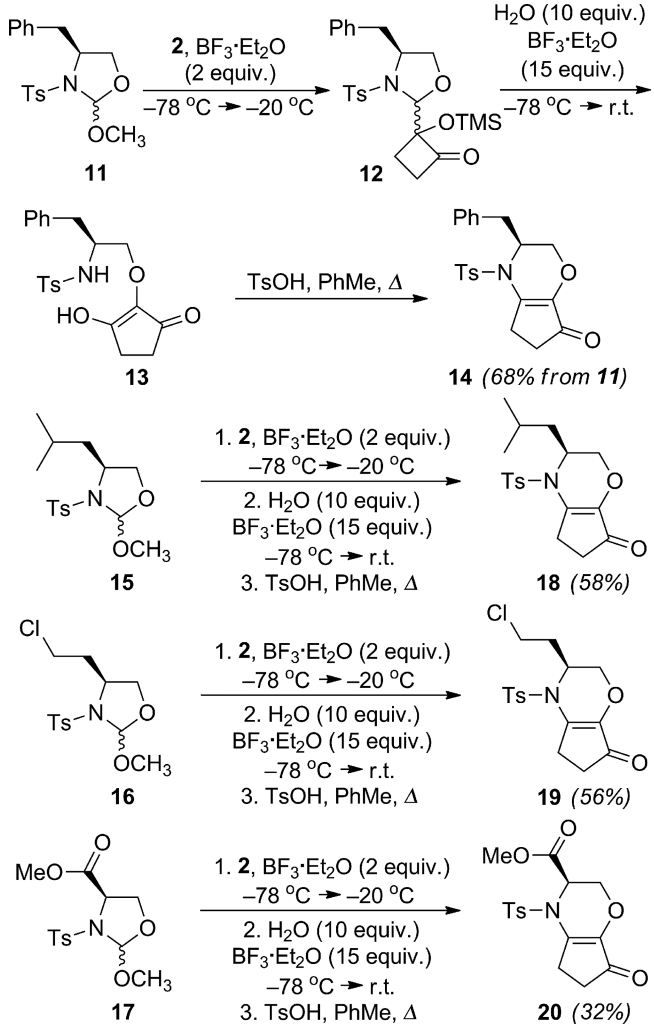
Results and Discussion

It was first decided to attenuate the basicity of the orthoamide nitrogen by having it in the form of a lactam rather than an amine. This idea was tested using orthoamide **9**[15] and acyloin **2**. In the presence of a large excess of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at –78 °C, geminal acylation of **9** took place to give **10** although the yield was only 24%. However, when a two-step one-pot protocol was followed, (i.e., the $BF_3{\cdot}Et_2O$-mediated Mukaiyama aldol was carried out first in CH_2Cl_2 solution and then ten equivalents of water and a large excess of $BF_3{\cdot}Et_2O$ were added), the yield of **10** over the two steps increased to a satisfactory level (Scheme 3). Thus, $BF_3{\cdot}Et_2O$ could mediate both steps, just as in the geminal acylation of ketals. Both of C–C bond-forming steps involved in generating **10** had also involved the loss of an oxygen function rather than that of the nitrogen.



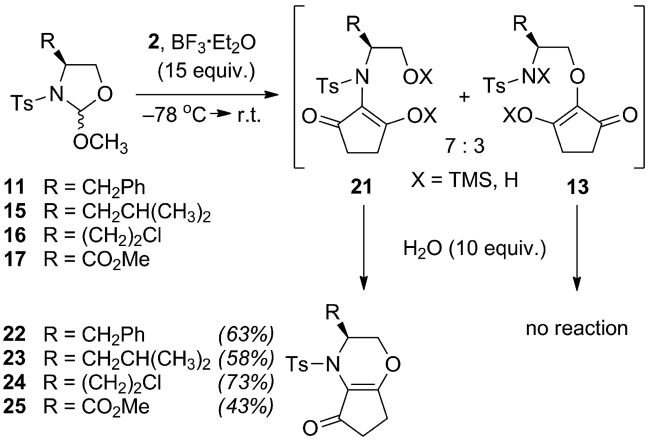
Scheme 3. Two-step one-pot geminal acylation of orthoamide **9** with acyloin **2**.

The three heteroatoms on C-2 of a 2-methoxyoxazolidine are distinct, whereas with **9** the two oxygen substituents of the orthoamide are the same. It was convenient to prepare 2-methoxyoxazolidine[16] **11** from the amino alcohol derived from L-phenylalanine. The nitrogen was in the form of a sulfonamide. Compound **11** was treated with acyloin **2** and two equiv. of $BF_3{\cdot}Et_2O$ at –78 °C to yield Mukaiyama aldol product **12** as a mixture of diastereomers. As expected, the extra-annular oxygen function had been lost. Addition of water and a large excess of $BF_3{\cdot}Et_2O$ provided geminally acylated product **13**. (This structure and the structures of other geminal acylation products were determined largely by 2-D NMR methods.) The transformation took place exclusively with the rupture of the annular C–N bond. Heating a solution of **13** in toluene in the presence of TsOH effected smooth cyclization affording a novel type of heterocycle, cyclopenta[*b*][1,4]oxazinone **14**. The only known compound closely related to **14** is a benzoxazine.[17] Indeed, the vast majority of the bicyclic 1,4-oxazines prepared to date are benzoxazines.[18] Repeating the geminal acylation following this "two-step one-pot" method and then cyclizing unpurified **13** gave heterocycle **14** in 68% yield from **11**. In the same way, 2-methoxyoxazolidines **15**–**17**, derived from L-leucine, L-methionine and D-serine, afforded heterocycles **18**–**20**, respectively (Scheme 4).



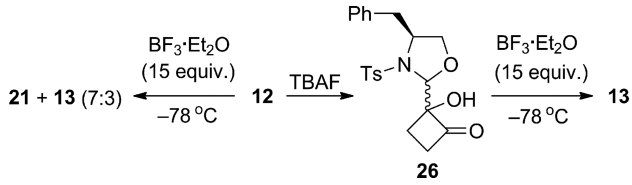
Scheme 4. Two-step one-pot geminal acylation of **11** and **15**–**17** with acyloin **2** followed by heterocyclization.

