A Novel and Selective Approach to Enantiomerically Pure Bicyclic-Trans-Lactams via a Titanium Enolate of a Thiopyridyl Ester

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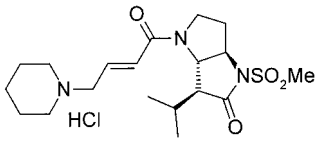
The bicyclic-trans-lactam **1** (GW311616A) is a potent inhibitor of human neutrophil elastase and is of interest due to its potential as a treatment for respiratory disease such as chronic bronchitis.[1]



1, GW311616A

Due to the requirements of a clinical program, we needed to develop efficient and robust chemistry that was suitable for scale-up. In an earlier paper,[1] workers from Glaxo Wellcome revealed several approaches to the bicyclic-trans-lactam core which introduced the isopropyl group with 3:1 selectivity in the *N*-acyliminium ion coupling chemistry. Furthermore, a trifluoroacetamide group was used as a protecting group and subsequently had to be removed. The current work has focused on improving the selectivity of the coupling and avoiding the use of additional protecting groups. We have now improved on these earlier routes by introducing a highly selective titanium enolate *N*-acyliminium ion coupling and using the methanesulfonamide group as both a protecting group and required substituent. A further advantage of the new route is that the methanesulfonamide group acts as an activating group, and hence, the coupling product **7** can be cyclized directly to bicyclic-trans-lactam **8** under mild conditions (see Scheme 1).

The dynamic kinetic resolution of racemic aminolactam **2**, via the (+)-di-*p*-toluoyltartaric acid (DPTT) salt **3**, has already been described.[1] Conversion of this salt into the sulfonamide lactam **4** was carried out by dissolution in hydrochloric acid, filtration of the DPTT, basification with $NaHCO_3$, and treatment with mesyl chloride to give **4** in 84% yield. The enantiomeric purity of **4** was determined by HPLC and found to be 70% ee. Reduction of **4** was carried out with $LiBH_4$ in THF and the resultant "lactol" converted in situ to the methyl ethers **5** (as an approximate 1:1 mixture of epimers) with methanolic HCl. Evaporation of the solvent gave the methyl ethers **5** as a viscous oil in 99% yield. Alternatively, on a larger scale a solvent exchange into dichloromethane (DCM) provided a solution of the methyl ethers suitable for the next step.

NOE experiments were conducted on the enolate formed when the known 2-pyridylthioester[2] **6** was treated with titanium tetrachloride and di-isopropylethylamine to generate the titanium enolate. The enolate was prepared at −20 °C and the sample was then warmed to the appropriate temperature and spectra recorded. The ratio of the *Z* (major) to the *E* (minor) isomer was monitored from −10 to +10 °C over 160 min and is summarized in Table 1. It is apparent that the ratio of *Z*/*E* enolates (initially 88.5:11.5) is slightly lower in this study than that found by previous authors (95:5).[3] Furthermore, it is interesting to note that the enolate appears to degrade over time and especially at higher temperatures, regenerating **6** and leading to a lower *Z*/*E* ratio.

The titanium enolate of **6** was treated with **5** at 0−5 °C and led, after workup, to a mixture of the major diastereoisomer **7** and minor diastereoisomer[4] in a ratio of ca. 12:1. This compares favorably with the 3:1 diastereoisomer ratio seen with silylketene acetals under $BF_3{\cdot}OEt_2$ catalysis.[1] The ratio of **6**:**5** required to achieve rapid conversion and optimum yield was found to be 2:1. No reaction was seen at −10 °C, and hence, the reaction temperature was determined by a compromise between the instability of the enolate and its reactivity.

A possible transition-state model to explain the observed selectivity is presented in Figure 1. The structure of the titanium enolate of **6** is the same as that proposed by Cinquini and Cozzi[5] but the *N*-acyliminium ion is not linked to titanium through nitrogen as with an imine condensation. It is conceivable that the sulfonamide coordinates the titanium and this may provide an explanation for the increased selectivity of the $NHSO_2Me$ versus $NHCOCF_3$ analogue (12:1 vs 2.4:1).

