Oxazolidinone Antibacterial Agents. An Enantioselective Synthesis of the [6,5,5] Tricyclic Fused Oxazolidinone Ring System and Application to the Synthesis of a Rigid DuP 721 Analogue

D. Mark Gleave* and Steven J. Brickner†

Medicinal Chemistry Research, Pharmacia & Upjohn, Inc., Kalamazoo, Michigan 49001

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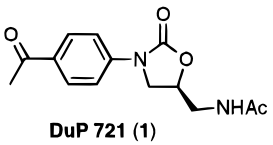
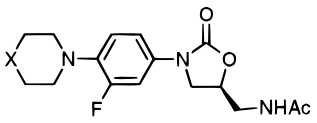
Oxazolidinones represent an exciting new class of synthetic antibacterial agents.[1,2] Key oxazolidinones synthesized to date include DuPont's seminal compound DuP 721 (**1**)[2] and Pharmacia & Upjohn's current clinical



DuP 721 (1)



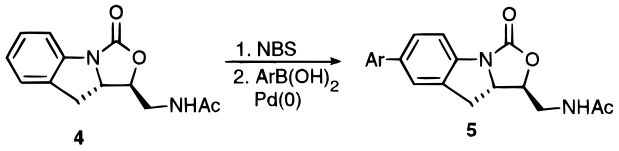
U-100592 (**2**) X = $NC(O)CH_2OH$
U-100766 (**3**) X = O

candidates U-100592 (**2**) and U-100766 (**3**).[1a] These compounds show potent *in vitro* and *in vivo* activity against multiple antibiotic resistant strains of Gram-positive bacteria.

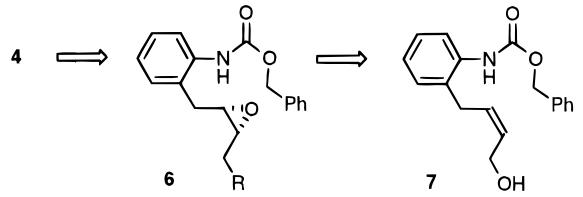
A number of rigid, tricyclic fused oxazolidinone antibacterial agents have been previously synthesized in racemic form.[3] A goal of this work was to gain an understanding of the importance of the spatial relationship and torsional angle between the aryl and oxazolidinone rings with regard to antibacterial activity. Among the more active compounds synthesized were several racemic [6,5,5] tricyclic fused oxazolidinones.[3a,b] A number of aryl analogues (**5**) were synthesized directly from the parent **4**, via bromination and Suzuki-type coupling (Scheme 1).[4] Only the *trans* compounds showed activity. In all cases tested, the corresponding *cis* isomers were inactive.

Given the high synthetic utility of the parent [6,5,5] tricyclic fused template **4** for constructing other potentially active tricyclic analogues, an asymmetric synthesis of this molecule was targeted.

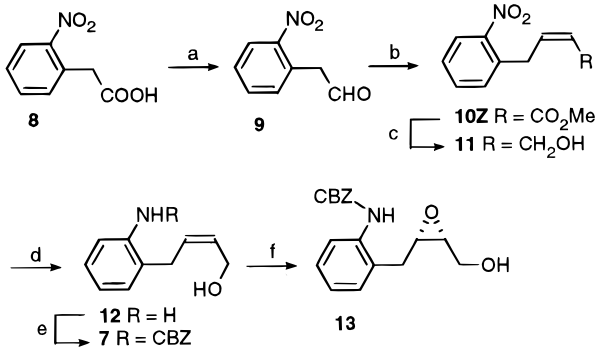
Scheme 1



Scheme 2



Scheme 3[a]



[a] Reagents: (a) BH_3·DMS, THF then PCC, CH_2Cl_2; (b) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-crown-6, THF, −78 °C, 43%; (c) DIBALH, $PhCH_3$, 0 °C, 100%; (d) $SnCl_2$·$2H_2O$, EtOH, 96%; (e) CBZCl, $NaHCO_3$, acetone, H_2O, 100%; (f) racemic series: m-CPBA, $CHCl_3$, 96%; asymmetric series: $Ti(i\text{-}PrO)_4$, L-(−)-DET, t-BuOOH, molecular sieves, CH_2Cl_2, 84% yield, >95% ee.

A key reaction in the synthesis of optically active 5(*R*)-(hydroxymethyl)-3-aryl-2-oxazolidinones is the previously reported aryl *N*-lithiocarbamate cyclization with (*R*)-(−)-glycidyl butyrate.[3a] We anticipated that an intramolecular version of this reaction might be employed to construct both five-membered rings of **4** in one step from the epoxy carbamate **6** (Scheme 2). The requisite epoxide would be best derived from the *cis*-olefin **7** using a Sharpless asymmetric epoxidation.[5]

2-Nitrophenyl acetaldehyde **9**[6] (Scheme 3) was considered an appropriate starting material; however, it was found to be unstable and difficult to purify. Decomposition occurred upon silica gel and also during attempted distillation. We found it most advantageous to purify **9** by immediately converting it to the ethylene acetal, which was readily purified by chromatography. Hydrolysis ($AcOH/H_2O$) then gave **9** in a high state of purity, suitable for carrying into the following Horner−Wadsorth−Emmons reaction. Using the Still conditions[7] with methyl bis(trifluoroethyl) phosphonoacetate and 5 equiv of 18-crown-6, **10** was obtained with a *Z:E* ratio of 15:1. In the absence of crown ether, the selectivity was only 4:1. The methyl acrylate isomers could be easily separated

* Phone: (616) 385-5499. Fax: (616) 833-2516. E-mail: dmgleav$@pwinet.upj.com.