Geminal acylations of **11** and **15**–**17** were also performed using "one-step" conditions, (i.e., using a large excess of $BF_3{\cdot}Et_2O$, initially at –78 °C and then warming to room temperature), in order to carry out both the Mukaiyama aldol and the acyl migration (Scheme 5). The product from **11** was a 7:3 mixture of compounds with similar ^1H NMR spectra of which **13** was the minor constituent, and the major constituent **21** had arisen by rupture of the annular C–O bond. Chromatographic separation of the two geminal acylation products from **11**, **15** and **16** was impractical. However, addition of water to the reaction medium led to facile cyclization of only the major geminal acylation products thus yielding heterocycles **22**–**24**, which differ from **14**, **18** and **19** by positioning of the carbonyl group. Notably, these heterocycles were prepared by conducting all three reaction steps in one pot. The structure of **22** was confirmed by X-ray crystallography. Although geminal acylation of **17** took place just as for **11**, **15** and **16**, heterocyclization to **25** required heating with TsOH. Because cyclization of the product of C–N cleavage was relatively slow, the formation of **20** could be avoided.



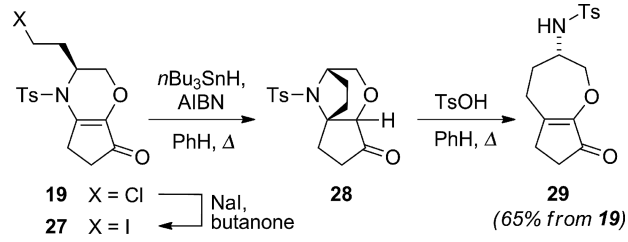
Scheme 5. One-pot geminal acylation of **11** and **15**–**17** with acyloin **2** and heterocyclization. (Overall yields are given. Heterocyclization to **25** required heating with TsOH.)

Whether the tertiary oxygen function on the cyclobutanone intermediate was OTMS or OH was the factor that dictated how the acyl migration step functioned. As noted above, treatment of **12** with excess $BF_3{\cdot}Et_2O$ gave a 7:3 mixture of **21** and **13**, respectively. However, when **12** was desilylated to **26**, and the resulting cyclobutanone–alcohol was exposed to excess $BF_3{\cdot}Et_2O$ in an anhydrous medium, only **13** was obtained (Scheme 6). This observation was consistent with water in the medium during the geminal acylation thus enabling cleavage of the silyloxy group on the cyclobutanone intermediate. Rupture of the annular C–O bond in the rearrangement of **12** is consistent with complexation of BF_3 by the annular oxygen. However, why it is that **26** so predominantly follows the pathway involving cleavage of the C–N bond is not presently known. We hypothesize that internal H-bonding between the OH and the annular oxygen might lead to complexation by the BF_3 favoring the nitrogen function, and/or that H-bonding might constrain **26** to a geometry that strongly biases the reaction pathway to C–N bond cleavage.



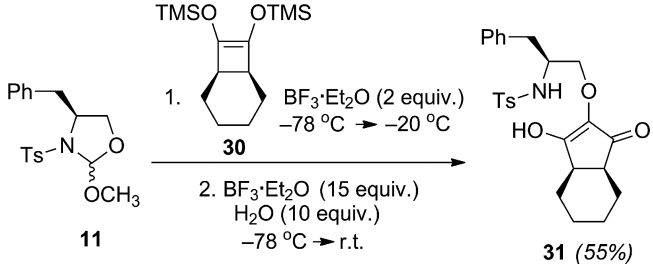
Scheme 6. $BF_3{\cdot}Et_2O$-mediated rearrangement of **12** vs. **26**.

Exchanging the Cl of **19** for I gave **27**. This was treated with nBu$_3$SnH and AIBN to yield **28**, with a bridged tricyclic structure, via a transannular 5-*exo* cyclization.[19] Subsequently, subjection of **28** to TsOH in boiling benzene yielded **29** (Scheme 7). Similar ring-fused tetrahydrooxepins have only been prepared previously by Nazarov cyclization.[20] In contrast, heating nBu$_3$SnH and AIBN with **24** or its iodo-analogue, which might have cyclized via a transannular 6-*exo* cyclization to another bridged tricyclic structure, led to an intractable mixture.



Scheme 7. Conversion of **19** into **29** (AIBN = azobisisobutyronitrile).

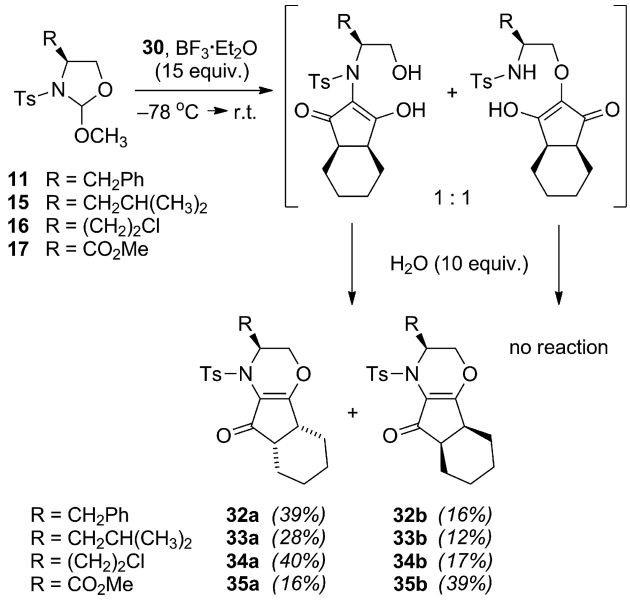
Substitution on the acyloin **2** had a significant effect on the course of the geminal acylation/heterocyclization. When the two-step one-pot procedure was employed with **11** and acyloin **30**,[3] the geminal acylation was successful, giving **31** via rupture of the annular C–N bond (Scheme 8). However, **31** simply decomposed during attempts under various acidic conditions to cyclize it to the corresponding heterocycle.



Scheme 8. Two-step one-pot geminal acylation of **11** with acyloin **30**.