Cyclization of the crude **7** was readily effected, due to the leaving group ability of 2-mercaptopyridine, using cesium carbonate in DCM to give the CBZ bicyclic-trans-lactam **8** directly in 33−39% yield for the two steps. The enantiomeric purity of this material was also determined by HPLC and found to be 99.4% ee after crystallization. It was demonstrated, from analyzing crude material, that the crystallization was crucial to enhance the modest enantiomeric excess seen in the sulfonamide lactam **4** to the high levels seen in purified **8**.

Deprotection of **8** was carried out under transfer hydrogenation conditions with Pd/C formic acid. The resultant lactam was acylated with the known[1] piperidinocrotonic acid **9** via a mixed anhydride with isobutyl chloroformate. The hydrochloride salt of **1** was crystallized from ethyl acetate/ethanol in 76% yield for the two steps. A single-crystal X-ray structure of **1** (see the

(1) Macdonald, S. J. F.; Clarke, G. D. E.; Dowle, M. A.; Harrison, L. A.; Hodgson, S. T.; Inglis, G. G. A.; Johnson, M. R.; Shah, P.; Upton, R. J.; Walls, S. B. *J. Org. Chem.* **1999**, *64*, 5166−5175 and references therein.

(2) Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Consolandi, E. *Tetrahedron* **1991**, *47*, 8767−8774.

(3) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G. *J. Org. Chem.* **1992**, *57*, 4155−4162. Enolisation was carried out with triethylamine.

(4) The minor diastereoisomer, the isopropyl group epimer, was not isolated and fully characterized but identified by LCMS.

(5) Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2000**, 563−572.

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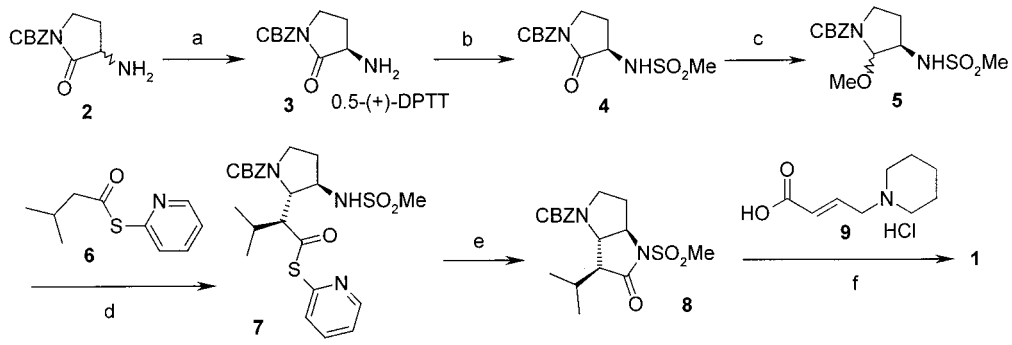
Scheme 1 [a]



[a] Key: (a) ref 1; (b) HCl then MsCl, $NaHCO_3$, DCM; (c) $LiBH_4$, THF then HCl, MeOH; (d) **6**, $TiCl_4$, *i*-Pr_2NEt, DCM then **5**; (e) Cs_2CO_3, DCM; (f) HCO_2H, Pd/C, DMF then **9**, *i*-BuOCOCl, Et_3N.

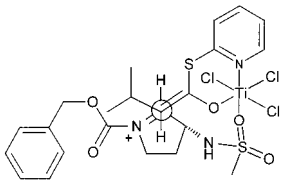


Figure 1. Possible transition-state model.

Table 1. NOE Study of Titanium Enolate of 6

time (min)	*T* (°C)	ratio *Z*/*E*	% **6**
0	−10	88.5:11.5	3.5
30	−10	86.6:13.4	6.1
60	−10	85.2:14.8	8.6
100	0	82.9:17.1	17.2
130	0	82.5:17.5	31
160	10	82.1:17.9	65.8

Supporting Information) was determined which confirmed both the relative and absolute configuration.

In conclusion, this *N*-acyliminium ion condensation with a titanium enolate of a 2-pyridylthioester represents a novel and selective method for the synthesis of these types of molecules. Furthermore, 2-mercaptopyridine is readily displaced offering a mild cyclization method to the sensitive bicyclic-trans-lactam core.