† Current address: Central Research, Pfizer, Inc., Groton, CT 06340.

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(4) The most active aryl analog was that having a 3-pyridyl appendage. This compound was equipotent to vancomycin *in vivo.*

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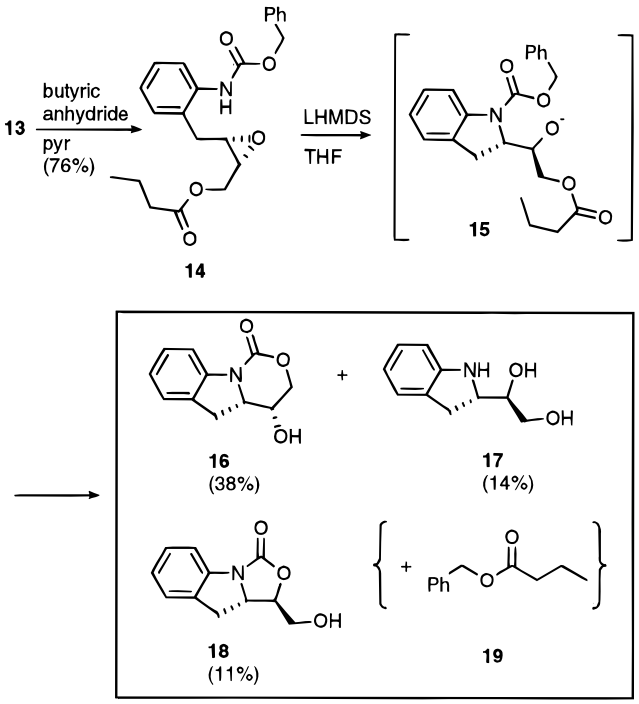
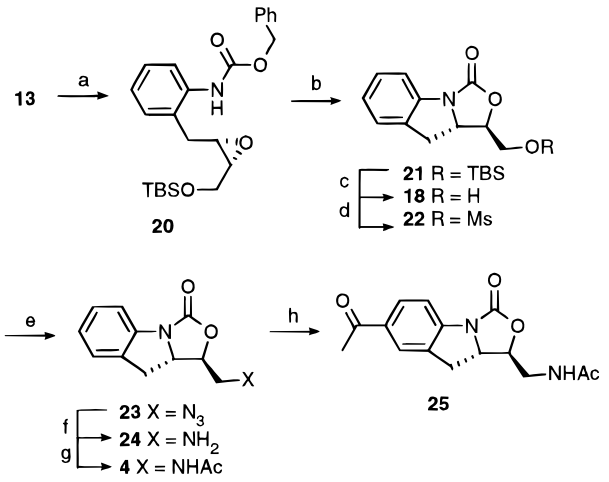
Scheme 4



Scheme 5[a]



[a] Reagents: (a) TBDMSCl, imidazole, CH_2Cl_2, 74%; (b) LHMDS, THF, −78 °C to rt, 100%; (c) n-Bu_4NF, THF, 73%; (d) MsCl, Et_3N, CH_2Cl_2, 100%; (e) NaN_3 DMF, 100%; (f) H_2, Pd/C, MeOH, 98%; (g) Ac_2O, pyr, 82%; (h) Ac_2O, MsOH, Ms_2O, 75%.

by chromatography.[8] The desired isomer **10Z** was then reduced with DIBALH[9] to give the allylic alcohol **11**. Reduction of the nitro group with stannous chloride[10] gave the aniline **12**, which was protected as the benzyl carbamate using standard Schotten−Baumann conditions to give intermediate **7** in 78% overall yield from **10Z**.

Treatment of **7** with *m*-CPBA gave epoxide **13** in 96% yield. Initial attempts to perform an asymmetric Sharpless epoxidation of **7**, using 10, 20 or 50 mol % of the $Ti(Oi\text{-}Pr)_4$ and L-(+)-diethyl tartrate reagents in the presence of 4 Å molecular sieves,[5b] gave very low yields of **13**. The reaction was successful when a stoichiometric amount of the reagents were used at −20 °C in the presence of molecular sieves,[11] giving optically active epoxide **13** in 84% yield. An ee of ≥95% was consistently achieved over a number of runs, as measured by ^{19}F and ^{1}H NMR of the corresponding Mosher ester.[12]