Using acyloin **30** under the one-pot conditions, geminal acylations of **11** and **15**–**17** were successful, but the modest

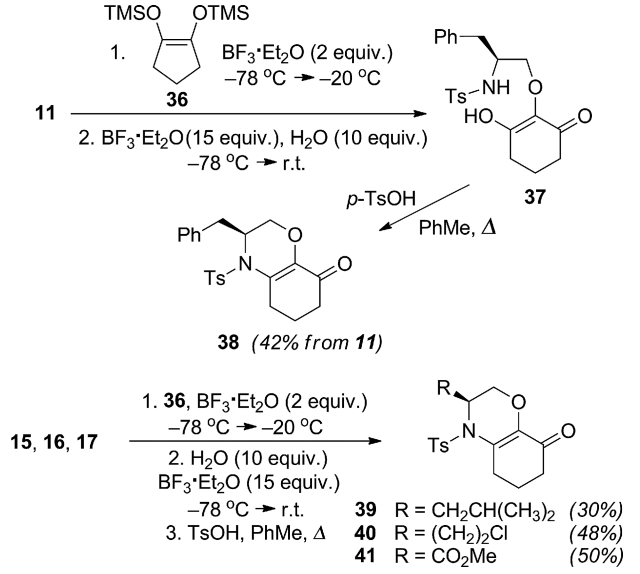
selectivity seen when using **2** was lost and chromatographically inseparable C–N and C–O bond cleavage products were obtained in about 1:1 ratios. Fortunately, as before, only the C–O cleavage products cyclized upon addition of water to the medium, although the heterocyclization step in the sequence from **17** required TsOH and heat. The product of C–N cleavage failed to cyclize, even under the harsher conditions. Heterocycles **32a**,**b**–**35a**,**b** were obtained as diastereomeric mixtures; these were separable by column chromatography. Overall yields of 40 to 57% were achieved (Scheme 9) although these yields reflect some difficulties encountered during diastereomer separation efforts. The structures of **32b**, **33a**, **34a**, **34b** and **35b** were determined by X-ray crystallography.



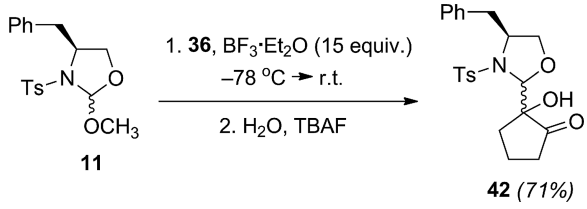
Scheme 9. One-pot geminal acylation of **11** and **15**–**17** with acyloin **30** followed by heterocyclization. (Overall yields are given. Heterocyclization to **35a**,**b** required heating with TsOH.).

The five-membered analogue of **2**, acyloin **36**,[2] was less reactive than **2** in geminal acylations of ketals.[8] However, **36** seemed to perform similarly to **2** in the two-step one-pot geminal acylation of **11** and **15**–**17**, with **37** representing the only detectable C–N bond cleavage product. As expected, heterocyclizations to **38**–**41** required heating with a protic acid (Scheme 10).

It was curious that when **36** was exposed to conditions of the one-pot geminal acylation-and-heterocyclization procedure with **11**, the only isolable product was **42**, as a 5:1 mixture of diastereomers (Scheme 11). Thus, the initial Mukaiyama aldol reaction had taken place, but not the acyl migration. The subsequent addition of water had merely led to cleavage of the silyl ether. When **42** was treated with a large excess of $BF_3{\cdot}Et_2O$ under anhydrous conditions, the product identified was **37**; none of the C–O bond cleavage product was observed. This result confirms the role of water in the two-step one-pot geminal acylation process.



Scheme 10. Two-step one-pot geminal acylation of **11** and **15**–**17** with acyloin **36** followed by heterocyclization.



Scheme 11. Attempted one-pot geminal acylation of **11** with acyloin **36**.

Conclusions

2-Methoxyoxazolidines underwent $BF_3{\cdot}Et_2O$-mediated geminal acylation. In the first Mukaiyama aldol step the methoxy group was ejected. However, in the second step which involves ring-expanding acyl migration, the chemoselectivity was highly dependent on the presence or absence of water. Under anhydrous conditions the rearrangement took place with relatively indiscriminate rupture of the annular C–O or C–N bond; addition of ten equivalents of water shifted bond rupture exclusively to the annular C–N bond. The addition of water leads to siloxy group cleavage from the Mukaiyama aldol-derived intermediate and it is rearrangement of this transient hydroxy-substituted intermediate that proceeds with high selectivity. Subsequent heterocyclization of the geminal acylation products afforded twenty novel 1,4-oxazinones. The vast majority of previously known 1,4-oxazines are 1,4-benzoxazines. Importantly, the methodology presented here now makes readily available 1,4-oxazines that are not fused to an aromatic ring.

Experimental Section

General: Reactions were carried out in oven-dried glassware under an atmosphere of dry nitrogen. Reagents were used as received

from commercial sources, except $BF_3{\cdot}OEt_2$ was freshly distilled. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. EtOAc and hexanes were distilled. Amberlyst-15 was dried overnight under vacuum with modest heating. Reagents **2**, **30** and **36** were prepared by the acyloin method of Bloomfield.[2b] Reactions were followed by TLC analysis using precoated (silica gel 60 F254, 0.25 mm) plates with aluminum backing. Column chromatography was carried out with silica gel (40–63 μm particle size, 230–240 mesh). Evaporation of solvents was carried out under reduced pressure with modest heating. Melting points were uncorrected. IR spectra were recorded with an FT instrument on NaCl plates as neat liquid films, and only significant absorption bands (in cm^{-1}) are reported. ^1H NMR spectra were acquired at 500.1 MHz, and chemical shifts are relative to internal TMS (δ = 0.00 ppm). Diastereomeric ratios were determined by integration of clearly separated ^1H NMR signals. ^{13}C NMR spectra were acquired at 125.8 MHz, and chemical shifts are relative to the solvent signal ($CDCl_3$, δ = 77.16 ppm). Structural assignments were based on DEPT and 2-D NMR spectra (COSY, HSQC, HMBC). HRMS data were obtained with a TOF mass spectrometer by positive-ion ESI.

1-(2-Hydroxy-5-oxocyclopent-1-enyl)pyrrolidin-2-one (10): Compound **9** (159 mg, 1.00 mmol) and **2** (346 mg, 1.50 mmol) were dissolved in CH_2Cl_2 (10 mL). The solution was cooled to –78 °C with stirring. $BF_3{\cdot}OEt_2$ (0.250 mL, 2.00 mmol) was added dropwise, and the solution was warmed to –20 °C over 3 h. The solution was re-cooled to –78 °C, and $BF_3{\cdot}OEt_2$ (1.88 mL, 15.0 mmol) and H_2O (0.18 mL, 10 mmol) were added dropwise simultaneously. The solution was warmed to room temp. overnight and extracted with aqueous 1 M NaOH (3 × 20 mL). The aqueous layer was acidified with concentrated aqueous HCl and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were dried with Na_2SO_4, and the solvent was evaporated to afford **10** (115 mg, 64%) as a yellow solid; m.p. 129–131 °C. IR (film): $\tilde{\nu}$ = 3269, 1679, 1629 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 12.58 (broad s, 1 H), 4.18 (t, J = 7.3 Hz, 2 H), 2.56 (s, 4 H), 2.51 (t, J = 8.1 Hz, 2 H), 2.19 (pentet, J = 7.6 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.1, 179.4, 177.8, 115.9, 48.0, 33.6, 30.9, 25.8, 20.0 ppm. HRMS (ESI): 204.0624, $[C_9H_{11}NO_3Na]^+$ requires 204.0631.