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were recorded at 400 MHz, all coupling constants are in Hz and ^{13}C NMR spectra at 100 MHz. FTIR spectra were recorded in Nujol mull. Elemental analyses were performed by Butterworth Laboratories Limited. HPLC was carried out using the following method: a gradient from 100% A to 95% B over 8min (A = water/TFA 1000:0.5. B = acetonitrile/TFA 1000:0.5); column 50 mm × 2.0 mm Luna C18(2), 3μm; flow rate 1.0 mL/min; temperature 40 °C; UV detection at 220 nm. HRMS were run on a quadrupole time-of-flight mass spectrometer using +ve ion electrospray and erythromycin as lock mass. Chiral HPLC was carried out using the following method: isocratic with heptane/ethanol mixtures, column Chiralcel AD or OD-H 250 × 4.6 mm, 5 μm; flow rate 1.0 mL/min; temperature ambient − 50 °C; UV detection at 215 nm.

Sulfonamide Lactam 4. A solution of **3** (3.4 g, 4.0 mmol) in 2 M hydrochloric acid (30 mL, 60 mmol) was stirred at 20 °C for 1 h. The solid precipitate (DPTT) was filtered off and washed with water (10 mL). To the filtrate was added a solution of mesyl chloride (0.93 mL, 11.9 mmol) in DCM (30 mL) followed by aqueous $NaHCO_3$ (50 mL) and the mixture stirred vigorously for 30 min. Aqueous $NaHCO_3$ (5 mL) was added and stirring continued for 18 h with further additions of aqueous $NaHCO_3$ to maintain the mixture at pH 8. The organic layer was separated and the aqueous layer extracted with DCM. The combined organic layer was washed with water and concentrated to give **4** as a pale pink solid in 84% yield (2.1 g, 6.7 mmol). Recrystallization from IMS gave colorless needles (1.4 g): mp 116−120 °C; $[\alpha]^{20}_D$ = +44 (*c* 0.5, MeOH); HPLC t_R 3.61min, 99.3% area. Chiral HPLC (Chiralcel AD, heptane/ethanol 40:60, oven ambient, typical retention times: **4**, 8.5min; enantiomer, 10.7min) 70% ee; ^1H NMR (DMSO) δ 7.71 (1H, d, *J* = 9.0), 7.46−7.34 (5H, m), 5.25 (2H, s), 4.33 (1H, dt, *J* = 11.6, 8.8), 3.75 (1H, t, *J* = 9.4), 3.58 (1H, td, *J* = 10.5, 6.6), 3.05 (3H, s), 2.36 (1H, m), 1.83 (1H, m); ^{13}C NMR (DMSO) δ 172.1, 151.2, 136.0, 128.8, 128.5, 128.2, 67.6, 55.1, 42.8, 42.7, 26.2; HRMS calcd for $C_{13}H_{16}N_2O_5S{\cdot}H$ *m*/*z* 313.0861, found 313.0858. Anal. Calcd for $C_{13}H_{16}N_2O_5S$: C, 50.0; H, 5.2; N, 9.0; S, 10.3. Found: C, 49.8; H, 4.9; N, 8.6; S, 10.3.