The new cyclization reaction was initially examined using racemic, rather than optically active, epoxide **13** for the following reasons: (i) to demonstrate proof of concept, (ii) to provide both enantiomers to facilitate analysis of the ee in the asymmetric synthesis, and (iii) to optimize reaction conditions. Opening of the epoxide to form the desired five-membered ring (5-exo vs 6-endo closure) was expected.[13] The cyclization reaction was first performed with the hydroxy group of **13** protected as the butyrate ester **14** (Scheme 4), in direct analogy to the intermolecular version of the cyclization which uses glycidyl butyrate.[3a] Using lithium hexamethyldisilazane (LiHMDS) as base, the major product was the undesired [6,5,6] isomer **16**[14] (38% isolated yield). Only a small amount of the desired [6,5,5] isomer **18** (11%) was observed, together with the ring-opened product **17** (14%). The fact that the undesired [6,5,6] product was being formed implied that the butyrate protecting group of intermediate **15** was either cleaved or migrated to the adjacent oxygen atom. This would liberate a terminal alkoxide which could attack the carbamate carbonyl to generate the unwanted six-membered ring. Both NaHMDS and KHMDS were tried as alternative bases; their use led to a decrease in the amount of **16** and an increase in the amount of **17**. The desired oxazolidinone **18** was again formed only in very low yield (<10%). Not surprisingly, when the cyclization was attempted on the unprotected alcohol **13** using 2 equiv of LiHMDS, the undesired **16** was formed as the major product in 46% isolated yield.

It became clear that the terminal hydroxy group would require a nonlabile protecting group which would preclude formation of the six-membered tetrahydrooxazinone ring in **16**. The (*tert*-butyldimethyl)silyl protecting group proved suitable. The cyclization reaction with **20** ran smoothly using LiHMDS as base (Scheme 5).[15] The desired (crude) silyl-protected oxazolidinone **21** was produced in quantitative yield. Deprotection of the silylated oxazolidinone with Bu_4NF furnished the free alcohol **18** (73%). In the asymmetric series, **18** was converted to the Mosher ester and the ee was shown to be ≥95% (^{1}H and ^{19}F NMR). The remaining steps in the synthesis (conversion of ROH to RNHAc) were performed using methodology similar to that described previously.[1] Alcohol **18** was converted to mesylate **22**, which was readily displaced with sodium azide at 70 °C. Hydrogenation of azide **23** followed by acylation furnished the target acetamide **4** in good overall yield (73%) from the alcohol **18**. In the asymmetric series the ee of **4** was determined by chiral HPLC to be 98.8%.[16]

(8) Isolated yields of the *cis* olefin **10Z** were often only 40−50%. This was due to partial isomerization of the olefin upon silica gel or on prolonged storage. It isomerized fairly readily to an inseparable mixture, presumed to be the *trans* α,β-unsaturated ester and the *trans*-styrene. To circumvent this, the ester **10** was immediately reduced to **11** with DIBALH.

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(11) For a successful Sharpless asymmetric epoxidation performed on a related system, see: Sharpless, K. B. *et al.*, *Pure Appl. Chem* **1983**, *55*, 589 (*cis*-$PhCH_2CH{=}CHCH_2OH$, 83% yield, 91% ee).

(12) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *49*, 7165.

(13) Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734.

(14) The structure of the [6,5,6] isomer **16** was confirmed by X-ray crystallography (W. Watt and F. Han, Pharmacia & Upjohn, Inc.).

(15) The reaction was unsuccessful when KHMDS was used as base. Less than 10% of the desired oxazolidinone was observed. Isolated reaction products seemed to indicate that 6-endo cyclization of the epoxide had occurred.

As a demonstration of the synthetic utility of the parent tricyclic oxazolidinone **4**, it was converted in one step to **25**,[17] the tricyclic analogue of DuP 721, by Friedel−Crafts acylation.[2b,3c]

In summary, a novel intramolecular version of the aryl *N*-lithiocarbamate−epoxide cyclization has been demonstrated in the synthesis of [6,5,5] tricyclic fused oxazolidinones **4** and **25**. In this reaction both five-membered rings are constructed in one step with complete regiochemical control. High enantioselectivity was achieved through the use of an asymmetric Sharpless epoxidation, which furnished product of 98.8% ee. The parent **4** is a useful intermediate for the potential synthesis of a large number of novel oxazolidinone antibiotics.[3a]