2-[(4*S*)-4-Benzyl-3-tosyloxazolidin-2-yl]-2-(trimethylsilyloxy)cyclobutanone (12): Compound **11** (347 mg, 1.00 mmol) and **2** (346 mg, 1.50 mmol) were dissolved in CH_2Cl_2 (10 mL). The solution was cooled to –78 °C with stirring. $BF_3{\cdot}OEt_2$ (0.25 mL, 2.0 mmol) was added dropwise, and the solution was warmed to –20 °C over 3 h, after which time TLC indicated the complete consumption of **11**. The solution was warmed to room temp., and then it was washed with an equal volume of H_2O. The organic fraction was dried with Na_2SO_4, and the solvent was evaporated. Column chromatography with 4:1 hexanes/EtOAc provided **12** (170 mg, 71%), which was by ^1H NMR a 2:1 mixture of epimers, as a colorless oil. IR (film): $\tilde{\nu}$ = 1795, 1168 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) for the major isomer: δ = 7.81 (d, J = 8.2 Hz, 2 H), 7.35 (d, J = 8.1 Hz, 2 H), 7.29–7.24 (m, 2 H), 7.22–7.18 (m, 1 H), 7.08 (d, J = 7.9 Hz, 2 H), 5.39 (s, 1 H), 3.91 (dd, J = 8.6, 6.9 Hz, 1 H), 3.84–3.77 (m, 1 H), 3.54 (dd, J = 8.5, 7.1 Hz, 1 H), 3.17 (dd, J = 13.3, 4.0 Hz, 1 H), 3.14–3.05 (m, 1 H), 2.88–2.79 (m, 2 H), 2.69 (dd, J = 13.1, 11.2 Hz, 1 H), 2.43 (s, 3 H), 2.08–2.00 (m, 1 H), 0.22 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) for major isomer: δ = 207.3, 144.8, 137.5, 133.9, 130.2, 129.0, 128.9, 128.5, 126.9, 95.6, 93.7, 71.4, 61.5, 40.8, 40.1, 24.7, 21.8, 1.8 ppm. ^1H NMR (500 MHz, $CDCl_3$) for the minor isomer: δ = 7.76 (d, J = 8.3 Hz, 2 H), 7.34 (d, J = 8.1 Hz, 2 H), 7.31–7.26 (m, 2 H), 7.24–7.20 (m, 2 H), 7.13 (d, J = 7.7 Hz, 2 H), 5.28 (s, 1 H), 3.98 (dd, J = 8.2, 6.2 Hz, 1 H), 3.89–3.82 (m, 1 H), 3.49 (apparent t, J = 7.9 Hz, 1 H), 3.32 (dd, J = 13.4, 3.8 Hz, 1 H), 3.07–2.94 (m, 2 H), 2.86–2.82 (m, 1 H), 2.43 (s, 3 H), 2.11–2.04 (m, 1 H), 0.27 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) for minor isomer: δ = 207.5, 144.7, 137.9, 133.8, 130.2, 129.1, 129.0, 128.2, 126.9, 95.7, 92.6, 72.5, 61.7, 40.7, 39.7, 24.4, 21.7, 1.9 ppm. HRMS (ESI): 496.1575, $[C_{24}H_{31}NO_5SSiNa]^+$ requires 496.1584.

(*S*)-*N*-[1-(2-Hydroxy-5-oxocyclopent-1-enyloxy)-3-phenylpropan-2-yl] Tosylate (13): Compound **12** (970 mg, 2.0 mmol) was dissolved in CH_2Cl_2 (13 mL). The solution was cooled to –78 °C with stirring. $BF_3{\cdot}OEt_2$ (3.8 mL, 30 mmol) and H_2O (0.37 mL, 21 mmol) were added dropwise, and the solution was warmed to room temp. overnight. The solution was then washed with an equal volume of water. The organic fraction was dried with Na_2SO_4, and the solvent was evaporated to afford **13** (750 mg, 92%) as an oil (which was used without further purification). IR (film): $\tilde{\nu}$ = 3295, 1707, 1610 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.58 (d, J = 8.3 Hz, 2 H), 7.21–7.18 (m, 5 H), 7.04–7.01 (m, 2 H), 5.65 (d, J = 8.1 Hz, 1 H), 4.02 (dd, J = 10.5, 3.2 Hz, 1 H), 3.93 (dd, J = 10.6, 6.4 Hz, 1 H), 3.71–3.63 (m, 1 H), 2.80 (dd, J = 13.8, 7.1 Hz, 1 H), 2.69 (dd, J = 13.9, 7.1 Hz, 1 H), 2.43 (s, 4 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) (slow exchange): δ = 143.7, 137.1, 136.8, 134.8, 129.8, 129.5, 128.8, 127.2, 126.9, 72.6, 55.6, 38.1, 21.7 ppm. HRMS (ESI): 402.1372, $[C_{21}H_{24}NO_5S]^+$ requires 402.1370.

Procedure for Two-Step One-Pot Geminal Acylation with 2 Followed by Heterocyclization: The 2-methoxyoxazolidine (1 equiv.) and **2** (1.5 equiv.) were dissolved in CH_2Cl_2 (10 mL/mmol). The solution was cooled to –78 °C with stirring. $BF_3{\cdot}OEt_2$ (2 equiv.) was added dropwise, and the solution was warmed to –20 °C over 3 h, after which time TLC indicated complete consumption of the 2-methoxyoxazolidine. The solution was re-cooled to –78 °C, and $BF_3{\cdot}OEt_2$ (15 equiv.) and H_2O (10 equiv.) were added dropwise simultaneously. The mixture was warmed to room temp. overnight, and then it was washed with an equal volume of H_2O. The organic fraction was dried with Na_2SO_4, and the solvent was evaporated. A solution of the residual oil in toluene (50 mL/mmol) was heated under reflux for 24 h in the presence of TsOH (2 equiv.) using a Dean–Stark apparatus. The mixture was cooled and washed with an equal volume of saturated aqueous $NaHCO_3$. The organic fraction was dried with Na_2SO_4, and the solvent was evaporated. Column chromatography provided the heterocycle.