Methyl Ethers 5. A suspension of sulfonamide lactam **4** (5.0 g, 16.0 mmol) in THF (40 mL) was cooled to −15 °C and treated with a 2 M solution of $LiBH_4$ in THF (8.2 mL, 16.4 mmol) over 20 min. The solution was allowed to warm to 20 °C over 1 h and then added dropwise to a solution of HCl in MeOH (from AcCl 2 mL and MeOH 40 mL) at 0 °C over 45 min. The solution was allowed to warm to 20 °C over 45 min and then added dropwise to a solution of saturated $NaHCO_3$ (40 mL) over 1 h at 20 °C. The solution was concentrated to 40 mL and then extracted with DCM (2 × 40 mL). The extracts were concentrated to an oil, redissolved in DCM (80 mL), and concentrated to give **5** (as a mixture of diastereoisomers) as a viscous, pale yellow oil (5.2 g, 15.8 mmol, 99%): IR 1696; HPLC t_R 3.99 min, 39.6% area, t_R 4.03 min, 48.2% area; ^1H NMR (DMSO at 100 °C) δ 7.38−7.31 (5H, m), 7.07 and 6.62 (1H, 2 × br d), 5.18−4.99 (3H, m), 3.82−3.76 (1H, m), 3.63−3.25 (2H, m), 3.38 and 3.30 (3H, 2 × s), 2.94 and 2.93 (3H, 2 × s), 1.25−0.93 (2H, m); ^{13}C NMR (DMSO at 100 °C) δ 137.5, 137.4, 129.0, 128.5, 128.4, 128.2, 128.1, 94.0, 87.8, 67.1, 67.0, 57.8, 57.2, 55.9, 55.3, 44.6, 43.4, 41.7, 29.0, 28.1; HRMS calcd for $C_{14}H_{20}N_2O_5S{\cdot}NH_4$ *m*/*z* 346.1437, found 346.1432.

Pyrrolidine Thioester 7. A solution of 2-pyridylthioester **6** (5.4 g, 27.6 mmol) in DCM (80 mL) was cooled to 0 °C and treated with titanium tetrachloride (3.1 mL, 28.2 mmol) dropwise over 10 min. To the mixture was added diisopropylethylamine (4.9 mL, 28.2 mmol) over 5 min to generate the titanium enolate. To the black enolate solution was added a solution of **5** (4.5 g, 13.7 mmol) in DCM (10 mL). The solution was stirred at 0−4 °C for 1 h and then quenched with 5% w/v aqueous citric acid (30 mL). The phases were separated, and the organic layer was washed with 5% w/v aqueous citric acid (30 mL) and brine (30 mL). The solution was concentrated to an orange oil (containing mainly **6**, **7**, and minor amounts of the isopropyl group epimer: HPLC-MS t_R 4.99min, 2.7% area, t_R 5.19min, 32.1% area, both peaks give *m*/*z* 492 MH^+) which can either be used directly in the cyclization step or purified for characterization. The major diastereoisomer **7** was isolated by crystallization from ethyl acetate and cyclohexane (1:1) in 25% yield. Data for the major isomer **7**: mp 142−143 °C; $[\alpha]^{20}_D$ = +8 (*c* 0.5, MeOH); IR 1675; ^1H NMR (DMSO, mixture of rotamers, ratio 5:3) δ 8.63 (1H, br d, *J* = 3.0), 7.91 (1H, td, *J* = 7.7, 1.8), 7.61−7.27 (8H, m), 5.24−5.01 (2H, m), 4.12−4.00 (2H, m), 3.66−3.56 (1H, m), 3.30−3.24 (1H, m), 3.13 (1H, dd, *J* = 9.0, 5.4), 2.92, 2.90 (3H, 2s), 2.17−1.75 (3H, m), 1.06, 0.96, 0.92, 0.83 (6h, 4d, *J* = 6.5); ^{13}C NMR

(DMSO) δ 199.3, 199.2, 154.6, 151.0, 150.8, 138.2, 137.4, 130.44, 128.8, 128.7, 128.5, 128.4, 128.1, 127.7, 124.6, 66.9, 66.4, 64.9, 64.4, 63.0, 61.8, 54.9, 54.0, 45.3, 44.9, 41.3, 41.2, 31.5, 30.7, 28.1, 28.0, 21.2, 21.1, 21.0, 20.9; HRMS calcd for $C_{23}H_{29}N_3O_5S_2$·H *m*/*z* 492.1627, found 492.1621. Anal. calcd for $C_{23}H_{29}N_3O_5S_2$: C, 56.2; H, 6.0; N, 8.6; S, 13.0. Found: C, 56.1; H, 5.8; N, 8.3; S, 12.9.