Experimental Section

2-Nitrophenylacetaldehyde (9). To a solution of 2-nitrophenylacetic acid (**8**) (27.173 g, 150 mmol) in THF (150 mL) was added dropwise, via addition funnel, borane−methyl sulfide complex (77.5 mL of a 2.0 M solution in diethyl ether). The mixture was heated to reflux for 1 h. After cooling to rt the THF was removed *in vacuo*. The intermediate borane was then dissolved in CH_2Cl_2 (75 mL) and was added dropwise to a suspension of PCC (48.501 g, 225 mmol) in CH_2Cl_2 (200 mL). The mixture was heated to reflux for 1 h. After cooling to rt, Et_2O (300 mL) was added and the suspension stirred for 20 min. The mixture was filtered through diatomaceous earth (an additional 3 × 200 mL of Et_2O was passed through the filter pad). Removal of solvents *in vacuo* gave 18.68 g (75%) of crude 2-nitrophenylacetaldehyde (**9**). This procedure provides material of about 80% purity. Attempts to purify by distillation or chromatography led to significant decomposition. To a solution of crude **9** (18.68 g, 113 mmol) in toluene (400 mL) were added PPTS (5.680 g, 22.6 mmol) and ethylene glycol (15.75 mL, 283 mmol). The mixture was heated to reflux in the presence of a Dean−Stark trap. After 2 h the mixture was cooled to rt and washed with saturated $NaHCO_3$ solution and brine and then dried (sodium sulfate). Removal of the solvents *in vacuo* yielded 24.21 g of a dark orange oil. Chromatography (SiO_2, 10% → 20% EtOAc/hexane) gave 12.033 g (51%) of the intermediate 2-nitrophenylacetaldehyde ethylene acetal as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.89 (d, J = 8.1 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.39 (m, 2H), 5.18 (t, J = 4.5 Hz, 1H), 3.84 (m, 4H), 3.35 (d, J = 4.5 Hz, 2H). A solution of the acetal (6.904 g, 33.0 mmol) in acetic acid (30 mL) and water (7 mL) was heated in an oil bath to 80 °C for 42 h. After cooling to rt, water (200 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organics were then washed with saturated aqueous $NaHCO_3$ (3 × 200 mL, **Caution!** CO_2 evolution). Solvents were removed to provide 5.53 g (100%) of 2-nitrophenylacetaldehyde (**9**) (>90% purity) as an orange oil. Spectral data were identical to that previously reported.[6]

(*Z*)-Methyl 4-(2-nitrophenyl)but-2-enoate (10Z). To a solution of bis(2,2,2-trifluoroethyl ((methoxycarbonyl)methyl) phosphonate (0.66 mL, 3.1 mmol) in THF (60 mL) at −78 °C was added KHMDS (6.2 mL of a 0.5 M solution in toluene) dropwise. After 5 min a solution of 2-nitrophenylacetaldehyde (**9**) (0.51 g) in THF (2 mL) was added dropwise, at which point the solution turned purple. After 2 h the reaction was quenched with saturated NH_4Cl solution (20 mL) and allowed to warm to rt. The mixture was extracted with EtOAc (2 × 20 mL), and the organics were then washed with brine. After drying (sodium sulfate) and removal of solvents, the crude product was chromatographed (SiO_2, 5% ethyl acetate/hexane) to give 238 mg (43%) of the *cis*-olefin **10Z** as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.97 (d, J = 9.3 Hz, 1H), 7.56 (dd, J = 8.0 Hz, J' = 6.3 Hz, 1H), 7.49 (d, J = 6.4 Hz, 1H), 7.42 (dd, J = 7.7 Hz, J' = 7.0 Hz, 1H), 6.40 (dt, J = 11.4, J' = 7.3 Hz, 1H), 5.9 (d, J = 11.4 Hz, 1H), 4.32 (d, J = 7.3 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 166.9, 149.4, 146.1, 134.8, 133.7, 132.7, 128.0, 125.1, 120.9, 51.6, 32.6. Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.63; H, 5.09; N, 6.17.

(*Z*)-4-(2-Nitrophenyl)but-2-enol (11). To a solution of ester **10Z** (3.527 g, 15.9 mmol) in dry toluene at 0 °C was added, dropwise, a solution of DIBALH (35.1 mL of a 1 M solution in toluene). After stirring for 1 h at 0 °C, the reaction was quenched with MeOH (15 mL) and 1 N HCl (15 mL). The solution was warmed to rt and an additional 150 mL of 1 N HCl was added to dissolve the precipitated aluminum salts. The mixture was extracted with CH_2Cl_2 (3 × 75 mL), and the combined organics were washed with brine. Drying over $MgSO_4$ followed by removal of solvents *in vacuo* yielded 3.072 g (100%) of **10Z** as an orange oil which was of sufficient purity to be used in the next reaction. An analytically pure sample was obtained by bulb-to-bulb distillation (0.1 mmHg, 150−175 °C): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.93 (d, J = 8.2 Hz, 1H), 7.55 (dd, J = 7.5 Hz, J' = 7.0 Hz, 1H), 7.39 (d + dd, J = 8.2 Hz, J' = 7.5 Hz, J'' = 7.0 Hz, 2H), 5.80 (m, 1H), 5.62 (m, 1H), 4.32 (d, J = 6.6 Hz, 2H), 3.76 (d, J = 7.3 Hz, 2H), 1.51 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 149.6, 135.5, 133.6, 132.0, 131.3, 128.5, 127.8, 125.1, 58.8, 31.4. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.78; H, 5.88; N, 7.22.