(*S*)-3-Benzyl-4-tosyl-3,4,6,7-tetrahydrocyclopenta[*b*][1,4]oxazin-7(2*H*)-one (14): By the two-step one-pot procedure above, **11** (347 mg, 1.00 mmol) and **2** (346 mg, 1.50 mmol) gave, after column chromatography with 2:1 hexanes/EtOAc, **14** (260 mg, 68%) as a colorless solid; m.p. 142–143 °C. IR (film): $\tilde{\nu}$ = 1711, 1632 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.3 Hz, 2 H), 7.36–7.30 (m, 4 H), 7.28–7.24 (m, 3 H), 4.25–4.19 (m, 1 H), 3.98 (dd, J = 11.5, 1.3 Hz, 1 H), 3.10–2.94 (m, 4 H), 2.79 (dd, J = 13.0, 10.9 Hz, 1 H), 2.49–2.44 (m, 2 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.6, 145.3, 143.0, 137.9, 136.4, 135.1, 130.5, 129.8, 128.9, 127.3, 127.1, 64.2, 57.0, 37.2, 31.7, 24.8, 21.7 ppm. HRMS (ESI): 406.1076, $[C_{21}H_{21}NO_4SNa]^+$ requires 406.1083.

Procedure for One-pot Geminal Acylation with 2 and Heterocyclization: The 2-methoxyoxazolidine (1 equiv.) and **2** (1.5 equiv.) were dissolved in CH_2Cl_2 (10 mL/mmol). The solution was cooled to –78 °C with stirring. $BF_3{\cdot}OEt_2$ (15 equiv.) was added dropwise, and the mixture was warmed to room temp. overnight, after which time the TLC indicated complete consumption of the 2-methoxyoxazolidine. The mixture was re-cooled to –78 °C, and H_2O (10 equiv.) was added dropwise. The mixture was warmed to room temp. overnight, and it was then washed with an equal volume of H_2O. The

organic fraction was dried with Na_2SO_4, the solvent was evaporated, and column chromatography of the residue gave the heterocycle.

(*S*)-3-Benzyl-4-tosyl-3,4,6,7-tetrahydrocyclopenta[*b*][1,4]oxazin-5(2*H*)-one (22) via 21: By the one-pot procedure above, **11** (347 mg, 1.00 mmol) and **2** (346 mg, 1.50 mmol) gave, after column chromatography with 4:1 hexanes/EtOAc, **22** (240 mg, 63%) as a colorless solid; m.p. 173–175 °C. IR (film): $\tilde{\nu}$ = 1711, 1642 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.4 Hz, 2 H), 7.14–7.06 (m, 5 H), 6.90 (dd, J = 7.8, 1.7 Hz, 2 H), 4.36 (dd, J = 11.3, 1.1 Hz, 1 H), 4.23 (tdd, J = 7.9, 2.9, 1.1 Hz, 1 H), 4.15 (dd, J = 11.0, 2.8 Hz, 1 H), 2.75–2.57 (m, 3 H), 2.51 (d, J = 7.8 Hz, 2 H), 2.45 (ddd, J = 17.0, 6.9, 2.6 Hz, 1 H), 2.38 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.8, 172.4, 143.7, 136.6, 136.4, 129.4, 129.3, 128.6, 128.1, 126.7, 115.0, 70.1, 54.2, 36.2, 32.0, 24.4, 21.7 ppm. HRMS (ESI): 406.1075, $[C_{21}H_{21}NO_4SNa]^+$ requires 406.1083. In one instance, instead of addition of the H_2O, the reaction was quenched with base, and from the resulting solution a small amount of the intermediate **21** was obtained. ^1H NMR (500 MHz, CD_3SOCD_3): δ = 7.82 (d, J = 8.2 Hz, 2 H), 7.29 (d, J = 8.1 Hz, 2 H), 7.22 (dd, J = 7.9, 7.4 Hz, 2 H), 7.15 (dd, J = 8.2, 7.4 Hz, 1 H), 7.01 (d, J = 7.4 Hz, 2 H), 3.85–3.77 (m, 1 H), 3.16 (s, 1 H), 3.03–2.98 (m, 2 H), 2.83 (dd, J = 13.7, 3.4 Hz, 1 H), 2.38–2.34 (m, 5 H), 2.34–2.29 (m, 2 H), 2.25 (dd, J = 13.2, 10.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3SOCD_3): δ = 199.6, 195.9, 142.0, 139.0, 139.0, 128.8, 128.7, 128.2, 127.7, 125.9, 108.9, 62.8, 60.4, 37.1, 29.8, 29.3, 20.9 ppm.

2-[(4*S*)-4-Benzyl-3-tosyloxazolidin-2-yl]-2-hydroxycyclobutanone (26): 2-Methoxyoxazolidine (**11**, 350 mg, 1 mmol) and **2** (350 mg, 1.5 mmol) were dissolved in CH_2Cl_2 (10 mL). The solution was cooled to –78 °C, after which $BF_3{\cdot}OEt_2$ (0.25 mL, 2 mmol) was added dropwise. After stirring for 5 min at –78 °C, the mixture was warmed to –20 °C over 2 h. The mixture was diluted with CH_2Cl_2 (50 mL), and it was washed with an equal volume of H_2O. The organic layer was dried with Na_2SO_4, and the solvent was evaporated. THF (10 mL) was added, followed by a 1.0 M solution of TBAF in THF (2 mL, 2 mmol), and the mixture was stirred at room temp. for 1 h. The solvent was evaporated, and CH_2Cl_2 (50 mL) was added. After washing with saturated aqueous NH_4Cl, the organic layer was dried with Na_2SO_4 and the solvent was evaporated. Column chromatography with 2:1 hexanes/EtOAc, afforded **26** (201 mg, 50%), a mixture of diastereomers, as a colorless oil. IR (film): $\tilde{\nu}$ = 1790 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) for the major isomer: δ = 7.79 (d, J = 8.4 Hz, 2 H), 7.38 (d, J = 8.0 Hz, 2 H), 7.34–7.20 (m, 3 H), 7.17 (d, J = 7.6 Hz, 2 H), 5.12 (s, 1 H), 3.93 (s, 1 H), 3.87 (dd, J = 9.0, 5.2 Hz, 1 H), 3.84–3.78 (m, 1 H), 3.34–3.24 (m, 2 H), 3.18–3.06 (m, 1 H), 3.01–2.85 (m, 1 H), 2.80–2.68 (m, 2 H), 2.44 (s, 3 H), 2.17–2.07 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) for the major isomer: δ = 208.2, 145.3, 137.0, 132.6, 130.4, 129.2, 129.0, 128.4, 127.1, 92.8, 92.7, 70.2, 61.9, 42.6, 40.6, 23.4, 21.8 ppm. ^1H NMR (500 MHz, $CDCl_3$) for the minor isomer: δ = 7.79 (d, J = 8.4 Hz, 2 H), 7.38 (d, J = 8.0 Hz, 2 H), 7.34–7.20 (m, 3 H), 7.12 (d, J = 7.8 Hz, 2 H), 5.15 (s, 1 H), 4.38 (s, 1 H), 3.96–3.91 (m, 1 H), 3.70 (dd, J = 9.0, 3.7 Hz, 1 H), 3.26 (dd, J = 8.9, 6.4 Hz, 1 H), 3.18–3.06 (m, 1 H), 3.01–2.85 (m, 2 H), 2.80–2.68 (m, 1 H), 2.63–2.56 (m, 1 H), 2.43 (s, 3 H), 2.17–2.07 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) for the minor isomer: δ = 208.6, 145.3, 137.3, 133.0, 130.4, 129.3, 128.9, 128.3, 126.9, 92.8, 92.3, 70.4, 62.2, 42.1, 40.7, 25.0, 21.8 ppm. HRMS (ESI): 424.1182, $[C_{21}H_{23}NO_5SNa]^+$ requires 424.1189.