CBZ Bicyclic-Trans-Lactam 8. A solution of the crude pyrrolidine thioester **7** in DCM (70 mL) was treated with cesium carbonate (7.5 g, 23.0 mmol) and the mixture stirred at 20 °C overnight. Water (30 mL) was added and stirred to dissolve the solids before the phases were separated. The DCM solution was washed with 2 M HCl (30 mL) and then concentrated to 25 mL. Ethyl acetate (25 mL) was added and the solution concentrated to 25 mL, which initiated crystallization. The suspension was treated with cyclohexane (50 mL) over 30 min at 55 °C and then cooled to 20 °C and stirred for 5 h. The solid was collected by filtration, washed with cyclohexane (2 × 40 mL), and dried in vacuo overnight to give **8** in 39% yield over two steps (2.05 g, 5.4 mmol): mp 182 °C; $[\alpha]^{20}_D = +59$ (*c* 0.5, DCM); HPLC t_R 5.13min, 0.2% area (isopropyl group epimer), t_R 5.28min, 98.8% area (**8**); chiral HPLC (Chiralcel OD-H, heptane/ethanol 90:10, oven 30°, typical retention times: **8** at 25 min, enantiomer at 24 min) 99.4% ee; IR 1749, 1707; ^{1}H NMR ($CDCl_3$) δ 7.39−7.32 (5H, m), 5.12, 5.10 (2H, AB system, J = 12.0), 3.87−3.75 (2H, m), 3.47 (1H, m), 3.29 (1H, d, J = 11.7), 3.24 (3H, s), 2.77 (1H, d, J = 11.8), 2.70 (1H, br s), 2.55 (1H, m), 2.02 (1H, m), 1.16, 0.95 (6H, 2d, J = 6.4).

Bicyclic-Trans-Lactam 1. To a mixture of **8** (10 g, 26.3 mmol) and 10% palladium on charcoal (4 g, dry powder) in DMF (200 mL) at 40 °C was added 98−100% formic acid (1.5 mL, 40 mmol) and the mixture stirred for 2.5 h. The reaction was cooled to 20 °C before cyclohexene (3 mL, 30 mol) was added. After being stirred for 1 h, the reaction mixture was filtered through Harborlite and concentrated to 70 mL. A suspension of **9** (6.6 g, 32 mmol) in DMF (150 mL) at 5 °C was treated with Et_3N (4.5 mL, 32.3 mmol) and stirred for 15 min before the addition of isobutyl chloroformate (3.8 mL, 29.3 mmol). The suspension was stirred for 30 min at 5 °C before the solution of deprotected sulfonamide was added. The mixture was stirred at 23 °C for 16 h and then the solids were filtered off and the filtrate concentrated to 45 mL. The concentrate was partitioned between EtOAc (100 mL) and 10% aqueous $KHCO_3$ (100 mL). The aqueous layer was separated and extracted with EtOAc (100 mL). The organic layers were washed with brine and then combined and stirred for 15 min with Norit charcoal (2 g). The mixture was filtered through Harborlite and concentrated to 32 mL. More EtOAc (40 mL) and EtOH (20 mL) were added, and the solution was warmed to 30 °C and treated with acetyl chloride (3 mL, 42 mmol). The resulting suspension was cooled in ice, and the solid was collected by filtration, washed with a mixture of EtOAc (52 mL) and EtOH (8 mL), and dried in vacuo at 45 °C to give **1** as a white solid in 76% yield (8.7 g, 20 mmol): mp 235 °C dec; $[\alpha]^{20}_D = +52$ (*c* 0.5, MeOH); HPLC t_R 3.00min, 99.7% area. Chiral HPLC (Chiralcel OD-H, heptane/ethanol 90:10, oven 50 °C, typical retention times: **1** at 30.4 min, enantiomer at 22.7 min) 99.9% ee; IR 1743, 1667, 1626; ^{1}H NMR (CD_3OD + DCl) δ 6.76 (2H, m), 4.02 (2H, m), 3.95 (2H, m), 3.73 (1H, td, J = 11.7, 5.2), 3.49 (3H, m), 3.30 (1H, pent, J = 1.6), 3.26 (3H, s), 3.03 (4H, m), 2.52 (1H, m), 2.15 (1H, m), 1.97−1.79 (5H, m), 1.53 (1H, m), 1.25, 1.00 (6H, 2d, J = 7.1).

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Supporting Information Available: Crystal structure data for bicyclic-trans-lactam **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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