(*Z*)-4-(2-Anilino)but-2-enol (12). To a solution of aryl nitro compound **11** (3.00 g, 15.5 mmol) in EtOH (30 mL) was added $SnCl_2 \cdot 2H_2O$ (17.52 g, 77.6 mmol). The mixture was heated to 80 °C. After 40 min, the solution was cooled to rt and poured onto 65 g of ice. Water (100 mL) was added, followed by the careful addition of solid $NaHCO_3$ (13 g, 155 mmol) until the solution tested basic. The mixture was then extracted with EtOAc (5 × 150 mL). The combined organics were washed with brine and dried (sodium sulfate). Removal of solvents yielded 2.44 g (96%) of the aniline as an orange oil. The material was used without further purification in the next step of the synthesis. An analytically pure sample was obtained by chromatography (SiO_2; EtOAc/hexane 20 → 50%) which gave a yellow solid. Mp: 38−39 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.10−7.03 (m, 2H), 6.77 (dd, J = 7.5 Hz, J' = 7.2 Hz, 1H), 6.68 (d, J = 7.7 Hz, 1H), 5.79 (m, 1H), 5.66 (m, 1H), 4.29 (d, J = 6.7 Hz, 2H), 4.0−2.8 (br s, 3H) 3.33 (d, J = 7.2 Hz, 2H. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 144.8, 130.7, 130.0 (2C), 127.9, 125.1, 119.5, 116.5, 58.4, 30.5. Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.42; H, 8.19; N, 8.47.

(*Z*)-4-(2-((Benzyloxycarbonyl)amino)phenyl)but-2-enol (7). To a solution of the aniline **12** (2.166 g, 13.3 mmol) and $NaHCO_3$ (2.230 g, 26.5 mmol) in 2:1 acetone:water (90 mL), at 0 °C, was added, dropwise, benzyl chloroformate (2.27 mL, 15.9 mmol). The solution was allowed to slowly warm to rt and stirred overnight. The acetone was removed *in vacuo*, an additional 50 mL of water was added, and the aqueous solution was extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo* to yield 3.959 g (100%) of a cream colored solid. Mp: 82−83 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.78 (br s, NH), 7.45−7.30 (m, 6H), 7.27 (dd, J = 8.2, J' = 6.3, 1H), 7.18 (d, J = 6.3 Hz, 1H), 7.10 (dd, J = 7.5 Hz, J' = 7.1 Hz, 1H), 5.76 (m, 1H), 5.61 (m, 1H), 5.20 (s, 2H), 4.29 (dd, J = 5.9 Hz, J' = 5.8 Hz, 2H), 3.44 (d, J = 7.4 Hz, 2H), 1.70 (t, J = 5.9 Hz, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 155.1, 136.7, 136.3, 130.5, 130.1, 129.9, 129.0 (2C), 128.8, 128.7, 127.7, 125.5, 123.7, 67.4, 58.5, 30.9. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.48; H, 6.39; N, 4.55.

Intermediates in the asymmetric synthesis follow.

(−)-(2*S*,3*R*)-4-(2-((Benzyloxycarbonyl)amino)phenyl)-2,3-epoxybutanol (−)-13). To a suspension of powdered, activated 4 Å molecular sieves (350 mg) in dry CH_2Cl_2 (13 mL) at −10 °C was added a solution of (L)-(+)-diethyl tartrate (509 mg; 2.47 mmol) in CH_2Cl_2 (2 mL + 1mL rinse) followed by Ti(Oi-Pr)$_4$ (0.69 mL, 2.35 mmol). The reaction mixture was then cooled to −22 °C and a solution of t-BuOOH (1.03 mL of a 5−6 M solution in decane) was added. After stirring for 1 h (aging the reagent) a solution of allylic alcohol **7** (700 mg) in CH_2Cl_2 (7 mL + 2 mL rinse) was added dropwise over 10 min. Stirring was continued at −22 °C for 20 h before quenching with 10% aqueous tartaric acid (7 mL). The mixture was allowed to warm to rt and stirred for an additional 1 h. Brine (30 mL) was added and

(16) HPLC was performed on an (R,R) Whelk-01, 0.46 × 25 cm column, (Regis Technologies, Morton Grove, Il). The running conditions were 40% i-PrOH/hexane (v/v) at 1.0 mL/min, with the monitor set at 236 nm. Observed t_R = 12.0 and 15.4 min.

(17) Compound **25** exhibits strong antibacterial activity. It is approximately 2-fold less active than DuP 721.

the mixture was extracted with EtOAc (3 × 20 mL). The combined organics were dried (sodium sulfate) and solvents removed to give 1.310 g of a yellow oil comprising the desired epoxide **(−)-13**, together with diethyl tartrate. The crude oil was dissolved in Et_2O (20 mL) and cooled in an ice bath. 1 N NaOH (7 mL) was added to hydrolyze the tartrate ester. After stirring for 30 min, the organic phase was removed and washed with brine. Drying (sodium sulfate) followed by removal of solvent yielded 621 mg (84%) of **(−)-13** as a waxlike solid, which was of sufficient purity for the next reaction. An analytically pure sample was prepared by recrystallizing from EtOAc/hexanes: Mp: 43−45 °C. $[\alpha]^{25}_D = -7.07°$ (*c* 10.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.80 (br s, 1H), 7.45−7.27 (m, 7H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.10 (dd, *J* = 7.5 Hz, *J′* = 7.3 Hz, 1H), 5.22 (2 x d, *J* = 12.3 Hz, 2H), 3.96 (m, 2H), 3.27 (dd, *J* = 9.7 Hz, *J′* = 4.9 Hz, 1H), 3.21 (m, 1H), 2.98 (dd, *J* = 14.9 Hz, *J′* = 4.1 Hz, 1H), 2.90 (dd, *J* = 14.9 Hz, *J′* = 8.1 Hz, 1H), 1.85 (br s, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 155.0, 136.9, 136.8, 130.6, 129.8, 129.0, 128.6, 128.5, 128.2, 125.3, 123.8, 77.9, 67.4, 60.5, 58.0, 31.2. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47. Found: C, 68.70; H, 6.21; N, 4.60.