(*S*)-4-Methyl-*N*-(8-oxo-3,4,5,6,7,8-hexahydro-2*H*-cyclopenta[*b*]oxepin-3-yl) Tosylate (29) via 27 and 28: Compound **19** (220 mg, 0.618 mmol) was dissolved in butanone (3.09 mL). NaI (929 mg, 6.18 mmol) was added, and the mixture was heated under reflux for 3 h. The solvent was evaporated, and the solid was dissolved in CH_2Cl_2 (50 mL). This was washed with equal volumes of water and saturated aqueous Na_2SO_3, and finally dried with Na_2SO_4. The organic layer was then evaporated to afford crude **27** as a colorless oil that was used without further purification. From an aliquot: ^1H NMR (500 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.4 Hz, 2 H), 7.38 (d, J = 8.2 Hz, 2 H), 4.24–4.18 (m, 1 H), 4.03 (dd, J = 11.4, 1.4 Hz, 1 H), 3.36–3.29 (m, 1 H), 3.27–3.21 (m, 1 H), 3.15–3.07 (m, 1 H), 3.00–2.92 (m, 2 H), 2.48–2.44 (m, 5 H), 2.16–2.07 (m, 1 H), 2.01–1.93 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.8, 145.6, 142.3, 138.4, 134.4, 130.7, 127.2, 65.9, 55.9, 34.5, 31.8, 25.1, 21.8, 0.5 ppm. HRMS (ESI): 469.9893, $[C_{16}H_{18}INO_4SNa]^+$ requires 469.9905. Compound **27** was dissolved in benzene (250 mL), azobis(isobutyronitrile) (100 mg, 0.618 mmol) was added, and the mixture was heated under reflux. A solution of nBu$_3$SnH (728 mg, 2.50 mmol) in benzene (50 mL) was added over 48 h after which **27** was not apparent by TLC. An aliquot of the benzene solution was passed through a small chromatography column (3:1 hexanes/EtOAc) to provide some **28**. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.3 Hz, 2 H), 7.33 (d, J = 8.3 Hz, 2 H), 4.33–4.29 (m, 1 H), 3.99 (broad s, 1 H), 3.85–3.78 (m, 2 H), 2.64–2.56 (m, 1 H), 2.49–2.41 (m, 4 H), 2.33 (ddd, J = 13.2, 9.2, 1.0 Hz, 1 H), 2.21–2.12 (m, 1 H), 1.84–1.74 (m, 3 H), 1.52–1.44 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.2, 144.3, 137.8, 130.0, 127.8, 88.0, 74.2, 69.2, 59.7, 33.4, 30.2, 27.1, 24.5, 21.7 ppm. HRMS (ESI): 344.0921, $[C_{16}H_{19}NO_4SNa]^+$ requires 344.0927. To the benzene solution of **28** was added TsOH (476 mg, 2.5 mmol), and the mixture was heated under reflux for 24 h. The solution was washed with an equal volume of water, dried with Na_2SO_4, and concentrated. Column chromatography with 2:1 hexanes/EtOAc provided **29** (130 mg, 65% from **19**) as a colorless solid; m.p. 171–173 °C. IR (film): $\tilde{\nu}$ = 1707, 1645 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.77 (d, J = 8.3 Hz, 2 H), 7.31 (d, J = 8.5 Hz, 2 H), 5.18 (d, J = 8.2 Hz, 1 H), 3.85–3.79 (m, 1 H), 3.78–3.71 (m, 1 H), 3.71–3.67 (m, 1 H), 2.65–2.55 (m, 1 H), 2.47–2.42 (m, 5 H), 2.42–2.34 (m, 3 H), 2.10–2.01 (m, 1 H), 1.86–1.78 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.0, 154.3, 153.4, 143.9, 137.6, 130.0, 127.0, 74.6, 53.3, 32.8, 31.4, 27.3, 26.4, 21.7 ppm. HRMS (ESI): 344.0925, $[C_{16}H_{19}NO_4SNa]^+$ requires 344.0927.

***N*-((2*S*)-1-{[(*cis*)-3-Hydroxy-1-oxo-3a,4,5,6,7,7a-hexahydro-1*H*-inden-2-yl]oxy}-3-phenylpropan-2-yl) Tosylate (31):** A solution of **11** (347 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was cooled to –78 °C, and a solution of **30** (426 mg, 1.50 mmol) in CH_2Cl_2 (9 mL) was added. $BF_3{\cdot}Et_2O$ (0.25 mL, 2.0 mmol) was added slowly, the solution was stirred at –78 °C for 15 min, and then the solution was warmed to –20 °C. After 2 h, the solution was re-cooled to –78 °C, and H_2O (0.18 mL, 10 mmol) and $BF_3{\cdot}Et_2O$ (1.8 mL, 15 mmol) were added over 15 min. The solution was warmed to room temp. overnight and it was diluted with CH_2Cl_2 (50 mL). The solution was extracted with 1 M aqueous NaOH (50 mL). Acidification of the aqueous layer with 12 M HCl was followed by the re-extraction of the product into CH_2Cl_2 (3× 50 mL). The combined organic extracts were dried with Na_2SO_4, and then evaporated to give **31** (250 mg, 55%) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.59 (d, J = 8.2 Hz, 2 H), 7.21–7.15 (m, 5 H), 7.05 (d, J = 7.9 Hz, 2 H), 6.08 (d, J = 8.0 Hz, 1 H), 4.00 (dd, J = 10.6, 5.7 Hz, 1 H), 3.87 (dd, J = 10.5, 3.1 Hz, 1 H), 3.67–3.59 (m, 1 H), 2.83 (dd, J = 13.9, 7.6 Hz, 1 H), 2.73 (dd, J = 13.8, 6.9 Hz, 1 H), 2.38 (s, 3 H), 1.89–1.74 (m, 3 H), 1.68–1.50 (m, 3 H), 1.41–1.18 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) (slow exchange): δ = 143.5, 137.3, 137.1, 133.7, 129.8, 129.7, 129.5, 128.7, 128.7, 127.1, 126.7, 72.2,