(+)-(2*S*,3*R*)-4-(2-((Benzyloxycarbonyl)amino)phenyl)-1-(*tert*-butyldimethylsiloxy)-2,3-epoxybutane ((+)-20). To a solution of TBDMSCl (113 mg; 0.75 mmol), DMAP (ca. 1 mg), and imidazole (51 mg; 0.75 mmol) in DMF (0.5 mL) at 0 °C was added a solution of glycidol **(−)-13** (157 mg; 0.50 mmol) in DMF (0.5 mL + 0.2 mL rinse). The mixture was allowed to slowly warm to rt. After 2.5 h the mixture was poured onto water (10 mL) and extracted with hexanes (4 × 8 mL). The combined organics were then dried (sodium sulfate) and the volatiles removed to give 158 mg (74%) of the silylated alcohol **(+)-20** as a white solid which was of sufficient purity to be used in the next reaction. An analytically pure sample was obtained by recrystallizing from hexanes. Mp: 63−64 °C. $[\alpha]^{25}_D = +11.58°$ (*c* = 5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.84 (br s, NH), 7.43−7.27 (m, 7H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.08 (dd, *J* = 7.5, Hz, *J′* = 6.4 Hz, 1H), 5.21 (s, 2H), 3.93 (d, *J* = 5.2 Hz, 2H), 3.22 (m, 1H), 3.15 (m, 1H), 2.97 (dd, *J* = 15.0 Hz, *J′* = 3.1 Hz, 1H), 2.78 (*J* = 15.0 Hz, *J′* = 8.9 Hz, 1H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 154.6, 137.3, 136.9, 130.6, 129.2, 128.9, 128.6, 128.5, 128.3, 124.8, 123.2, 67.2, 61.8, 58.4, 58.0, 31.9, 26.3, 18.7, −4.8, −5.0. Anal. Calcd for $C_{24}H_{33}NO_4Si$: C, 67.42; H, 7.78; N, 3.28. Found: C, 67.07; H, 8.15; N, 3.30.

(−)-(1*R*,9a*S*)-((*tert*-Butyldimethylsiloxy)methyl)-9,9a-dihydro-3-oxo-1*H*,3*H*-oxazolo[3,4-*a*]indole ((−)-21). To a solution of epoxysilane **(+)-20** (408 mg; 0.95 mmol) in THF (5 mL), at −78 °C, was added, dropwise, a solution of LHMDS (1.14 mL of a 1M solution in hexanes). The reaction temperature was maintained at −78 °C for 2 h. The dry ice bath was allowed to slowly warm to ambient temperature. Stirring was continued overnight. The solution was then cooled in an ice bath and quenched with saturated NH_4Cl solution. The reaction mixture was extracted with EtOAc (4 × 5 mL) and the combined organics then washed with brine. Drying over sodium sulfate and removal of solvents yielded 304 mg (quant.) of a yellow oil which slowly crystallized upon standing. This material was of sufficient purity to be used in the next reaction. An analytically pure sample was obtained by recrystallizing from hexane which gave white feathery crystals. Mp: 81−83 °C. $[\alpha]^{25}_D = -47.00°$ (*c* = 2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.45 (d, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.10 (dd, *J* = 7.3 Hz, *J′* = 6.8 Hz, 1H), 4.68 (m, 1H), 4.50 (m, 1H), 3.98 (dd, *J* = 10.9 Hz, *J′* = 4.1 Hz, 1H), 3.93 (dd, *J* = 10.9 Hz, *J′* = 5.4 Hz, 1H), 3.26 (dd, *J* = 15.9 Hz, *J′* = 9.1 Hz, 1H), 3.11 (dd, *J* = 15.9 Hz, *J′* = 9.3 Hz, 1H), 0.93 (s, 9H), 0.13 (2 x s, 6H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 156.6, 141.1, 132.6, 128.5, 125.5, 125.1, 115.8, 83.6, 63.4, 62.1, 35.8, 26.1 (2C), 18.6, −5.0. Anal. Calcd for $C_{17}H_{25}NO_3Si$: C, 63.92; H, 7.89; N, 4.38. Found: C, 63.81; H, 7.97; N, 4.36.

(−)-(1*R*,9a*S*)-(9,9a-Dihydro-3-oxo-1*H*,3*H*-oxazolo[3,4-*a*]-indol-1-yl)methanol ((−)-18). To a solution of the silylated oxazolidinone **(−)-21** (270 mg; 0.85 mmol) in THF (4 mL) at 0 °C, under nitrogen, was added tetrabutylammonium fluoride (1.54 mL of a 1.1 M solution in THF). The mixture was stirred at 0 °C for 30 min. Water (6 mL) was added and the mixture was extracted with EtOAc (4 × 5 mL). The combined organics were washed with brine and dried over sodium sulfate. Solvents were removed *in vacuo* and the resulting brown oil was purified by chromatography (SiO_2, MeOH/CH_2Cl_2 0% → 3%) to give a colorless oil (108 mg; 62%) which slowly crystallized upon standing to give **(−)-18** as colorless needles. Mp: 99−102 °C. $[\alpha]^{25}_D = -77.6°$ (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43 (d, *J* = 7.8 Hz, 1H), 7.26 (t, *J* = 6.8 Hz, 1H), 7.22 (d, *J* = 8.2, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 4.75 (m, 1H), 4.59 (m, 1H), 4.05 (br d, *J*= 12 Hz, 1H), 3.87 (br d, *J* = 12 Hz, 1H), 3.27 (dd, *J* = 15.8 Hz, *J′* = 9.0 Hz, 1H), 3.12 (dd, *J* = 15.8 Hz, *J′* = 9.3 Hz, 1H), 2.76 (br s, OH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 156.5, 140.2, 132.3, 128.0, 125.2, 124.8, 115.2, 84.0, 62.0, 60.6, 34.9. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.39; H, 5.40; N, 6.83. Found: C, 64.72; H, 5.36; N, 6.78.

(−)-[(1*R*,9a*S*)-(9,9a-Dihydro-3-oxo-1*H*,3*H*-oxazolo[3,4-*a*]-indol-1-yl)methyl]methanesulfonate ((−)-22). To a mixture of the alcohol **(−)-18** (89 mg; 0.43 mmol) and Et_3N (0.13 mL, 0.95 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added, dropwise, MsCl (40.2 μL; 0.52 mmol). The mixture was allowed to slowly warm to rt and stirred overnight. Water (6 mL) was added and the mixture extracted with CH_2Cl_2 (2 × 5 mL). The combined organics were washed with brine (10 mL) and dried (sodium sulfate), and the solvents were removed *in vacuo* to give 137 mg of a colorless oil which was purified by chromatography (SiO_2, 20% → 40% EtOAc/hexane) to give 122 mg (100%) of **(−)-22** as a colorless oil which solidified upon standing: Mp: 53−55 °C. $[\alpha]^{25}_D = -66.45°$ (*c* = 2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43 (d, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 4.74 (m, 1H), 4.66 (m, 1H), 4.65 (dd, *J* = 11.6 Hz, *J′* = 3.7 Hz, 1H), 4.50 (dd, *J* = 11.6 Hz, *J′* = 4.6 Hz, 1H), 3.32 (dd, *J* = 15.9 Hz, *J′* = 8.9 Hz, 1H), 3.16 (dd, *J* = 15.9 Hz, *J′* = 9.2 Hz, 1H), 3.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 155.6, 140.5, 132.1, 128.7, 125.7, 125.6, 115.9, 80.2, 68.0, 61.5, 38.3, 35.5. Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 50.88; H, 4.63; N, 4.94. Found: C, 50.90; H, 4.60; N, 5.01.

(−)-(1*R*,9a*S*)-1-(Azidomethyl)-9,9a-dihydro-3-oxo-1*H*,3*H*-oxazolo[3,4-*a*]indole ((−)-23). A mixture of mesylate **(−)-22** (99 mg; 0.35 mmol) and sodium azide (79 mg; 1.22 mmol) in DMF (2.5 mL) was heated to 70 °C and stirred overnight. The reaction mixture was cooled to rt then water (10 mL) was added and the mixture extracted with EtOAc (3 × 5 mL). The combined organics were dried (sodium sulfate) and the solvents removed *in vacuo* to yield 74 mg (91%) of a colorless oil which solidified overnight. This material was of sufficient purity to be used in the next step of the synthesis. An analytically pure sample of azide **(−)-23** was obtained by recrystallizing from EtOAc/hexane. Mp: 90−91 °C. $[\alpha]^{25}_D = -111.0°$ (*c* = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.45 (d, *J* = 7.8 Hz, 1H), 7.28 (dd {obscured by $CHCl_3$ peak}, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.11 (dd, *J* = 7.6 Hz, *J′* = 7.3 Hz, 1H), 4.61 (m, 2H), 3.75 (dd, *J* = 13.1 Hz, *J′* = 4.5 Hz, 1H), 3.69 (dd, *J* = 13.1 Hz, *J′* = 4.4 Hz, 1H), 3.29 (dd, *J* = 15.7 Hz, 1H), 3.12 (dd, *J* = 15.7 Hz, *J′* = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 155.8, 140.7, 132.3, 128.6, 125.7, 125.4, 115.8, 81.7, 62.4, 52.8, 35.4; exact mass calcd for $C_{11}H_{10}N_4O_2$ 230.0804, found 230.0806.