55.7, 38.2, 23.5, 21.6, 21.5, 19.8, 17.9 ppm. HRMS (ESI): 478.1670, $[C_{25}H_{29}NO_5SNa]^+$ requires 478.1659.

Procedure for the One-Pot Geminal Acylation with 30 and Heterocyclization: 2-Methoxyoxazolidine (1 equiv.) and **30** (1.5 equiv.) were dissolved in CH_2Cl_2 (10 mL/mmol). The mixture was cooled to –78 °C with stirring. $BF_3{\cdot}OEt_2$ (15 equiv.) was added dropwise, and the solution was warmed to room temp. overnight, after which the 2-methoxyoxazolidine was no longer apparent by TLC. The solution was re-cooled to –78 °C, and H_2O (10 equiv.) was added dropwise. The mixture was warmed to room temp. overnight, and it was washed with an equal volume of H_2O. The organic fraction was dried with Na_2SO_4, and the solvent was evaporated. Careful column chromatography afforded the heterocycles.

(3*S*,5a*S*,9a*R*)-3-Benzyl-4-tosyl-3,4,5a,6,7,8,9,9a-octahydroindeno-[1,2-*b*][1,4]oxazin-5(2*H*)-one (32a) and (3*S*,5a*R*,9a*S*)-3-Benzyl-4-tosyl-3,4,5a,6,7,8,9,9a-octahydroindeno[1,2-*b*][1,4]oxazin-5(2*H*)-one (32b): By the one-pot procedure described above, **11** (347 mg, 1.00 mmol) and **30** (427 mg, 1.50 mmol) gave, after column chromatography with 4:1 hexanes/EtOAc, **32a** (169 mg, 39%) and **32b** (72 mg, 16%). For **32a**: yellow solid; m.p. 141–144 °C. IR (film): $\tilde{\nu}$ = 1715, 1634 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.71 (d, J = 8.4 Hz, 2 H), 7.15–7.08 (m, 5 H), 6.92 (d, J = 7.3 Hz, 2 H), 4.35 (d, J = 11.2 Hz, 1 H), 4.22 (dd, J = 8.7, 7.8 Hz, 1 H), 4.06 (dd, J = 11.2, 2.8 Hz, 1 H), 3.01 (dd, J = 12.9, 6.2 Hz, 1 H), 2.60–2.47 (m, 3 H), 2.39 (s, 3 H), 2.00–1.91 (m, 1 H), 1.82–1.63 (m, 4 H), 1.58–1.50 (m, 1 H), 1.49–1.39 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 220.2, 173.7, 143.7, 136.7, 136.4, 129.4, 129.3, 128.6, 128.1, 126.7, 113.8, 70.0, 54.3, 43.6, 36.2, 36.1, 24.3, 23.2, 21.7, 20.5, 19.9 ppm. HRMS (ESI): 460.1561, $[C_{25}H_{27}NO_4SNa]^+$ requires 460.1553. For **32b**: yellow solid; m.p. 126–128 °C. IR (film): $\tilde{\nu}$ = 1715, 1634 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.3 Hz, 2 H), 7.13–7.07 (m, 5 H), 6.88 (d, J = 7.5 Hz, 2 H), 4.35 (d, J = 10.9 Hz, 1 H), 4.22 (dd, J = 8.7, 7.8 Hz, 1 H), 4.16 (dd, J = 11.1, 2.8 Hz, 1 H), 3.02–2.96 (dd, J = 15.1, 6.5 Hz, 1 H), 2.78–2.72 (m, 1 H), 2.50 (d, J = 7.8 Hz, 2 H), 2.38 (s, 3 H), 2.26–2.18 (m, 2 H), 1.68–1.56 (m, 2 H), 1.42–1.21 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.3, 174.7, 143.7, 136.6, 136.4, 129.4, 129.3, 128.7, 128.0, 126.7, 113.3, 70.0, 54.5, 42.5, 36.6, 36.1, 27.7, 21.7, 21.3, 21.3, 21.1 ppm. HRMS (ESI): 460.1540, $[C_{25}H_{27}NO_4SNa]^+$ requires 460.1553.

(*S*)-*N*-[1-(2-Hydroxy-6-oxocyclohex-1-enyloxy)-3-phenylpropan-2-yl] Tosylate (37): 2-Methoxyoxazolidine **11** (347 mg, 1.00 mmol) and **36** (367 mg, 1.50 mmol) were dissolved in CH_2Cl_2 (10 mL). The solution was cooled to –78 °C with stirring. $BF_3{\cdot}OEt_2$ (0.25 mL, 2.0 mmol) was added dropwise, and the mixture was warmed to –20 °C over 3 h, at which time **11** was no longer apparent by TLC. The solution was re-cooled to –78 °C, and $BF_3{\cdot}OEt_2$ (1.88 mL, 15.0 mmol) and H_2O (0.18 mL, 10 mmol) were added dropwise simultaneously. The mixture was warmed to room temp. overnight. The solution was extracted with 1 M aqueous NaOH (3 × 50 mL). The combined aqueous solutions were acidified with 12 M aqueous HCl. The resulting mixture was then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were dried with Na_2SO_4, and the solvent was evaporated to afford **37** (359 mg, 86%) as a yellow oil. IR (film): $\tilde{\nu}$ = 1737, 1601 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.61 (d, J = 8.3 Hz, 2 H), 7.24–7.17 (m, 5 H), 7.05–7.00 (m, 2 H), 5.72 (d, J = 6.0 Hz, 1 H), 3.96 (dd, J = 9.9, 2.7 Hz, 1 H), 3.68–3.58 (m, 2 H), 2.80 (d, J = 6.8 Hz, 2 H), 2.46 (t, J = 6.3 Hz, 4 H), 2.41 (s, 3 H), 1.94 (pentet, J = 6.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) (slow exchange): δ = 143.5, 136.8, 136.8, 134.1, 129.7, 129.4, 128.9, 127.4, 127.0, 74.1, 55.6, 38.5, 21.7, 20.4 ppm. HRMS (ESI): 438.1329, $[C_{22}H_{25}NO_5SNa]^+$ requires 438.1346.