(−)-(1*R*,9a*S*)-1-(Aminomethyl)-9,9a-dihydro-3-oxo-1*H*,3*H*-oxazolo[3,4-*a*]indole ((−)-24). To a solution of azide **(−)-23** (5.9 mg; 25.6 μmol) in MeOH (0.75 mL) was added 10% Pd/C (1.5 mg). The mixture was stirred at rt under an atmosphere of hydrogen (balloon). After 2 h the reaction mixture was washed through a small plug of diatomaceous earth using an additional 1.5 mL of MeOH. Removal of solvent yielded 5.1 mg (98%) of **(−)-24** as a white solid, which was of sufficient purity to be used in the next reaction. Melting point 106−108 °C. $[\alpha]^{25}_D = -76.1°$ (*c* = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.45 (d, *J* = 7.8 Hz, 1H), 7.27 (dd obscured by $CHCl_3$ peak, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.11 (dd, *J* = 7.6 Hz, *J′* = 7.3 Hz, 1H), 4.60 (m, 1H), 4.51 (m, 1H), 3.27 (dd, *J* = 15.8 Hz, *J′* = 8.8 Hz, 1H), 3.18 (dd, *J* = 13.6 Hz, *J′* = 4.2 Hz, 1H), 3.13 (m, 2H), 0.93 (br s, NH_2). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 156.6, 141.0, 132.5, 128.5, 125.6, 125.2, 115.8, 85.4, 62.4, 45.0, 35.6; exact mass calcd for $C_{11}H_{12}N_2O_2$ 204.0899, found 204.0901.

(−)-(1*R*,9a*S*)-*N*-[(9,9a-Dihydro-3-oxo-1*H*,3*H*-oxazolo[3,4-*a*]indol-1-yl)methyl]acetamide ((−)-4). To a solution of amine **(−)-24** (5.0 mg; 24.5 μmol) in CH_2Cl_2 (0.75 mL), under nitrogen, were added pyridine (10 μL, 123 μmol) and acetic anhydride (6 μL, 61.3 μmol). The mixture was stirred at rt for 30 min. Solvents were removed *in vacuo* to yield 6.6 mg of the crude acetamide. Purification by chromatography (SiO_2; 0 →

2% MeOH/CH_2Cl_2) yielded 4.9 mg (82%) of acetamide **(−)-4** as a colorless oil. $[\alpha]^{25}_D = -53.48°$ ($c = 0.89$, CH_2Cl_2). ^{1}H NMR (CDCl3, 400 MHz) δ: 7.40 (d, $J = 7.8$ Hz, 1H), 7.24 (m, 2H), 7.10 (dd, $J = 7.5$ Hz, $J' = 7.3$ Hz, 1H), 6.29 (br s, 1H), 4.60 (m, 1H), 4.50 (m, 1H), 3.79 (ddd, $J = 14.7$ Hz, $J' = 6.1$ Hz, $J'' = 3.2$ Hz, 1H), 3.68 (dt, $J = 14.7$ Hz, $J' = 6.0$ Hz, 1H), 3.28 (dd, $J = 15.9$ Hz, $J' = 9.0$ Hz, 1H), 3.11 (dd, $J = 15.9$ Hz, $J' = 9.2$ Hz, 1H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 171.0, 155.8, 140.1, 132.1, 128.2, 125.4, 125.0, 115.3, 82.6, 61.8, 41.4, 34.9, 23.1. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.59; H, 5.66; N, 11.29.

(+)-(1*R*,9a*S*)-*N*-[(7-Acetyl-9,9a-dihydro-3-oxo-1*H*,3*H*-oxazolo[3,4-*a*]indol-1-yl)methyl]acetamide ((+)-25). To a mixture of the tricyclic parent oxazolidinone **(−)-4** (11.1 mg; 45.1 μmol), Ms_2O (17.8 mg; 102 μmol), and MsOH (250 μL) in CH_2Cl_2 (50 μL) at 0 °C was added acetic anhydride (28.4 L; 301 mol). The temperature was maintained between 0 and 10 °C for 6 h and then allowed to slowly warm to rt overnight. The mixture was then added to ice-cold saturated aqueous $NaHCO_3$ (1 mL) and extracted with EtOAc (3 × 1 mL). The combined organics were washed with brine and dried (Na_2SO_4) and the solvents removed *in vacuo* to give 16.5 mg of a brown oil. The oil was purified by chromatography (SiO_2; 0 → 2% MeOH/CH_2Cl_2) to give 9.8 mg (75%) of a pale yellow oil which solidified upon standing: Mp: 171−173 °C. $[\alpha]^{25}_D = +15.5°$ ($c = 0.20$, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.89 (d, $J = 8.2$ Hz, 1H), 7.85 (s, 1H), 7.46 (d, $J = 8.2$ Hz, 1H), 6.16 (br s, NH), 4.62 (m, 1H), 4.57 (m, 1H), 3.85−3.65 (m, 2H), 3.36 (dd, $J = 16.2$ Hz, $J' = 8.9$ Hz, 1H), 3.14 (dd, $J = 16.2$ Hz, $J' = 8.9$ Hz, 1H), 2.58 (s, 3H), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 197.1, 171.3, 155.3, 144.5, 134.6, 133.3, 130.2, 125.9, 114.7, 83.6, 62.2, 41.4, 34.6, 27.0, 23.5. Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.21; H, 5.33; N, 9.72.

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Supporting Information Available: Additional experimental data including IR and MS data for all compounds, experimental procedures for intermediates in the racemic synthesis, Mosher ester data and procedures and copies of ^{13}C NMR for compounds **23** and **24** (10 pages). This information is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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