Procedure for Two-Step One-Pot Geminal Acylation with 36 Followed by Heterocyclization: 2-Methoxyoxazolidine (1 equiv.) and **36** (1.5 equiv.) were dissolved in CH_2Cl_2 (10 mL/mmol). The solution was cooled to –78 °C with stirring. $BF_3{\cdot}OEt_2$ (2 equiv.) was added dropwise. The mixture was warmed to –20 °C over 3 h, at which time the 2-methoxyoxazolidine was no longer apparent by TLC. The solution was re-cooled to –78 °C, and $BF_3{\cdot}OEt_2$ (15 equiv.) and H_2O (10 equiv.) were added dropwise simultaneously. The mixture was warmed to room temp. overnight, and then it was washed with an equal volume of H_2O. The organic fraction was dried with Na_2SO_4, and the solvent was evaporated. The residual oil was dissolved in toluene (50 mL/mmol) and heated under reflux for 24 h in the presence of TsOH (2 equiv.) using a Dean–Stark apparatus. The mixture was cooled and washed with an equal volume of saturated aqueous $NaHCO_3$. The organic fraction was dried with Na_2SO_4, and the solvent was evaporated. Column chromatography provided the heterocycle.

(*S*)-3-Benzyl-4-tosyl-3,4,6,7-tetrahydro-2*H*-benzo[*b*][1,4]oxazin-8(5*H*)-one (38): By the two-step one-pot procedure above, **11** (347 mg, 1.00 mmol) and **36** (367 mg, 1.50 mmol) gave, after column chromatography with 2:1 hexanes/EtOAc, **38** (165 mg, 42%) as a yellow oil. IR (film): $\tilde{\nu}$ = 1683, 1610 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.53 (d, J = 8.4 Hz, 2 H), 7.32–7.19 (m, 7 H), 4.38–4.32 (m, 1 H), 3.99 (dd, J = 11.1, 1.4 Hz, 1 H), 3.22–3.13 (m, 1 H), 3.05 (dd, J = 11.1, 2.2 Hz, 1 H), 2.84 (dd, J = 13.3, 6.1 Hz, 1 H), 2.78–2.71 (m, 2 H), 2.55–2.50 (m, 2 H), 2.42 (s, 3 H), 2.08–1.96 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.1, 144.9, 136.7, 136.2, 135.3, 131.2, 130.3, 129.7, 128.8, 127.1, 127.1, 63.7, 55.5, 37.5, 36.6, 28.8, 22.2, 21.7 ppm. HRMS (ESI): 420.1229, $[C_{22}H_{23}NO_4SNa]^+$ requires 420.1240.

2-[(*S*)-4-Benzyl-2-hydroxy-3-tosyloxazolidin-2-yl]cyclopentanone (42): 2-Methoxyoxazolidine (**11**, 347 mg, 1.00 mmol) and **36** (367 mg, 1.50 mmol) were dissolved in CH_2Cl_2 (10 mL). The solution was cooled to –78 °C with stirring. $BF_3{\cdot}OEt_2$ (0.25 mL, 2.0 mmol) was added dropwise, and the mixture was warmed to –20 °C over 3 h, at which time **11** was no longer apparent by TLC. The solution was warmed to room temp., and then it was washed with an equal volume of H_2O. The organic fraction was dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was dissolved in THF (50 mL). A 1.0 M solution of TBAF (2.0 mL, 2.0 mmol) was added, and the mixture was stirred at room temp. until complete desilylation was evidenced by TLC. Column chromatography with 2:1 pentane/Et_2O provided **42** (294 mg, 71%), which was by ^1H NMR a 5:1 mixture of epimers, as a colorless solid. IR (film): $\tilde{\nu}$ = 1750 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) for the major isomer: δ = 7.79 (d, J = 8.3 Hz, 2 H), 7.36 (d, J = 8.3 Hz, 2 H), 7.32–7.20 (m, 3 H), 7.15 (d, J = 8.3 Hz, 2 H), 5.14 (s, 1 H), 3.89–3.83 (m, 3 H), 3.30–3.25 (m, 1 H), 3.12 (dd, J = 13.0, 3.1 Hz, 1 H), 2.83 (dd, J = 13.4, 10.3 Hz, 1 H), 2.57–2.38 (m, 6 H), 2.12–1.94 (m, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) for major isomer: δ = 215.7, 145.1, 137.3, 133.4, 130.3, 129.4, 129.0, 128.4, 127.1, 92.8, 80.0, 70.3, 61.8, 40.9, 36.0, 32.7, 21.8, 17.3 ppm. ^1H NMR (500 MHz, $CDCl_3$) for the minor isomer: δ = 7.75 (d, J = 8.2 Hz, 2 H), 7.33 (d, J = 8.3 Hz, 2 H), 7.32–7.20 (m, 3 H), 7.17–7.12 (m, 2 H), 5.17 (s, 1 H), 3.96–3.90 (m, 1 H), 3.89–3.83 (m, 1 H), 3.81 (dd, J = 8.6, 3.5 Hz, 1 H), 3.19 (dd, J = 13.5, 4.3 Hz, 1 H), 2.91 (dd, J = 13.5, 10.7 Hz, 1 H), 2.72–2.66 (m, 1 H), 2.57–2.38 (m, 6 H), 2.12–1.94 (m, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) for minor isomer: δ = 216.8, 144.9, 137.7, 133.8, 130.3, 129.4, 128.9, 128.3, 126.9, 92.1, 80.4, 70.9, 61.9, 40.6, 35.8, 33.4, 21.8, 17.0 ppm. HRMS (ESI): 438.1357, $[C_{22}H_{25}NO_5SNa]^+$ requires 438.1346.

X-ray Crystallographic Data: CCDC-1029589 (for **22**), -1029590 (for **32b**), -1029591 (for **33a**), -1029592 (for **34a**), -1029593 (for **34b**), and -1029594 (for **35b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Procedures and characterization data for compounds **11**, **15–20**, **23–25**, **33a**,**b–35a**,**b** and **39–41**. ^{1}H and ^{13}C NMR spectra of new numbered compounds.

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